

The City College of New York

EXECUTIVE COUNSEL TO THE PRESIDENT

Wille Administration Bldg., Rm. 200
160 Convent Avenue
New York, NY 10031
tel.: 212.650.8276
www.ccny.cuny.edu

November 16, 2021

BY EMAIL ONLY (curtis@summitpointcapital.com)

Mr. Curtis J. Boulanger, CIO
Summit Point Capital Management
16 East 18th Street, 5th floor
New York, NY 10003

Dear Mr. Boulanger:

I write in response to your request dated October 4, 2021 (copy attached for reference), as amended by our subsequent email correspondence on October 18, 2021, pursuant to the New York Freedom of Information Law (Public Officers Law §§ 84-90), as follows:

REQUEST: “I hereby request records or portions thereof pertaining to (or containing the following): all emails sent to/from/cc’d hywang@med.cuny.edu containing any of the following keywords,” which were, as amended by your October 18, 2021 email, “Simufilam, western blot(s), Cassava, PTI-125, filamin, FLNA,” dated from January 1, 2021 through October 4, 2021.

Response: Your request is hereby granted in full. Attached please find a PDF of 498 pages that are responsive to your request, except please note that I have redacted personal information, including personal email addresses and the names and ages of children, pursuant to Public Officers Law §§ 89(2)(a) and 89(2)(c)(i).

No responsive records that have been located have been withheld, except as noted above.

Sincerely,

/s/ Paul F. Occhiogrosso

Paul F. Occhiogrosso
Executive Counsel to the President

Enclosures

PFO/kk

October 4, 2021

Paul F. Occhiogrosso, Esq.
Executive Counsel to the President
The City College of New York
Wille Administration Building, Rm. 200
160 Convent Avenue
New York, NY 10031



Re: Freedom of Information Law Request

Records Access Officer:

Under the provisions of the New York Freedom of Information Law, Article 6 of the Public Officers Law, I hereby request records or portions thereof pertaining to (or containing the following): all emails sent to/from/cc'd hywang@med.cuny.edu containing any of the following keywords: Simufilam, Cassava, Western Blots, Pain Therapeutics, PTI-125, SavaDx, Naloxone, NLX, Filamin, FLNA, Biomarkers, ELISA, Trial or Patent, between and including, the periods of October 2015 and October 2021.

If my request appears to be extensive or fails to reasonably describe the records, please contact me in writing or by phone at +1-646-750-7914.

If there are any fees for copying the records requested, please inform me before filling the request or please supply the records without informing me if the fees are not in excess of \$50.

As you know, the Freedom of Information Law requires that an agency respond to a request within five business days of receipt of a request. Therefore, I would appreciate a response as soon as possible and look forward to hearing from you shortly. If for any reason any portion of my request is denied, please inform me of the reasons for the denial in writing and provide the name and address of the person or body to whom an appeal should be directed.

Sincerely,

Curtis J. Boulanger

Curtis J. Boulanger, CIO
Summit Point Capital Management
16 E 18 Street, FI 5
New York, NY 10003

From: Qiang Xu <qxx07a@acu.edu>
Sent time: 01/24/2021 10:48:30 PM
To: Ben Thornton <gthornton@cassavasciences.com>; Ben Thornton <gbt20a@acu.edu>; Hoau-Yan wang <[REDACTED]@gmail.com>; Hoau-yan Wang
Subject: [EXTERNAL] 20210124 results
Attachments: 20210124 Western blot results.xlsx

Hi Ben and Hoau,

Hope you are well! Attached is today's results and analysis.

Blessings,

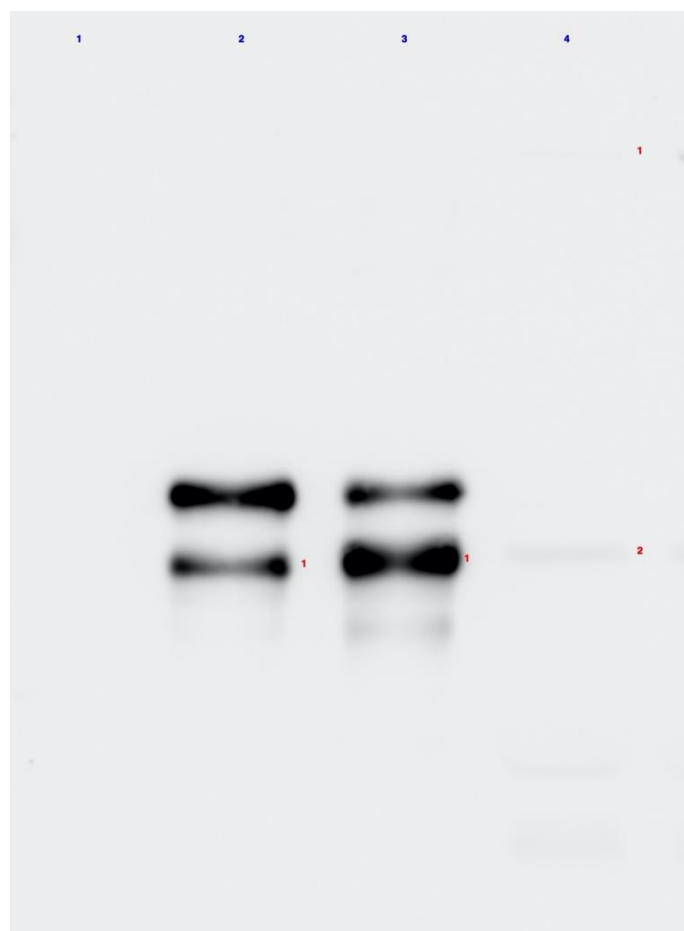
John

--

Qiang (John) Xu, Ph.D.
Professor
Department of Biology
Abilene Christian University
ACU Box 27868
Abilene, Texas 79699-7868
325-674-4883
fax 325-674-2009
qxu@acu.edu

20210124 Western blot results

Note: The densitometric analysis was conducted using chemiluminacent data .



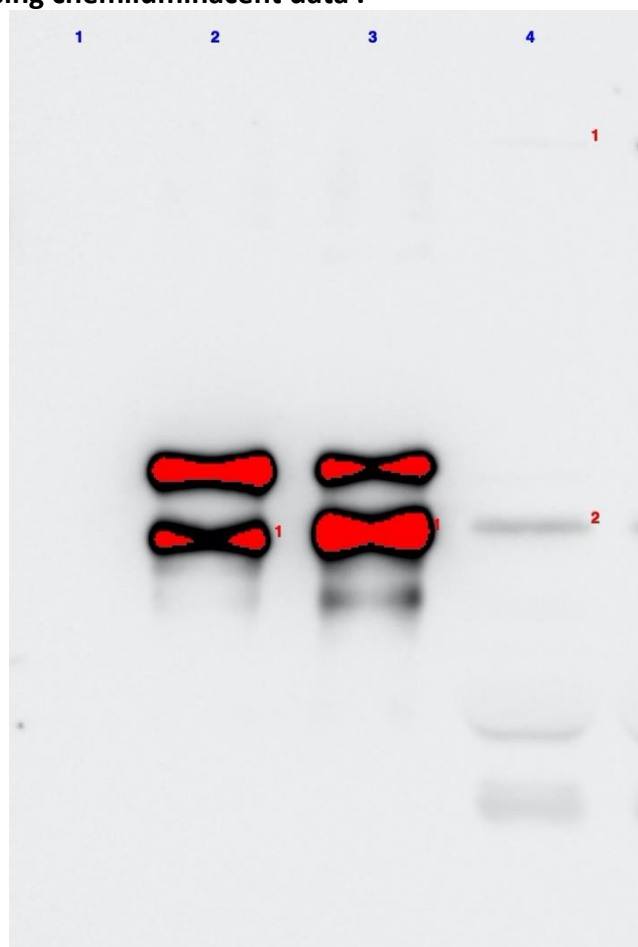
antibody: Origene 3881 (1:1000 dilution) in PBST 1.5 mm gels were made using Boston Bioproducts primary antibody: GE donkey anti-Rabbit IgG (1:7500) BioRad Trans-Blot Turbo RTA Midi 0.2um Nitrocellulose exposure time: 120 s Highest Resolution (1*1) BioRad Trans-Blot Turbo Transfer System was used for 10% milk in PBST used as blocking buffer. 1st antibody incubation was at 4 °C overnight and 2nd antibody

Xu Lab 2021-01-24 16h24m00s M1WSHR					
Lane	Band No.	Band Label	Mol. Wt. (KDa)	Relative Front	Adj. Volume (Int)
1: 20 ul Bio-Rad 1/60unstained MW Marker					
2: λPP treated 60ng A3 + 60ng A4 Peptides			90	0.602484	87775704
3: 60ng 1740 + 60ng A3 + 60ng A4 Peptides	1		90	0.596273	251789688
4: 1 uL of Sample 03-004 Day 0	1		280	0.117322	257715
4	2		90	0.587302	2920023
5: 1 uL of Sample 03-004 Day28	1		280	0.122153	2550480
5	2		90	0.585921	2369040
6: 1 uL of Sample 03-006 Day 0	1		280	0.124224	218924
6	2		90	0.581781	430200

7: 1 uL of Sample 03-006 Day 28	1		280	0.126294	8829562
7	2		90	0.583161	34422178
8: 1 uL of Sample 03-011 Day 0	1		280	0.127674	1616969
8	2		90	0.582471	1321101
9: 1 uL of Sample 03-011 Day 28	1		280	0.127674	1633828
9	2		90	0.592823	5153532

20210124 Western blot resu

Note: The densitometric analysis was conducted using chemiluminacent data .



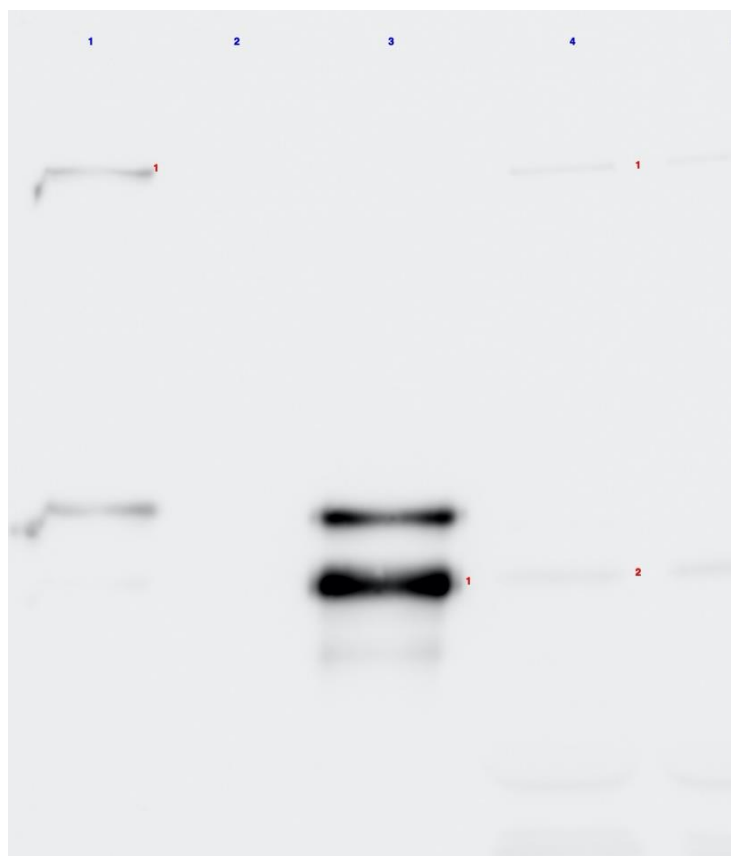
antibody:Origene 3881 (1:1000 dilution) in PBST 1.5 mm gels were made using Boston Bioproduc
 ury antibody: GE donkey anti-Rabbit IgG (1:7500) BioRad Trans-Blot Turbo RTA Midi 0.2um Nitrocellul
 posure time: 47 S Medim Resolution (4*4) BioRad Trans-Blot Turbo Transfer System was used fo
 10% milk in PBST used as blocking buffer. 1st antibody incrbation was at 4 °C over night and 2nd antib

Xu Lab 2021-01-24 16h19m08s M1WSMR					
Lane	Band No.	Band Label	Mol. Wt. (KDa)	Relative Front	Adj. Volume (Int)
1: 20 ul Bio-Rad 1/60unstained MW Marker					
2: λPP treated 60ng A3 + 60ng A4 Peptides	1		90	0.598338	31733664

3: 60ng 1740 + 60ng A3 + 60ng A4 Peptides	1		90	0.590028	54549860
4:1 uL of Sample 03-004 Day 0	1		280	0.110803	37393
4	2		90	0.581717	961909
5:1 uL of Sample 03-004 Day28	1		280	0.116343	897840
5	2		90	0.581717	762236
6: 1 uL of Sample 03-006 Day 0	1		280	0.119114	44688
6	2		90	0.576177	136136
7: 1 uL of Sample 03-006 Day 28	1		280	0.119114	3539766
7	2		90	0.578947	13675464
8: 1 uL of Sample 03-011 Day 0	1		280	0.121884	568233
8	2		90	0.578947	356991
9:1 uL of Sample 03-011 Day 28	1		280	0.121884	553148
9	2		90	0.587258	1787605

20210124 Western blot resu

Note: The densitometric analysis was conducted using chemiluminacient data.



antibody: Origene 3881 (1:1000 dilution) in PBST 1.5 mm gels were made using Boston Bioproducts primary antibody: GE donkey anti-Rabbit IgG (1:7500) BioRad Trans-Blot Turbo RTA Midi 0.2um Nitrocellulose exposure time: 120 S Highest Resolution (1*1) BioRad Trans-Blot Turbo Transfer System was used for 10% milk in PBST used as blocking buffer. 1st antibody incubation was at 4 °C over night and 2nd antibody

Xu Lab 2021-01-24 16h31m11s M2WSHR					
Lane	Band No.	Band Label	Mol. Wt. (KDa)	Relative Front	Adj. Volume (Int)
1: 0.5 ug of FLNA lysate (LC419924)	1		280	0.131815	6410581
2: 20 ul Bio-Rad 1/60unstained MW Marker					
3: 60ng 1740 + 60ng A3 + 60ng A4 Peptides	1		90	0.606625	211317080
4:1 uL of Sample 05-005 Day 0	1		280	0.128364	830502
4	2		90	0.596273	1911642
5:1 uL of Sample 05-005 Day 28	1		280	0.113872	520208
5	2		90	0.585921	2702336
6: 1 uL of Sample 06-002 Day 0	1		280	0.10559	464724
6	2		90	0.583161	3329352
7: 1 uL of Sample 06-002 Day 28	1		280	0.102139	166852
7	2		90	0.58109	809480
8: 1 uL of Sample 06-005 Day 0	1		280	0.097308	174440
8	2		90	0.58109	335405
9:1 uL of Sample 06-005 Day 28	1		280	0.091787	29298
9	2		90	0.57971	204315

20210124 Western blot results

Note: The densitometric analysis was conducted using chemiluminacient data.



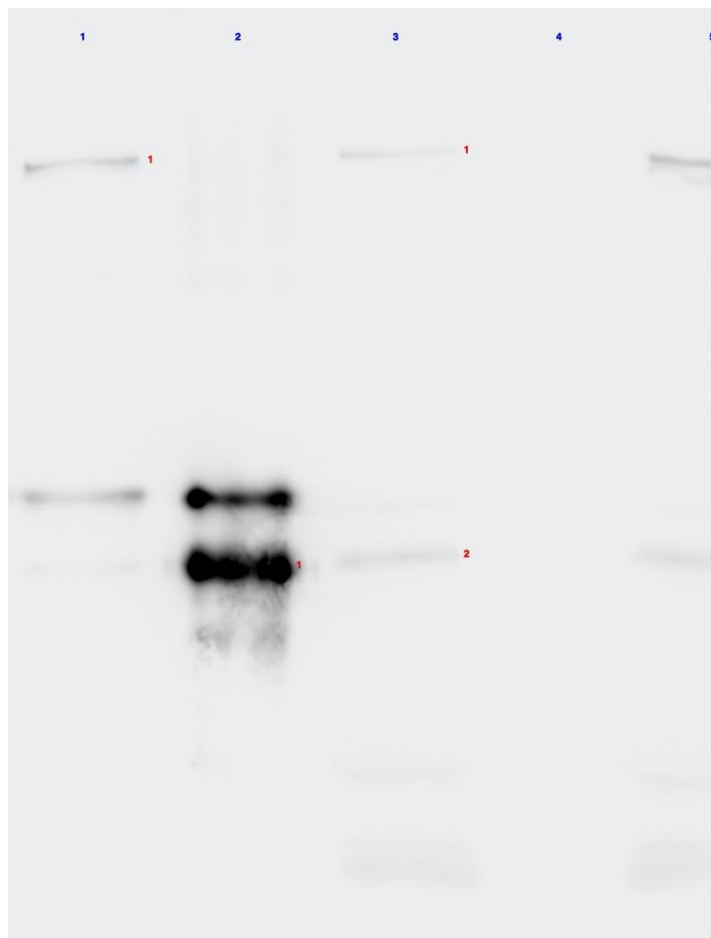


antibody: Origene 3881 (1:1000 dilution) in PBST 1.5 mm gels were made using Boston Bioproducts primary antibody: GE donkey anti-Rabbit IgG (1:7500) BioRad Trans-Blot Turbo RTA Midi 0.2um Nitrocellulose exposure time: 120 S Highest Resolution (1*1) BioRad Trans-Blot Turbo Transfer System was used for 10% milk in PBST used as blocking buffer. 1st antibody incubation was at 4 °C over night and 2nd antibody

Xu Lab 2021-01-24 16h39m04s M3WSHR					
Lane	Band No.	Band Label	Mol. Wt. (KDa)	Relative Front	Adj. Volume (Int)
1: 0.5 ug of FLNA lysate (LC419924)	1		280	0.136646	9172384
2: 60ng 1740 + 60ng A3 + 60ng A4 Peptides	1		90	0.621808	127746398
3: 20 ul Bio-Rad 1/60unstained MW Marker					
4: 1 uL of Sample 06-008 Day 0	1		280	0.148378	58624
4	2		90	0.610076	154804
5: 1 uL of Sample 06-008 Day 28	1		280	0.142167	1605856
5	2		90	0.603175	4600736
6: 1 uL of Sample 07-008 Day 0	1		280	0.135266	1789379
6	2		90	0.594893	860428
7: 1 uL of Sample 07-008 Day 28	1		280	0.131125	5118935
7	2		90	0.584541	3899455
8: 1 uL of Sample 12-001 Day 0	1		280	0.121463	1374515
8	2		90	0.57902	3203990
9: 1 uL of Sample 12-001 Day 28	1		280	0.111111	105410
9	2		90	0.569358	258318

20210124 Western blot results

Note: The densitometric analysis was conducted using chemiluminacent data.



antibody: Origene 3881 (1:1000 dilution) in PBST 1.5 mm gels were made using Boston Bioproducs
 1st antibody: GE donkey anti-Rabbit IgG (1:7500) BioRad Trans-Blot Turbo RTA Midi 0.2um Nitrocellulose
 exposure time: 120 S Highest Resolution (1*1) BioRad Trans-Blot Turbo Transfer System was used for
 10% milk in PBST used as blocking buffer. 1st antibody incubation was at 4 °C over night and 2nd antibody

Xu Lab 2021-01-24 16h46m59s M4WSHR					
Lane	Band No.	Band Label	Mol. Wt. (KDa)	Relative Front	Adj. Volume (Int)
1: 0.5 ug of FLNA lysate (LC419924)	1		280	0.127674	3911984
2: 60ng 1740 + 60ng A3 + 60ng A4 Peptides	1		90	0.597654	222448824
3: 1 uL of Sample 13-002 Day 0	1		280	0.116632	1400868
3	2		90	0.584541	3917480
4: 20 ul Bio-Rad 1/60unstained MW Marker					

5:1 uL of Sample 13-002 Day 28	1		280	0.127674	7901752
5	2		90	0.587302	4259564
6: 1 uL of Sample 13-003 Day 0	1		280	0.124224	90475
6	2		90	0.591442	191290
7: 1 uL of Sample 13-003 Day 28	1		280	0.129055	12045
7	2		90	0.592133	52560
8: 1 uL of Sample 13-011 Day 0	1		280	0.130435	5700030
8	2		90	0.612836	10649520
9:1 uL of Sample 13-011 Day 28	1		280	0.135956	1031184
9	2		90	0.605935	1160144

Results: Membrane 1 with sheet

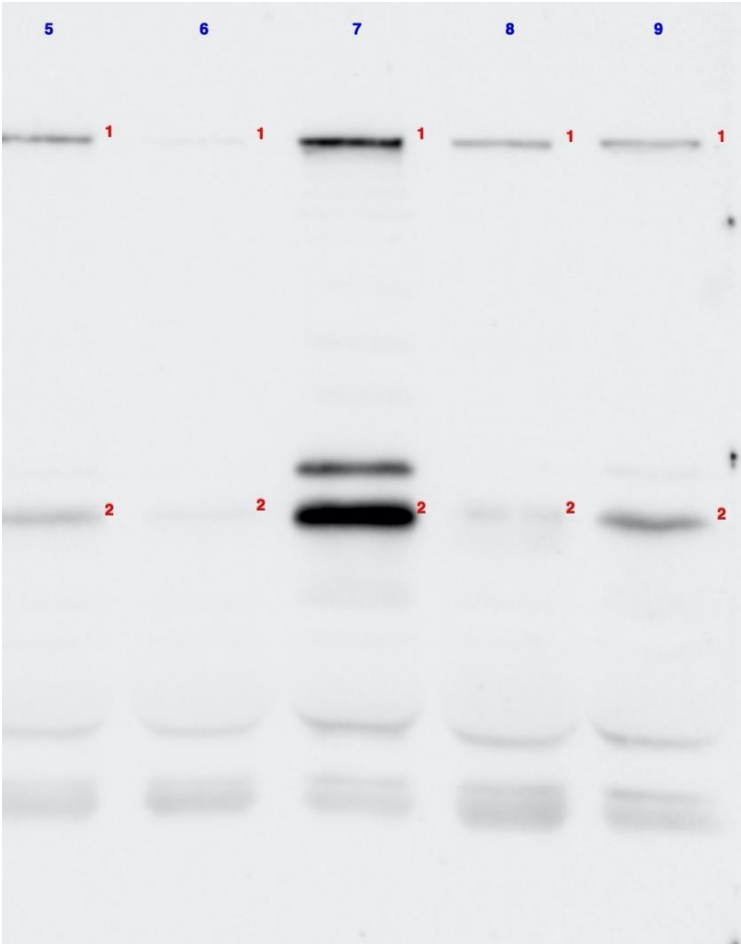


reagents: Acrylamide: Bis (37.5:1); 7% resolving gel and 4% stacking gel. Gel were run first at 64V for 1 hr.
 Transfer membrane (Cat # 1704271) was used.
 Transfer at 2.5A, 25V for 14 mins
 Primary antibody incubation was at room temp for 1 hr.

Volume (Int)	Abs. Quant.	Rel. Quant.	Band %	Lane %	90kD/280kD	D28/D0 of 90	D28/D0 of 90
101485872	N/A	N/A	100	28.142482			0.34860722
276382368	N/A	N/A	100	68.319484			
4505655	N/A	N/A	8.110014	3.04063	11.33043478		
14119794	N/A	N/A	91.889986	34.451658			
7635840	N/A	N/A	51.844082	24.819581			
10073520	N/A	N/A	48.155918	23.053927	0.92886045	0.08197924	0.81130868
3213355	N/A	N/A	33.726068	4.136561			
6790468	N/A	N/A	66.273932	8.128613	1.965065502		

13954654	N/A	N/A	20.414351	14.474156	3.898514785	1.98391086	80.0143608
45066252	N/A	N/A	79.585649	56.427713			
6731226	N/A	N/A	55.035074	14.225849	0.817023085		
9246791	N/A	N/A	44.964926	11.622847			
6726000	N/A	N/A	24.071627	10.793577	3.154268381	3.86068453	3.90093717
13592420	N/A	N/A	75.928373	34.045837			

ults: Membrane 1 with sheet



ts Acrylamide: Bis (37.5:1); 7% resolving gel and 4% stacking gel. Gel were run first at 64V fo
ose membrane (Cat # 1704271) was used.
or transfer at 2.5A, 25V for 14 mins
ody incubation was at room temp for 1 hr.

Volume (Int)	Abs. Quant.	Rel. Quant.	Band %	Lane %	90kD/280kD	D28/D0 of 90	D28/D0 of 90
35764483	N/A	N/A	100	39.53815			0.58173686

63347036	N/A	N/A	100	61.943691			
294447	N/A	N/A	3.741912	1.510113	25.72430669		
1810907	N/A	N/A	96.258088	38.846599			
1359752	N/A	N/A	54.084271	29.205343	0.848966408	0.0330025	0.79242007
1332898	N/A	N/A	45.915729	24.794355			
349832	N/A	N/A	24.713534	2.837333	3.046365915		
579320	N/A	N/A	75.286466	8.643556			
4013198	N/A	N/A	20.561828	15.483393	3.8633808	1.26819329	100.454428
15100596	N/A	N/A	79.438172	59.818244			
950931	N/A	N/A	61.415722	17.188524	0.628247567		
973218	N/A	N/A	38.584278	10.798648			
895236	N/A	N/A	23.631199	12.406622	3.231693869	5.14398151	5.00742316
2513932	N/A	N/A	76.368801	40.094404			

ults: Membrane 2 with sheet

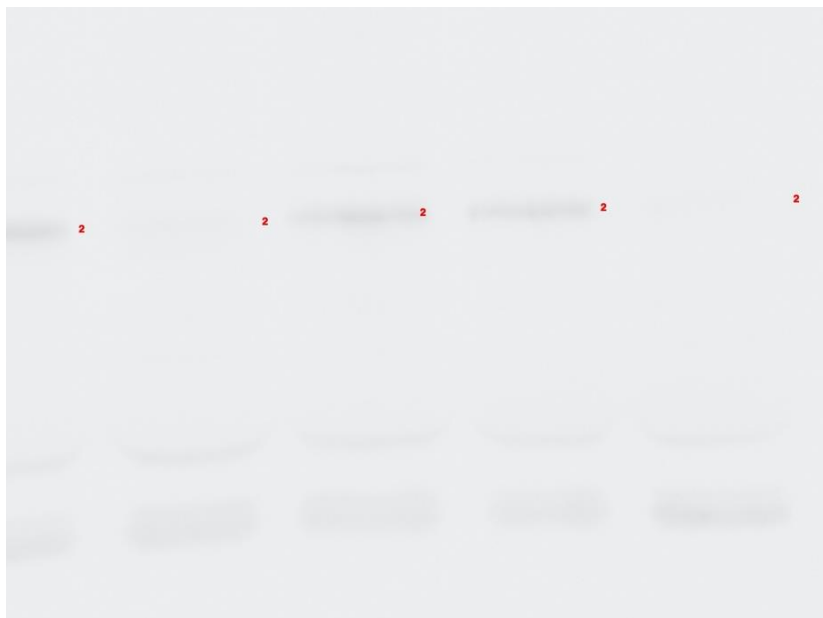


its Acrylamide: Bis (37.5:1); 7% resolving gel and 4% stacking gel. Gel were run first at 64V for
 ose membrane (Cat # 1704271) was used.
 or transfer at 2.5A, 25V for 14 mins
 ody incubation was at room temp for 1 hr.

Volume (Int)	Abs. Quant.	Rel. Quant.	Band %	Lane %	90kD/280kD	D28/D0 of 90	D28/D0 of 90
15448771	N/A	N/A	100	29.67126			
230076860	N/A	N/A	100	66.887827			
5403702	N/A	N/A	30.286593	8.390714	2.301790965		
9952482	N/A	N/A	69.713407	19.313671			
4960800	N/A	N/A	16.142774	5.18686			
10125648	N/A	N/A	83.857226	26.944295	5.194722111	2.25681749	1.41362033
4493034	N/A	N/A	12.248674	5.202494			
12603006	N/A	N/A	87.751326	37.271441	7.164149043		
4229120	N/A	N/A	17.089679	2.41602			
6760220	N/A	N/A	82.910321	11.721286	4.851485149	0.67718931	0.2431344
3697295	N/A	N/A	34.21432	2.097202			
5616135	N/A	N/A	65.78568	4.032401	1.922752809		
3013839	N/A	N/A	12.541254	0.347159			
4890453	N/A	N/A	87.458746	2.420976	6.973684211	3.62692707	0.60915908

ults: Membrane 3 with sheet





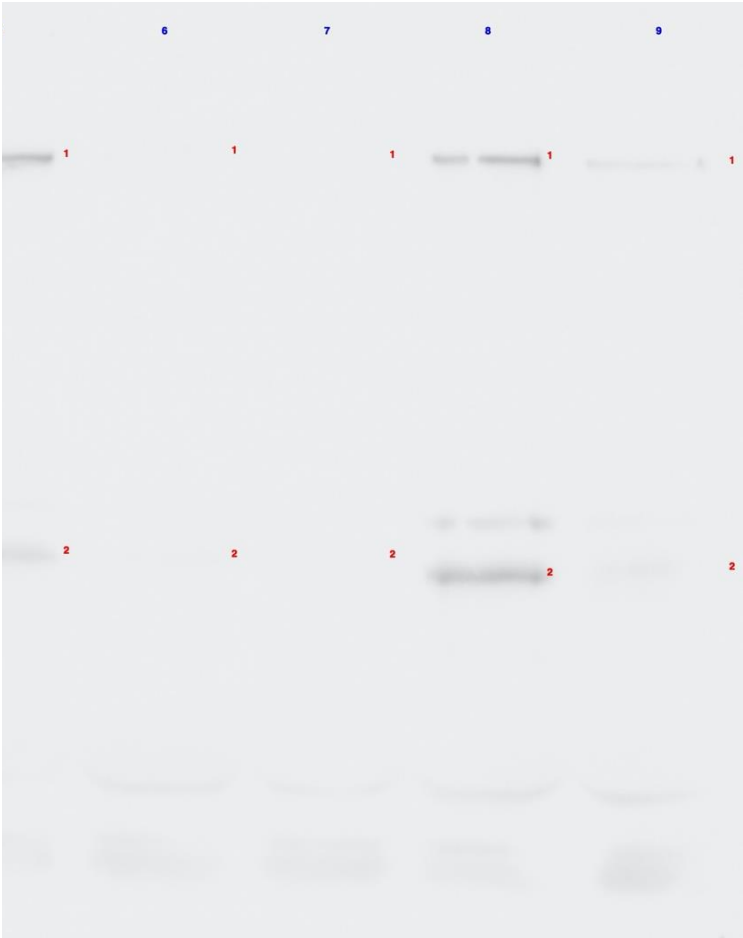
its Acrylamide: Bis (37.5:1); 7% resolving gel and 4% stacking gel. Gel were run first at 64V for
 ose membrane (Cat # 1704271) was used.

or transfer at 2.5A, 25V for 14 mins

ody incubation was at room temp for 1 hr.

Volume (Int)	Abs. Quant.	Rel. Quant.	Band %	Lane %	90kD/280kD	D28/D0 of 90	D28/D0 of 90
14686113	N/A	N/A	100	21.507784			
141787191	N/A	N/A	100	71.405736			
2399920	N/A	N/A	27.467811	2.08656	2.640625		
6308263	N/A	N/A	72.532189	5.509822			
5696544	N/A	N/A	25.873394	12.035187	2.864974194	1.08496064	29.7197488
13226752	N/A	N/A	74.126606	34.480501			
7666795	N/A	N/A	67.528654	17.023258	0.480852855		
9786741	N/A	N/A	32.471346	8.185682			
10682060	N/A	N/A	56.761074	30.389942	0.761770759	1.58420763	4.53199454
11898745	N/A	N/A	43.238926	23.150169			
6087440	N/A	N/A	30.021044	12.660447	2.330996752		
11738485	N/A	N/A	69.978956	29.511461			
4649470	N/A	N/A	28.980447	1.45115	2.45060241	1.05131095	0.08062385
6764020	N/A	N/A	71.019553	3.556193			

Results: Membrane 4 with sheet



Results Acrylamide: Bis (37.5:1); 7% resolving gel and 4% stacking gel. Gel were run first at 64V for 2 hrs. Transfer membrane (Cat # 1704271) was used. Transfer at 2.5A, 25V for 14 mins. Substrate incubation was at room temp for 1 hr.

Volume (Int)	Abs. Quant.	Rel. Quant.	Band %	Lane %	90kD/280kD	D28/D0 of 90	D28/D0 of 90
9767432	N/A	N/A	100	23.642405			
258286320	N/A	N/A	100	63.356647			
6635916	N/A	N/A	26.340285	10.670969			
12875086	N/A	N/A	73.659715	29.841005			
					2.796466191		

15224596	N/A	N/A	64.974481	40.404991	0.539065767	0.19276677	1.08732246
12217484	N/A	N/A	35.025519	21.780948			
4406955	N/A	N/A	32.110092	1.528506	2.114285714		
6577650	N/A	N/A	67.889908	3.231698			
1016160	N/A	N/A	18.644068	0.248869	4.363636364	2.06388206	0.27476606
4483806	N/A	N/A	81.355932	1.085973			
10950450	N/A	N/A	34.863528	23.222964	1.868327009		
18363870	N/A	N/A	65.136472	43.38809			
6091624	N/A	N/A	47.057492	11.120323	1.125060125	0.60217517	0.10893862
9856760	N/A	N/A	52.942508	12.511032			

r 25 mins then at 100V for 2 hr 15 mins.

kD



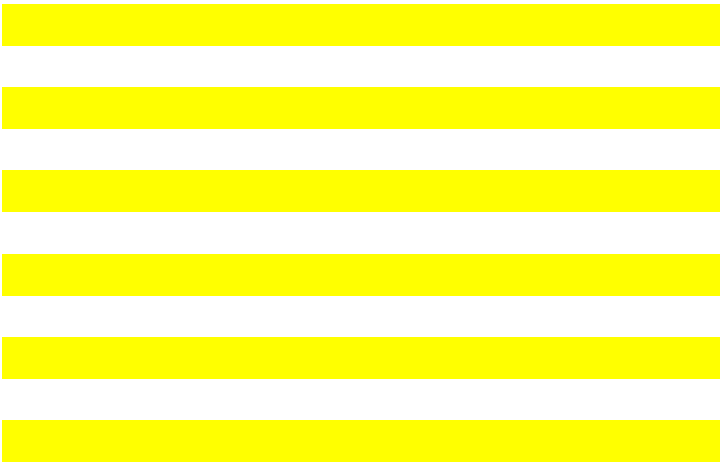


r 25 mins then at 100V for 2 hr 15 mins.

kD

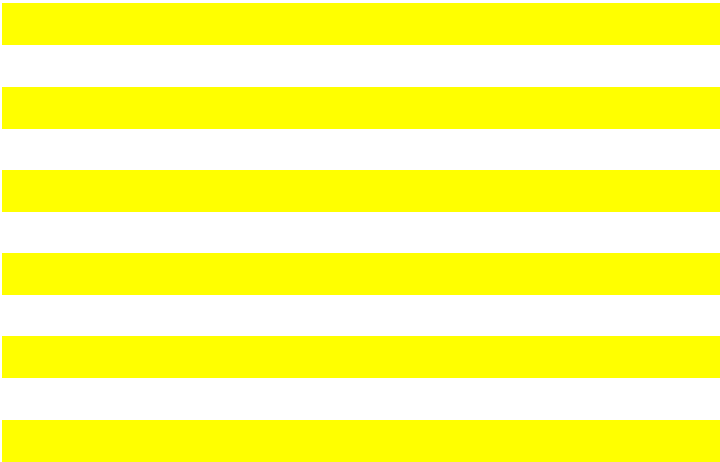
r 25 mins then at 100V for 2 hr 15 mins.

kD



r 25 mins then at 100V for 2 hr 15 mins.

kD



r 25 mins then at 100V for 2 hr 15 mins.

kD



From: Qiang Xu <qxx07a@acu.edu>
Sent time: 03/11/2021 03:27:59 PM
To: Hoau-yan Wang; Hoau-Yan wang <[REDACTED]@gmail.com>; Ben Thornton <gbt20a@acu.edu>
Subject: [EXTERNAL] Fwd: 20210310 results
Attachments: 20210310 Western blot results.xlsx

FYI

----- Forwarded message -----

From: **Qiang Xu** <qxx07a@acu.edu>
Date: Wed, Mar 10, 2021 at 11:24 PM
Subject: 20210310 results
To: Ben Thornton <gthornton@cassavasciences.com>

Hi Ben,

Hope you are well! Attached are today's results and analysis.

Blessings,

John

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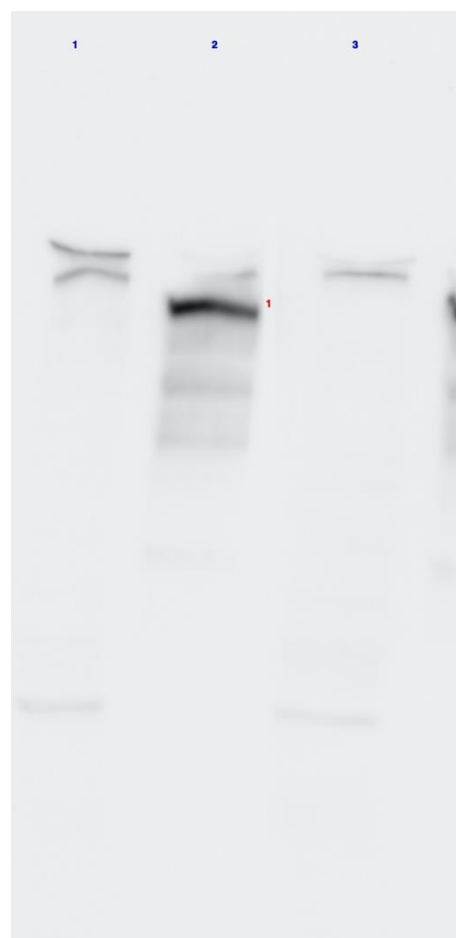
Qiang (John) Xu, Ph.D.
Professor
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ACU Box 27868
Abilene, Texas 79699-7868
325-674-4883
fax 325-674-2009
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Qiang (John) Xu, Ph.D.
Professor
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Abilene Christian University
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Abilene, Texas 79699-7868
325-674-4883
fax 325-674-2009
qxu@acu.edu

20210310 Western

Note: The densitometric analysis was conducted using chemiluminacent data .



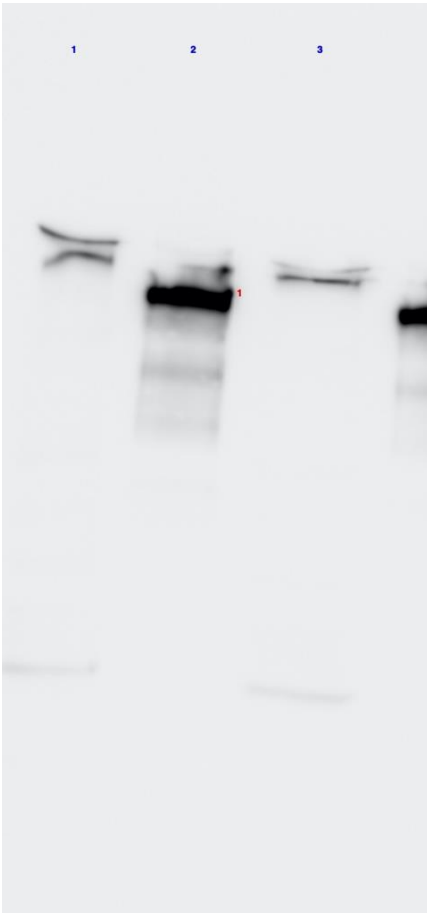
dy: Different Ab SC lines (1:100 dilution of original) in BioRad 7.5% Precasted gels ran at 200V, 4°C, 4h. 2nd antibody: GE sheep anti-mouse IgG (1:3000 dilution) BioRad Trans-Blot Turbo RTA Midi 0.2uL. Exposure time: 120 s. Highest Resolution (1*1) BioRad Trans-Blot Turbo Transfer System. 10% milk in PBST used as blocking buffer. 1st antibody and 2nd antibody incubation was at 37°C for 1h.

Xu Lab 2021-03-10 19h10m02s M1WSHR				
Lane	Band No.	1st antibody	Mol. Wt. (KDa)	Relative Front
1: 0.5 ug of FLNA lysate (LC419924)		SC01		
2: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1		175	0.279644
3: 0.5 ug of FLNA lysate (LC419924)		SC02		
4: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1		175	0.284441
5: 0.5 ug of FLNA lysate (LC419924)		SC03		
6: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1		175	0.29061
	2		110	0.484578
	3		90	0.544894

7: 0.5 ug of FLNA lysate (LC419924)				
8: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC04	175	0.296779
9: 0.5 ug of FLNA lysate (LC419924)				
10: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC05	175	0.302262

20210310 Western

Note: The densitometric analysis was conducted using chemiluminacent data.



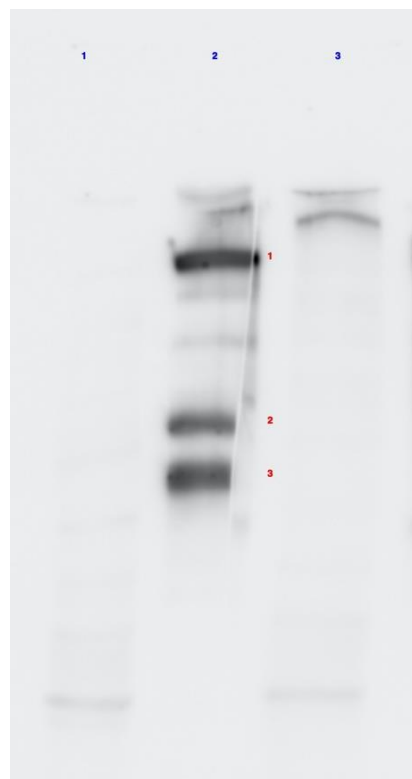
ly: Different Ab SC lines (1:100 dilution of original) ii BioRad 7.5% Precasted gels ran at 2 antibody: GE sheep anti-mouse IgG (1:3000 dilution) BioRad Trans-Blot Turbo RTA Midi 0.2u exposure time: 120 S Highest Resolution (1*1) BioRad Trans-Blot Turbo Transfer System 10% milk in PBST used as blocking buffer. 1st antibody 2nd antibody incubation was at room

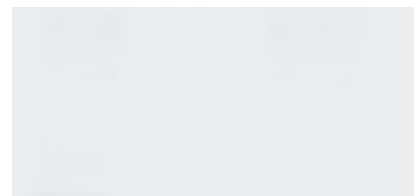
Xu Lab 2021-03-10 19h28m08s M2WSHR				
Lane	Band No.	1st antibody	Mol. Wt. (KDa)	Relative Front

1: 0.5 ug of FLNA lysate (LC419924)				
2: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC06	175	0.280883
3: 0.5 ug of FLNA lysate (LC419924)				
4: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC07	175	0.304348
5: 0.5 ug of FLNA lysate (LC419924)				
6: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC08	175	0.305038
7: 0.5 ug of FLNA lysate (LC419924)				
8: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC09	175	0.283644
9: 0.5 ug of FLNA lysate (LC419924)				
10: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1		175	0.26501
	2		110	0.450656
	3	SC10	90	0.505176

20210310 Western

Note: The densitometric analysis was conducted using chemiluminacient data.





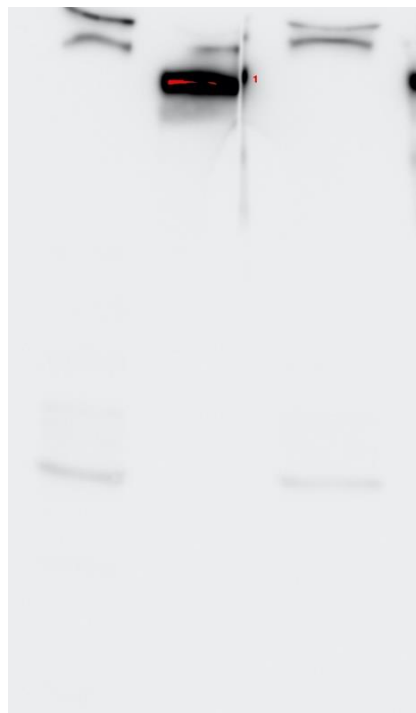
ly: Different Ab SC lines (1:100 dilution of original) in BioRad 7.5% Precasted gels ran at 200V, 4°C
 1st antibody: GE sheep anti-mouse IgG (1:3000 dilution) BioRad Trans-Blot Turbo RTA Midi 0.2uL
 exposure time: 120 S Highest Resolution (1*1) BioRad Trans-Blot Turbo Transfer System
 10% milk in PBST used as blocking buffer. 1st antibody 2nd antibody incubation was at room temperature

Xu Lab 2021-03-10 19h49m21s M3WSHR				
Lane	Band No.	1st antibody	Mol. Wt. (KDa)	Relative Front
1: 0.5 ug of FLNA lysate (LC419924)		SC11		
2: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1		175	0.229814
	2		110	0.429952
	3	SC11	90	0.494824
3: 0.5 ug of FLNA lysate (LC419924)		SC12		
4: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1		175	0.234645
5: 0.5 ug of FLNA lysate (LC419924)		SC13		
6: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1		175	0.253968
7: 0.5 ug of FLNA lysate (LC419924)		SC14		
8: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1		175	0.285714
9: 0.5 ug of FLNA lysate (LC419924)		SC15		
10: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1		175	0.305038

20210310 Western

Note: The densitometric analysis was conducted using chemiluminacent data.

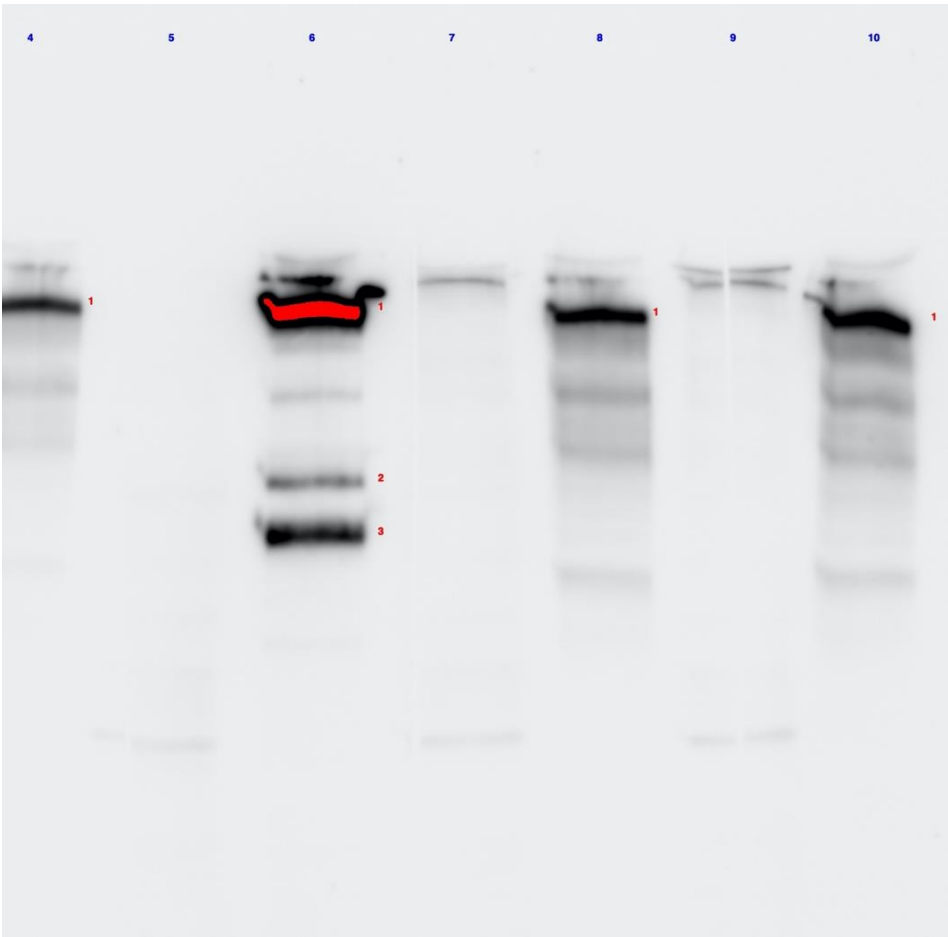




ly: Different Ab SC lines (1:100 dilution of original) in BioRad 7.5% Precasted gels ran at 200V, 4°C, 4h. 1st antibody: GE sheep anti-mouse IgG (1:3000 dilution) BioRad Trans-Blot Turbo RTA Midi 0.2u. Exposure time: 120 s. Highest Resolution (1*1) BioRad Trans-Blot Turbo Transfer System. 10% milk in PBST used as blocking buffer. 1st antibody and 2nd antibody incubation was at 37°C for 1h.

Xu Lab 2021-03-10 20h09m28s M4WSHR				
Lane	Band No.	1st antibody	Mol. Wt. (KDa)	Relative Front
1: 0.5 ug of FLNA lysate (LC419924)				
2: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC16	N/A	0.326432
3: 0.5 ug of FLNA lysate (LC419924)				
4: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC17	N/A	0.322291
5: 0.5 ug of FLNA lysate (LC419924)				
6: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC18	N/A	0.322291
7: 0.5 ug of FLNA lysate (LC419924)				
8: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC19	N/A	0.31815
9: 0.5 ug of FLNA lysate (LC419924)				
10: 100ng 1740 + 100ng A3 + 100ng A4 Peptides	1	SC20	N/A	0.307108

Western blot results: Membrane 1 with sheet

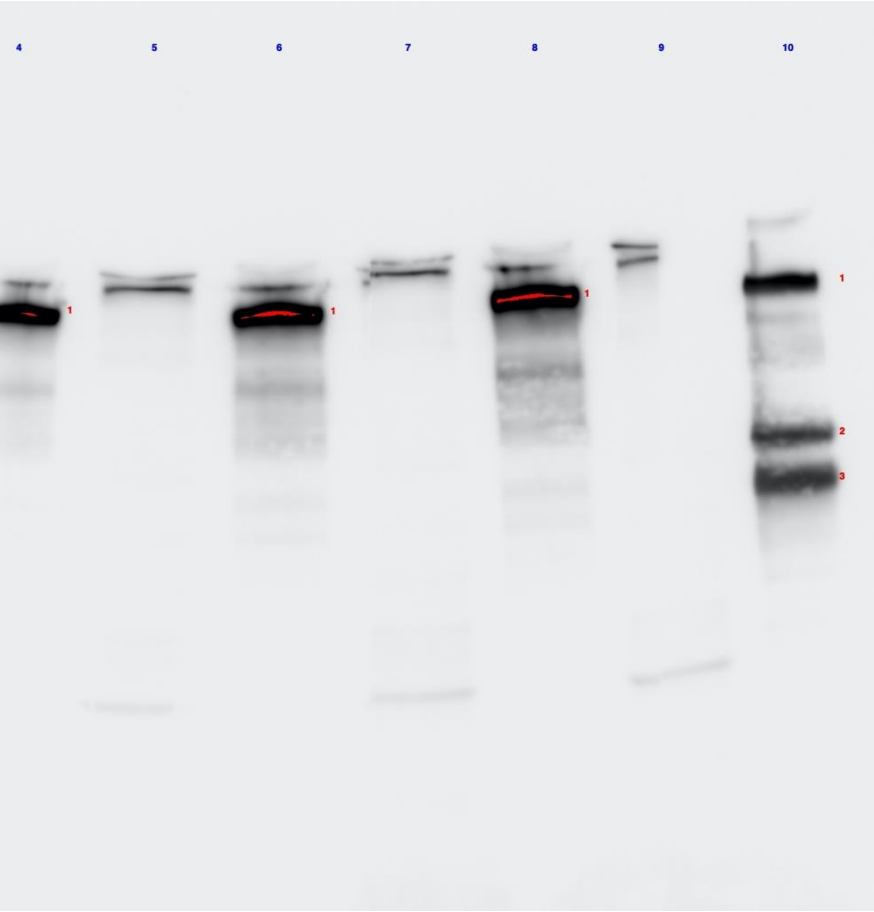


200V for 40 mins.
m Nitrocellulose membrane (Cat # 1704271) was used.
n was used for transfer at 2.5A, 25V for 10 mins
room temp for 1 hr.

Adj. Volume (Int)	Volume (Int)	Abs. Quant.	Rel. Quant.	Band %	Lane %	
58757608	70799638	N/A	N/A	100	74.112913	
71665344	82780845	N/A	N/A	100	68.581453	
504309525	521473991	N/A	N/A	79.811986	70.095154	
27199933	39186709	N/A	N/A	4.304659	3.780582	
100362456	114661674	N/A	N/A	15.883354	13.949611	

108671310	132063701	N/A	N/A	100	68.145759	
120833572	150898646	N/A	N/A	100	68.376774	

Western blot results: Membrane 2 with sheet

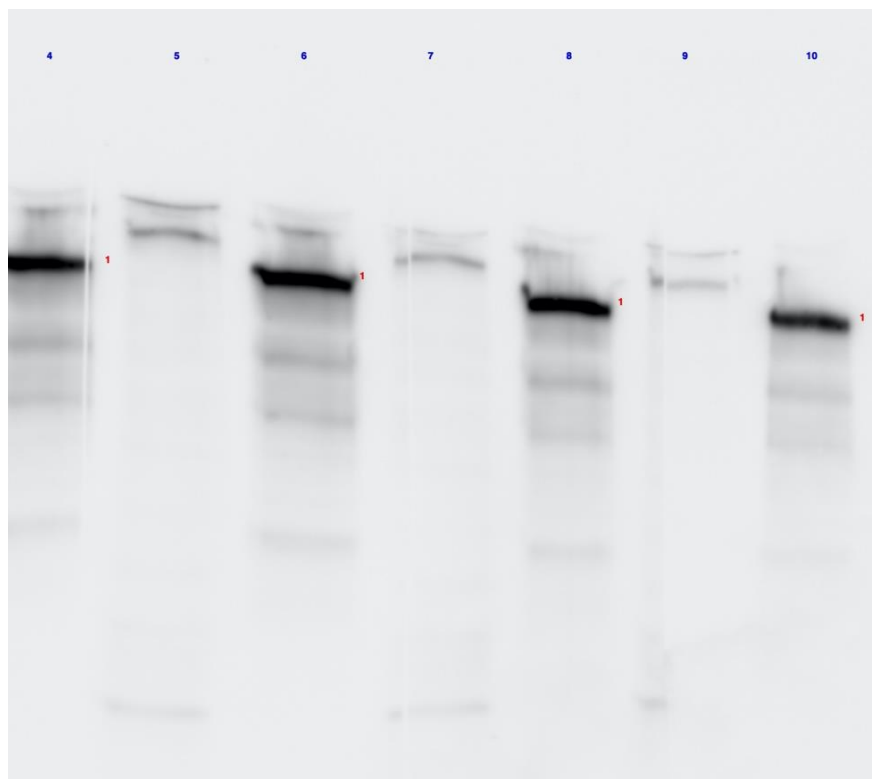


200V for 40 mins.
m Nitrocellulose membrane (Cat # 1704271) was used.
n was used for transfer at 2.5A, 25V for 10 mins
r temp for 1 hr.

Adj. Volume (Int)	Volume (Int)	Abs. Quant.	Rel. Quant.	Band %	Lane %	

208969605	222085284	N/A	N/A	100	81.939802	
210590562	221212264	N/A	N/A	100	85.523686	
281581403	304819375	N/A	N/A	100	81.397033	
303730920	331965512	N/A	N/A	100	78.392336	
87577224	96450013	N/A	N/A	38.676585	33.385374	
54793665	85891562	N/A	N/A	24.198436	20.887931	
84063852	128065536	N/A	N/A	37.12498	32.046039	

n blot results: Membrane 3 with sheet



200V for 40 mins.

m Nitrocellulose membrane (Cat # 1704271) was used.

n was used for transfer at 2.5A, 25V for 10 mins

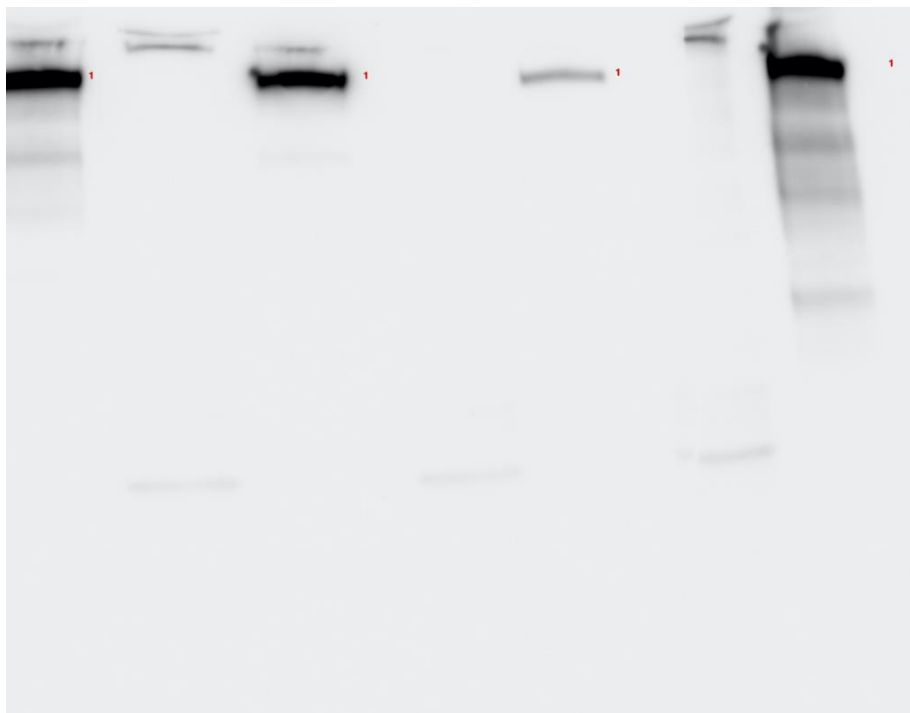
Secondary ant

n temp for 1 hr.

Adj. Volume (Int)	Volume (Int)	Abs. Quant.	Rel. Quant.	Band %	Lane %	
85494024	99222552	N/A	N/A	46.611806	36.801034	
39098070	59973804	N/A	N/A	21.31648	16.829824	
58825008	82892898	N/A	N/A	32.071714	25.321315	
106512678	130344795	N/A	N/A	100	70.417782	
145830168	174709997	N/A	N/A	100	71.589052	
120298568	140096472	N/A	N/A	100	73.227912	
75721828	90441442	N/A	N/A	100	79.692687	

n blot results: Membrane 4 with sheet





200V for 40 mins.

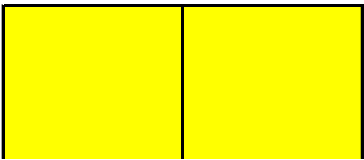
m Nitrocellulose membrane (Cat # 1704271) was used.

n was used for transfer at 2.5A, 25V for 10 mins

room temp for 1 hr.

Adj. Volume (Int)	Volume (Int)	Abs. Quant.	Rel. Quant.	Band %	Lane %	
279656574	288319794	N/A	N/A	100	87.342125	
209401090	221498200	N/A	N/A	100	82.978727	
145285949	154084649	N/A	N/A	100	88.162974	
12707344	18737243	N/A	N/A	100	89.719416	
177768840	209768136	N/A	N/A	100	75.856754	

ibody:GE donkey anti-Rabbit IgG (1:L118)



From: Hoau-yan Wang
Sent time: 03/26/2021 09:50:36 AM
To: Sonkusare, Swapnil K. (sks2n) <sks2n@virginia.edu>
Subject: Re: PTI-125

Dear Dr. Sonkusare,

Thanks for your email. Your research on the impaired blood pressure control by the integrin-FLNA-actin in obesity is very interesting. While I am definitive like the idea of testing PTI-125 in your system, PTI-125 is a proprietary compound of the Cassava Sciences that is currently undergoing clinical trial. Unfortunately, I have no authority to give out PTI-125. Please contact Dr. Lindsay Burns, the VP in neuroscience at the Cassava (lburns@cassavasciences.com).

Good luck with your interesting research.

Hoau

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY SOM

From: Sonkusare, Swapnil K. (sks2n) <sks2n@virginia.edu>
Sent: Thursday, March 25, 2021 3:01 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] PTI-125

Dear Dr. Wang,

Hope this e-mail finds you well.

I am a faculty in Physiology and the Cardiovascular Research Center at the University of Virginia. The research in my laboratory focuses on blood pressure control by vascular ion channels and calcium signaling mechanisms.

Recently, we have gotten interested in how integrin-filamin A-actin interaction controls vascular function and blood pressure, and how this mechanism is impaired in obesity.

I have read your multiple papers, and am well aware of your filamin A inhibitor (PTI-125). I was wondering whether it would be possible for us to obtain a small amount of PTI-125 to try on vascular functional measurements. Using this compound will give us definitive answers on the filamin A-dependent mechanisms that control vascular function, and may lead to new therapeutic uses for the compound. Please let me know if you need additional information on this project.

I look forward to hearing from you.

Best Regards,

Swapnil

Swapnil K. Sonkusare, Ph.D.
Associate Professor of Molecular Physiology and Biological Physics
Resident Faculty, Robert M. Berne Cardiovascular Research Center
University of Virginia - School of Medicine
409 Lane Road, P.O. Box 801394
Room 6051A, Medical Research Building 4 (MR4)
Charlottesville, VA 22908
phone: 434-297-7401
fax: 434-924-2828
<https://www.cvrc.virginia.edu/Sonkusare/index.html>
Pubmed: <https://pubmed.ncbi.nlm.nih.gov/?term=swapnil+sonkusare&sort=date&size=50>

From: Hoau-yan Wang
Sent time: 03/26/2021 10:03:43 AM
To: lburns@cassavasciences.com
Cc: [REDACTED]@gmail.com
Subject: Fw: PTI-125

See below. I have referred him to you. I think there is some relevant changes by PTI-125 to improve endothelial health that reduces amyloid angiopathy in the long run (unlike Abeta mAb) although I am doubtful the obesity-induced impaired integrin-FLNA-actin is correctable by PTI-125. This is because I think the changes he observed are derived from membranous defects brought upon by obesity - uncoupling due to altered phospholipid bilayers (especially when they use ob/ob mice as the model system).

Thanks.

Hoau

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Room 6051A, Medical Research Building 4 (MR4)
Charlottesville, VA 22908
phone: 434-297-7401
fax: 434-924-2828
<https://www.cvrc.virginia.edu/Sonkusare/index.html>
Pubmed: <https://pubmed.ncbi.nlm.nih.gov/?term=swapnil+sonkusare&sort=date&size=50>

From: Lindsay Burns <lburns@cassavasciences.com>
Sent time: 03/26/2021 10:06:18 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: PTI-125

Thanks. I heard from him. You could pass on your thoughts to him if you want.

Lindsay

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Friday, March 26, 2021 9:04 AM
To: Lindsay Burns <lburns@cassavasciences.com>
Cc: [REDACTED]@gmail.com
Subject: Fw: PTI-125

See below. I have referred him to you. I think there is some relevant changes by PTI-125 to improve endothelial health that reduces amyloid angiopathy in the long run (unlike Abeta mAb) although I am doubtful the obesity-induced impaired integrin-FLNA-actin is correctable by PTI-125. This is because I think the changes he observed are derived from membranous defects brought upon by obesity - uncoupling due to altered phospholipid bilayers (especially when they use ob/ob mice as the model system).

Thanks.

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fax: 434-924-2828

<https://www.cvrc.virginia.edu/Sonkusare/index.html>

Pubmed: <https://pubmed.ncbi.nlm.nih.gov/?term=swapnil+sonkusare&sort=date&size=50>

From: Sonkusare, Swapnil K. (sks2n) <sks2n@virginia.edu>
Sent time: 03/26/2021 12:55:21 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: PTI-125

Thank you Dr. Wang. I contacted Dr. Burns, am hoping that we will be able to obtain the compound and try it in our system soon.

Best,

Swapnil

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Friday, March 26, 2021 9:51 AM
To: Sonkusare, Swapnil K. (sks2n) <sks2n@virginia.edu>
Subject: Re: PTI-125

Dear Dr. Sonkusare,

Thanks for your email. Your research on the impaired blood pressure control by the integrin-FLNA-actin in obesity is very interesting. While I am definitive like the idea of testing PTI-125 in your system, PTI-125 is a proprietary compound of the Cassava Sciences that is currently undergoing clinical trial. Unfortunately, I have no authority to give out PTI-125. Please contact Dr. Lindsay Burns, the VP in neuroscience at the Cassava (lburns@cassavasciences.com).

Good luck with your interesting research.

Hoau

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY SOM

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<https://www.cvrc.virginia.edu/Sonkusare/index.html>

Pubmed: <https://pubmed.ncbi.nlm.nih.gov/?term=swapnil+sonkusare&sort=date&size=50>

From: Lindsay Burns <lburns@cassavasciences.com>
Sent time: 05/20/2021 10:48:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: NPC1 and simufilum

My thoughts too, unless the inflammatory component is significant. I'll look into it a bit more.

Lindsay

From: Hoau-Yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, May 19, 2021 10:24 PM
To: Lindsay Burns <lburns@cassavasciences.com>
Subject: Re: NPC1 and simufilum

Hi Lindsay,

Sorry for my late reply. Unfortunately, I don't see the rationale of simufilam reversing NPC1 misfolding since NPC1 protein and FLNA have no structural and sequence homology. NPC1 also has tauopathy and yes TREM2 that may indicate the inflammatory component. There is no compelling reason to look at cholesterol biomarker in AD despite dyslipidemia (more accurately abnormal lipid profiles) was shown in AD patients. Honestly, I don't know enough mechanism wise ...

Best,

Hoau

On Wed, May 19, 2021 at 5:11 PM Lindsay Burns <lburns@cassavasciences.com> wrote:

I get heart-breaking emails like this somewhat regularly. I think there is no relation/rationale, except maybe inflammation? And a pediatric population too.

Lindsay

Begin forwarded message:

From: Christopher Andrews [REDACTED] <[REDACTED]@gmail.com>
Date: May 19, 2021 at 4:05:37 PM CDT
To: Lindsay Burns <lburns@cassavasciences.com>
Subject: NPC1 and simufilum

Dr Burns,

My daughter [REDACTED] ([REDACTED] years old) and [REDACTED] ([REDACTED] years old) were diagnosed with Niemann Pick disease, type C-1, in March 2016. There have been some breakthroughs in the last few years. Both of my daughters began treatment with VTS-270 in May 2016. We are currently receiving our treatments at Dell Children's in Austin, Texas. We were featured in People magazine in March 2017.

<http://people.com/human-interest/familys-fight-to-save-daughters-who-both-have-childhood-alzheimers/>

<https://www.youtube.com/watch?v=RaGfMddzXHg&t=8s>

Below are links about our non-profit: The Andrews Firefly Fund.

<http://fireflyfund/>

<https://www.youtube.com/watch?v=B-dASfOWRzs>

<https://www.youtube.com/watch?v=h71fC-E-X4M>

I have a number question about simufilam:

80% of patients with NPC1 product enough NPC1 protein. However, the protein is misfolded and only partial functions. Is simufilum selective only to FLNA? Does it have similar effect on other misfolded proteins? If simufilam is not selective to FLNA, isn't possible that it could help NPC1 proteins fold correctly? Did the clinical trials look at any biomarkers related to cholesterol trafficking? Maybe CYP46a1? Might there be data related to cholesterol that Casava may not have seen as relevant to the

AD trial?

NPC1 and AD share a number of biomarkers. Of note, TREM2. I recent publication suggest that microglia activation may occur in NPC1 long before cholesterol accumulation.

[https://www.nature.com/articles/s41467-021-21428-5?
elqTrackId=5528b0a962844e2b88e9a79f76976761](https://www.nature.com/articles/s41467-021-21428-5?elqTrackId=5528b0a962844e2b88e9a79f76976761)

I would be very interested in discussing the possibility of looking at simufulum as treatment for NPC1. But first I need to explore if there is any logic in doing so. As such, I would appreciate the opportunity to engage the Cassava team in an exchange of ideas. I am literally right up the street. I work at Plaza on the Lake, under the 360 bridge.

Best,

Christopher Andrews

From: Hoau-yan Wang
Sent time: 05/20/2021 12:47:55 PM
To: Lindsay Burns <lburns@cassavasciences.com>
Cc: [REDACTED]@gmail.com
Subject: Re: NPC1 and simufulum

NPC1 is a transporter so that my bet is there is (are) critical post-translational modification(s) or amino acid substitution in the extracellular domains that cause it to flop. I have not looked at the sequence carefully to see whether there is obvious sites for nitration, phosphorylation or losing glycosylation (more important for transporter). I don't think the transcription/translation is the primary problem since most of NPC1 subjects produces 80% of NPC1 proteins.

Hoau

From: Lindsay Burns <lburns@cassavasciences.com>
Sent: Thursday, May 20, 2021 10:48 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: NPC1 and simufulum

My thoughts too, unless the inflammatory component is significant. I'll look into it a bit more.

Lindsay

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From: Christopher Andrews [REDACTED]@gmail.com>
Date: May 19, 2021 at 4:05:37 PM CDT
To: Lindsay Burns <lburns@cassavasciences.com>
Subject: NPC1 and simufulum

Dr Burns,

My daughter [REDACTED] ([REDACTED] years old) and [REDACTED] ([REDACTED] years old) were diagnosed with Niemann Pick disease, type C-1, in March 2016. There have been some breakthroughs in the last few years. Both of my daughters began treatment with VTS-270 in May 2016. We are currently receiving our treatments at Dell Children's in Austin, Texas. We were featured in People magazine in March 2017.

<http://people.com/human-interest/familys-fight-to-save-daughters-who-both-have-childhood-alzheimers/>

<https://www.youtube.com/watch?v=RaGfMddzXHg&t=8s>

Below are links about our non-profit: The Andrews Firefly Fund.

[http://firefly fund/](http://fireflyfund/)

<https://www.youtube.com/watch?v=B-dASfOWRzs>

<https://www.youtube.com/watch?v=h71fC-E-X4M>

I have a number question about simuflam:

80% of patients with NPC1 product enough NPC1 protein. However, the protein is misfolded and only partial functions. Is simuflam selective only to FLNA? Does it have similar effect on other misfolded proteins? If simuflam is not selective to FLNA, isn't possible that it could help NPC1 proteins fold correctly? Did the clinical trials look at any biomarkers related to cholesterol trafficking? Maybe CYP46a1? Might there be data related to cholesterol that Casava may not have seen as relevant to the AD trial?

NPC1 and AD share a number of biomarkers. Of note, TREM2. I recent publication suggest that microglia activation may occur in NPC1 long before cholesterol accumulation.

[https://www.nature.com/articles/s41467-021-21428-5?](https://www.nature.com/articles/s41467-021-21428-5?elqTrackId=5528b0a962844e2b88e9a79f76976761)

[elqTrackId=5528b0a962844e2b88e9a79f76976761](https://www.nature.com/articles/s41467-021-21428-5?elqTrackId=5528b0a962844e2b88e9a79f76976761)

I would be very interested in discussing the possibility of looking at simuflam as treatment for NPC1. But first I need to explore if there is any logic in doing so. As such, I would appreciate the opportunity to engage the Cassava team in an exchange of ideas. I am literally right up the street. I work at Plaza on the Lake, under the 360 bridge.

Best,

Christopher Andrews

From: Lindsay Burns <lburns@cassavasciences.com>
Sent time: 06/15/2021 11:44:29 PM
To: Hoau-yan Wang
Subject: Re: [EXTERNAL] Rethnakaran Pulikkoonattu sent you a message on ResearchGate
Attachments: TRCI-Phase 2b manuscript.pdf

They just asked for figures in pdf format last week so they could send it for review. Took 2 weeks to get that far. No idea. The only portal just says submission being processed. Here's the submission if you want it confidentially.

Lindsay

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, June 15, 2021 9:01 PM
To: Lindsay Burns <lburns@cassavasciences.com>
Subject: Fw: [EXTERNAL] Rethnakaran Pulikkoonattu sent you a message on ResearchGate

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Hi Lindsay,

Do you know how to ETA of our phase 2b publication and how to access it?

Thanks.

Best,

Hoau

From: Rethnakaran Pulikkoonattu via ResearchGate <no-reply@researchgatemail.net>
Sent: Monday, June 14, 2021 11:19 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Rethnakaran Pulikkoonattu sent you a message on ResearchGate

ResearchGate

Rethnakaran sent you a message



Rethnakaran Pulikkoonattu

Broadcom Corporation

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Alzheimer's & Dementia: Translational Research & Clinical Interventions

Effects of simufilam on cerebrospinal fluid biomarkers in Alzheimer's disease: A randomized clinical trial

--Manuscript Draft--

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Abstract:	<p>BACKGROUND: Simufilam is a first-in-class drug targeting altered filamin A, a proteopathy in Alzheimer's disease, and is being assessed for disease-modifying potential.</p> <p>METHODS: In a randomized, placebo-controlled trial, 64 mild-to-moderate Alzheimer's disease patients were randomized to simufilam 50 or 100 mg b.i.d. or placebo for 28 days. Co-primary endpoints were changes in CSF Aβ 42, total tau, phospho-tau (P-tau181), neurogranin, neurofilament light chain, and YKL-40. Secondary endpoints included CSF biomarkers of neuroinflammation and blood brain barrier integrity, and cognitive tests.</p> <p>RESULTS: Adjusting for multiplicity ($p < 0.008$ for significance), both doses significantly reduced CSF total tau, P-tau181, neurogranin, neurofilament light chain and YKL-40. Simufilam 50 mg significantly increased CSF Aβ 42. Simufilam showed effect sizes versus placebo (0.23-0.46) in episodic memory and spatial working memory.</p> <p>CONCLUSIONS: Simufilam was well-tolerated and induced significant changes in eleven CSF biomarkers in Alzheimer's disease patients, implying disease modification. Simufilam will be further evaluated in large, definitive clinical trials.</p>



May 25, 2021

Dear TCRI Editor,

We are submitting this manuscript of results of a Phase 2b clinical trial of simufilam, a new small molecule therapeutic candidate in Alzheimer's disease. These results were presented at the Clinical Trials for Alzheimer's disease virtual conference November 7. The trial was a randomized placebo-controlled study in 64 mild-to-moderate AD patients with diagnosis confirmed by the total tau/Abeta42 ratio in CSF. This CSF sample also served as our baseline for biomarkers that were measured again after just 28 days of treatment. Biomarkers were measured by an outside lab, blind to treatment and timepoint. We measured the core AD biomarkers as well as biomarkers of neurodegeneration, neuroinflammation and blood-brain barrier integrity. We saw significant improvements versus placebo in all eleven biomarkers for both 50 and 100 mg doses. Six of the eleven were pre-specified as primary endpoints on clinicaltrials.gov and were adjusted for multiplicity accordingly. We demonstrated target engagement using patient lymphocytes. Most encouragingly, episodic memory and spatial working memory showed promising effect sizes versus placebo for both dose groups. Thank you for your consideration of this manuscript.

Best regards,

A handwritten signature in black ink that reads "Lindsay H. Burns". The signature is written in a cursive, flowing style.

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SVP, Neuroscience
Cassava Sciences, Inc.
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Austin, TX 78731

Effects of simufilam on cerebrospinal fluid biomarkers in Alzheimer's disease: A randomized clinical trial

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Research in Context (150 words)

1. **Systematic Review:** We searched clinicaltrials.gov and PubMed to determine if randomized controlled trials (RCTs) of other therapeutic candidates for Alzheimer's disease have reported significant treatment effects on multiple cerebrospinal fluid (CSF) biomarkers. A recent review is cited.
2. **Interpretation:** The significant improvements in eleven CSF biomarkers of Alzheimer's disease pathology, neurodegeneration, neuroinflammation and blood-brain barrier integrity in an RCT of mild-to-moderate Alzheimer's disease patients following one-month oral treatment suggests simufilam may slow disease progression.
3. **Future Directions:** Simufilam will be further evaluated in large, definitive clinical trials of Alzheimer's disease dementia.

ABSTRACT (150 words)

BACKGROUND: Simufilam is a first-in-class drug targeting altered filamin A, a proteopathy in Alzheimer's disease, and is being assessed for disease-modifying potential.

METHODS: In a randomized, placebo-controlled trial, 64 mild-to-moderate Alzheimer's disease patients were randomized to simufilam 50 or 100 mg b.i.d. or placebo for 28 days. Co-primary endpoints were changes in CSF A β_{42} , total tau, phospho-tau (P-tau181), neurogranin, neurofilament light chain, and YKL-40. Secondary endpoints included CSF biomarkers of neuroinflammation and blood brain barrier integrity, and cognitive tests.

RESULTS: Adjusting for multiplicity ($p < 0.008$ for significance), both doses significantly reduced CSF total tau, P-tau181, neurogranin, neurofilament light chain and YKL-40. Simufilam 50 mg significantly increased CSF A β_{42} . Simufilam showed effect sizes versus placebo (0.23-0.46) in episodic memory and spatial working memory.

CONCLUSIONS: Simufilam was well-tolerated and induced significant changes in eleven CSF biomarkers in Alzheimer's disease patients, implying disease modification. Simufilam will be further evaluated in large, definitive clinical trials.

Keywords: filamin A, tau hyperphosphorylation, neuroinflammation, blood-brain barrier

Abbreviations: amyloid-beta1-42 (A β_{42}), phospho-tau181 (P-tau181), $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR), toll-like receptor 4 (TLR4), cluster-of-differentiation14 (CD14), National Institute on Aging (NIA), Alzheimer's Association (AA), Mini-Mental State Exam (MMSE), soluble triggering receptor expressed on myeloid cells 2 (sTREM2), high mobility group box 1 (HMGB1), Cambridge Neuropsychological Test Automated Battery (CANTAB), analysis of covariance (ANCOVA), analysis of variance (ANOVA)

There are no approved treatments to slow the progression of Alzheimer's disease, expected to affect 13.8 million in the U.S. by 2050.¹ Biomarkers may facilitate drug development in Alzheimer's disease by quantifying disease stage, demonstrating target engagement, and supporting disease modification.²

Core CSF biomarkers of Alzheimer's disease are amyloid-beta1-42 ($A\beta_{42}$), total tau and phospho-tau181 (P-tau181).^{3,4} $A\beta_{42}$ decreases while tau and phosphorylated tau, including P-tau181, increase as disease progresses and cognition declines. Neurogranin and neurofilament light chain, indicating damage to dendrites and axons respectively, are used to track disease progression.⁵⁻⁷ Interestingly, neurogranin appears specific to Alzheimer's disease.⁷ The current clinical trial measured CSF biomarkers in Alzheimer's disease dementia patients to evaluate drug candidate simufilam.

Simufilam represents a novel approach to combat amyloid toxicity and resulting neurodegeneration in Alzheimer's disease. Soluble $A\beta_{42}$ initiates a predominant pathogenic pathway by binding the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7nAChR$), the only known sub-nanomolar-affinity binding site of soluble $A\beta_{42}$.⁸⁻¹⁰ This femtomolar interaction poses enormous competition for any agent aiming to reduce soluble $A\beta_{42}$ interactions. $A\beta_{42}$ binds and signals through this receptor to activate kinases that hyperphosphorylate the protein tau,¹⁰⁻¹³ impairing tau's ability to stabilize microtubules. This loss of functional tau is one major driver of the neuronal degeneration and cognitive impairment in Alzheimer's disease.¹⁴

Without directly competing with the femtomolar binding of $A\beta_{42}$ to $\alpha 7nAChR$, simufilam disrupts this ultra-high-affinity interaction by binding a critical accomplice to $A\beta_{42}$: an altered conformation of filamin A. An intracellular scaffolding protein, filamin A is highly expressed in brain and interacts with over 90 proteins to coordinate signaling processes.¹⁵ $A\beta_{42}$ initiates toxic signaling by binding $\alpha 7nAChR$ to recruit filamin A.^{16,17} Without directly contacting filamin A, and likely working through $\alpha 7nAChR$ and other receptors that link to or recruit filamin A, $A\beta_{42}$ induces the altered conformation of the filamin A protein.¹⁷ Simufilam binds altered filamin A, restores its normal shape and disrupts the aberrant filamin A

– $\alpha 7$ nAChR linkage, $A\beta_{42}$'s femtomolar binding to $\alpha 7$ nAChR and the ensuing toxic signaling that hyperphosphorylates tau.^{17,18}

$A\beta_{42}$ also binds the toll-like receptor 4 (TLR4) co-receptor cluster-of-differentiation14 (CD14)¹⁹ to recruit and alter filamin A.¹⁷ The filamin A – TLR4 linkage enables persistent TLR4 activation by $A\beta_{42}$, causing inflammatory cytokine release and neuroinflammation. Simufilam's reversal of the filamin A proteopathy also blocks this $A\beta_{42}$ -induced neuroinflammation.^{17,18}

In a previous open-label, 28-day trial in patients with mild-to-moderate Alzheimer's disease dementia (NCT03748706), simufilam significantly reduced CSF total tau, P-tau181 and biomarkers of neurodegeneration and neuroinflammation in all patients, with no safety issues.²⁰ Biomarker reductions implied reduced disease pathophysiology and neurodegeneration, consistent with simufilam's mechanism of action and preclinical data. Data from mouse models and postmortem human Alzheimer's disease and age-matched control brain tissue also suggest cognitive enhancement potential: improved function of $\alpha 7$ nAChR, N-methyl D-aspartate (NMDA) and insulin receptors and improvement in an index of synaptic plasticity.¹⁷ Based on these encouraging clinical and preclinical data, we evaluated simufilam in a randomized, double-blind, placebo-controlled Phase 2 trial. We hypothesized simufilam would impact CSF biomarkers and enhance cognition.

METHODS

Patient Population

Patients were 50-85 years old, diagnosed with probable Alzheimer's disease dementia according to National Institute on Aging (NIA)/Alzheimer's Association (AA) criteria and a Mini-Mental State Exam (MMSE) score ≥ 16 and ≤ 26 . Diagnosis was confirmed by CSF total tau/ $A\beta_{42}$ ≥ 0.28 , a ratio selected to exclude dementia due to other causes (0.28 is intermediate between early and late mild cognitive impairment in amyloid-confirmed patients from the Alzheimer's Disease Neuroimaging Initiative²¹). Patients could be receiving acetylcholinesterase inhibitors, memantine and other medications if stable.

Chronic opioids, tricyclic antidepressants, monoamine oxidase inhibitors, nicotine therapy (or smokers) were exclusions, as were uncontrolled medical illnesses, other neurodegenerative diseases, or clinically significant laboratory results.

Trial Design

This double-blind, placebo-controlled, trial randomized 64 patients 1:1:1 to placebo or simufilam 50 or 100 mg oral tablets b.i.d. for 28 days. Patients, caregivers, clinic staff, the study sponsor and the laboratory analyzing biomarkers were blind to treatment. A randomization algorithm was generated by an outside vendor using Interactive Response Technology. Doses were selected by body surface area conversion of effective daily doses in mouse efficacy models and prior clinical experience. Sample sizes of 20 per arm were selected based on highly significant changes from baseline in CSF biomarkers by paired t-test in a prior open-label trial in mild-to-moderate Alzheimer's disease dementia patients.²²

After initial screening, a second screening visit included a CSF draw and a practice cognitive test. Cognitive tests were conducted Days 1 and 28. Blood samples were collected Days 1, 7, 14 and 28, with the Day 28 blood sample following the second CSF draw for CSF/plasma ratios of simufilam. Electrocardiograms and physical examinations were conducted Days 1 and 28.

Oversight and Settings

This trial was conducted between September 2019 and March 2020 at nine U.S. sites. All patients signed an informed consent form approved by a central institutional review board. An independent Data and Safety Monitoring Board approved the protocol and assessed safety mid-study. CSF samples were analyzed at City University School of Medicine. Simufilam levels in plasma and CSF were analyzed with a qualified assay at Worldwide Clinical Trials Bioanalytical Sciences. Data were analyzed by a data management and statistics contractor. Data was 100% monitored by independent clinical research associates. No protocol changes were made.

Assessments

Eleven CSF biomarkers were measured in screening and Day 28 samples. CSF samples (5 mL) were collected into lo-bind Sarstedt tubes and stored at -70°C until analysis. Six CSF biomarkers were designated primary: biomarkers of Alzheimer's disease pathology ($A\beta_{42}$, total tau and P-tau181), neurodegeneration (neurofilament light chain and neurogranin) and neuroinflammation (YKL-40). Also assessed were interleukin-6, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), and high mobility group box 1 (HMGB1). These nine biomarkers were measured using commercial enzyme-linked immunosorbent assay plates (Lifespan Biosciences for neurofilament light chain, neurogranin and YKL-40; Biomatik for HMGB1; Invitrogen Corporation for all others) and an automated plate reader, with samples assayed in triplicate. Each run was validated by the R^2 value of the fit of standards to a standard curve (range 0.84-0.99). CSF albumin and immunoglobulin G assessed blood-brain barrier integrity and were measured by immunoblot with densitometric quantitation.

Target engagement was evaluated by measuring filamin A linkages to $\alpha 7nAChR$ and TLR4 in patient lymphocytes by co-immunoprecipitation.¹⁷ Immunoblots of anti-filamin A immunoprecipitates of solubilized lymphocyte membranes were probed with specific antibodies to $\alpha 7nAChR$ or TLR4 and assessed by densitometric quantitation.

Cognition was assessed on Day 1 and Day 28 by the Paired Associates Learning (an episodic memory test) and Spatial Working Memory tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Both tests increase progressively in difficulty, with errors imputed for levels not reached. Reductions in the total error scores indicate improvement. The CANTAB Reaction Time test assessed psychomotor speed in milliseconds. No other cognitive tests were conducted.

Safety was assessed by adverse event monitoring, clinical laboratory tests, electrocardiography, physical examinations and the Columbia-Suicide Severity Rating Scale.

Outcomes

The six co-primary outcome measures were changes in CSF A β ₄₂, total tau, P-tau181, neurogranin, neurofilament light chain, and YKL-40 levels from screening to Day 28. These six biomarkers were prospectively listed in the trial registration. A β ₄₂, total tau and P-tau181 are considered core biomarkers of Alzheimer's disease pathology. Neurogranin and neurofilament light chain are intracellular proteins in dendrites and axons, respectively, that indicate neurodegeneration when found in CSF. YKL-40 is a glycoprotein involved in tissue remodeling after inflammation. Secondary biomarker outcomes included changes in CSF interleukin-6, sTREM2, HMGB1, albumin and immunoglobulin G. Interleukin-6 is an inflammatory cytokine. A marker of microglial-induced inflammation, sTREM2 is the ectodomain of the transmembrane receptor TREM2 that is cleaved and shed by microglia when activated during inflammation.²³ HMGB1 is a damage-associated molecular pattern protein released by necrotic cells and actively secreted by immune cells to further neuroinflammation and neurite damage.²⁴ Albumin and immunoglobulin G are blood proteins that indicate blood-brain barrier compromise when found in CSF.²⁵ Secondary cognitive outcome measures were drug-placebo differences in change from Day 1 to Day 28 in total errors on Paired Associates Learning and Spatial Working Memory tests. The Reaction Time test exploratory outcome was median response time in milliseconds.

The target engagement assay measured changes in filamin A linkages to α 7nAChR and TLR4 in patient lymphocytes from Day 1 to Day 28.

Statistical Analysis

The pre-specified analysis for biomarkers was drug-placebo differences in change from baseline, analyzed by the analysis of covariance (ANCOVA) with a two-sided 95% confidence interval and baseline CSF measurement as the covariate. Multiplicity of the six co-primary endpoints was addressed by the significance requirement: $p < 0.008$ (i.e., $p < 0.05/6$).

The Full Analysis Set included all subjects with two CSF samples. Although plasma samples were collected at all visits to confirm compliance, the primary analyses were conducted on all patients. The secondary analyses excluded three subjects with no detectable simufilam in plasma at any visit. Percent change from baseline of compliers in active treatment compared to placebo-treated participants was analyzed by ANCOVA.

Lymphocyte biomarkers were analyzed by the analysis of variance (ANOVA): comparing to each patient's own baseline was considered more appropriate than adjusting for baseline value by ANCOVA, given the wider range of baseline values. The FLNA – $\alpha 7$ nAChR linkage for the 100 mg dose arm versus placebo was the only comparison significantly different by ANOVA but not by ANCOVA.

Tests of cognition were not powered for statistical significance and were therefore evaluated by effect size, a standardized measure of relative size of treatment effect. Effect sizes of 20-25% are considered noteworthy, and a 25% effect size is typically considered clinically meaningful if significance is achieved in later, appropriately powered trials. For cognitive tests, effect sizes for each simufilam dose versus placebo were calculated by Hedge's g , appropriate for groups of 20, and these were identical or nearly identical to those calculated by Cohen's d . For the Paired Associates Learning test, the most and least impaired subjects were excluded by baseline score (≤ 11 or ≥ 54 of 70 total possible errors) prior to calculation of effect size. These cutoffs were employed to remove subjects with very few errors (ceiling effects), as well as subjects who performed so poorly that they may not have understood the task. Analyses of both cognitive tests excluded subjects with no detectable plasma simufilam or who were >25% noncompliant by pill counts. Reaction time was measured in milliseconds between stimulus onset and response.

RESULTS

Trial Population

Of 115 patients screened, 64 patients enrolled. Twenty-two were randomized to placebo and 21 each to simufilam 50 mg and 100 mg. One participant discontinued for non-medical reasons (Figure 1). One completer was excluded from the primary analyses due to a missing Day 28 sample. One patient in the 50 mg arm and two in the 100 mg arm were excluded from the secondary analyses due to no detectable plasma levels of simufilam at return visits. Excluding these non-compliers, CSF/plasma simufilam levels ($\sim 1\text{-}2$ h post-dose on Day 28) in simufilam arms were 0.29 ± 0.21 . Baseline demographics, MMSE, cognitive assessment scores, concomitant cholinesterase inhibitor or memantine use, and baseline biomarker levels were well balanced between groups despite small between group ANOVA effects for P-tau181 and IL-6 (Table 1).

CSF Biomarker Change from Baseline

The pre-specified primary analysis was change from baseline to Day 28 on six CSF biomarkers ($A\beta_{42}$, total tau, P-tau181, neurogranin, neurofilament light chain and YKL-40) in the drug arms versus the placebo arm. Significance levels were adjusted for multiplicity ($p < 0.05/6$ or $p < 0.008$). Both dose arms showed significant changes from baseline on five of the six primary biomarkers, with the increase in $A\beta_{42}$ in the 100 mg dose arm not significant, likely due to the range of baseline values (Table 2). The secondary analysis of change from baseline with three non-compliers excluded produced similar results to the primary analysis. Individual patients' Screening and Day 28 values (pg/mL) are shown by spaghetti plots for each treatment arm (Figure 2). Note there is one placebo outlier with high $A\beta_{42}$ who nevertheless met the total tau/ $A\beta_{42}$ screening criterion.

CSF Biomarker Percent Change from Baseline

The secondary analysis of percent change from baseline showed significant differences for both dose arms versus placebo on all eleven CSF biomarkers, adjusted for multiplicity for the six primary biomarkers (Figure 3A). P values for change and percent change from baseline were similar, with A β ₄₂ in the 100 mg dose arm the sole comparison that was significant by percent change but not by change from baseline, due to the range in baseline values.

Biomarkers of AD Pathology and Neurodegeneration

Low in Alzheimer's disease, CSF A β ₄₂ significantly increased 17% and 14% in the 50 and 100 mg arms, respectively (p=0.0004 and p=0.004). CSF total tau decreased 16% and 18% (p=0.0002 and p=0.00001) and CSF P-tau181 decreased 8% and 11% (p=0.002 and p=0.003) in 50 and 100 mg dose arms compared to placebo, respectively. CSF neurofilament light chain, reflecting axonal damage, decreased 28% and 34% in respective dose arms (p=0.002 and p=0.0003). Neurogranin, indicating post-synaptic damage, significantly decreased 36% and 43% in respective dose arms (p=0.0004 and p=0.0001).

Biomarkers of Neuroinflammation

Simufilam treatment significantly decreased four CSF biomarkers of neuroinflammation compared to placebo. YKL-40 decreased 10% and 11% in the 50 and 100 mg arms, respectively (p=0.0003 and p=0.0002). Inflammatory cytokine interleukin-6 decreased 10% and 11% in the 50 and 100 mg arms (p=0.017 and p=0.007). Indicating reduced microglial activation, sTREM2 decreased 43% and 46% in the 50 and 100 mg arms (p=0.0009 and p=0.0003). Finally, the damage-associated molecular pattern protein HMGB1 decreased 33% and 32% in the 50 and 100 mg arms (p=0.0002 and p=0.0001).

Biomarkers of Blood-Brain Barrier Integrity

Simufilam improved blood-brain barrier integrity, evidenced by lower levels of albumin and immunoglobulin G in CSF. Simufilam 50 and 100 mg significantly decreased CSF albumin by 15% and 29%,

respectively ($p=0.04$ and $p=0.0001$). CSF immunoglobulin G decreased 30% in both drug arms (both $p=0.02$).

Validation of Biomarker Analyses

The statistical validation of biomarker data is supported by the placebo dataset: modest changes ($\sim 2\%$, on average) and robust correlations (mean $R^2=0.96$) between all pair combinations among total tau, P-tau181, neurogranin, neurofilament light chain, YKL-40 and IL-6 in *change from baseline*. This strong correlation shows that these biomarkers are not moving independently over the weeks between screening and Day 28; the small degree of decline in individual patients, or lack thereof, was consistent between biomarkers. Because $A\beta_{42}$ decreases in CSF in Alzheimer's disease as other markers increase, $A\beta_{42}$ movement negatively correlated with changes in those six biomarkers (mean $R^2=-0.82$ in placebo). Biomarker changes from baseline also correlated in simufilam arms (mean $R^2=0.77$, excluding $A\beta_{42}$), indicating that the magnitude of change in individual patients was generally consistent across biomarkers.

Target Engagement

Both $\alpha 7nAChR$ and TLR4 receptors and filamin A are present in lymphocytes, allowing assessment of target engagement in patients' lymphocytes. Filamin A linkages to $\alpha 7nAChR$ and TLR4 in lymphocytes were significantly reduced 31-34% from baseline in both drug arms ($p\leq 0.01$) (Figure 3B).

Cognition

On the Paired Associate Learning test assessing episodic memory, patients in the 50 mg arm made on average 5.7 fewer errors on Day 28, patients in the 100 mg arm made 4.5 fewer errors, and placebo patients made 1.5 fewer errors (Figure 4). These differences represent 0.37 and 0.23 effect sizes for 50 and 100 mg arms, respectively, versus placebo. The most and least impaired subjects were removed by baseline score (\geq

54 and ≤ 11 of 70 possible total errors) to eliminate ceiling effects (those with very few errors) and subjects who performed so poorly that they may not have understood the task. Standard deviations for change from baseline in PAL total errors were 8.5, 13.6, 17.7 for placebo, 50 and 100 mg, respectively.

In Spatial Working Memory, patients in 50 and 100 mg arms made 2.3 and 3.3 fewer errors, respectively, compared to 0.4 in placebo, representing 0.25 and 0.46 effect sizes. Standard deviations for change from baseline in Spatial Working Memory total errors were 7.5, 7.5, 4.7 for placebo, 50 and 100 mg, respectively.

Improvements in episodic memory, correlated most strongly with decreases in P-tau181 ($R^2=0.48$).

Interleukin-6, total tau, albumin, neurofilament light chain and YKL-40 also correlated (R^2 values 0.41, 0.37, 0.37, 0.36 and 0.30, respectively). These correlations included all arms.

In reaction time, placebo, 50 and 100 mg arms showed mean (SD) changes from baseline in median reaction time of -11 (57), -19 (38) and 11 (66) milliseconds, respectively.

Safety

Simufilam was safe and well-tolerated. There were no serious adverse events. Adverse events were mostly mild; none caused discontinuation; none were noted likely to be drug related. Total adverse events were 20, 9 and 15 in placebo, 50 and 100 mg arms, respectively. Adverse events that occurred in 3 or more patients were headache (3, 1 and 2), fatigue (2, 1 and 0), nausea (2, 0 and 1), and upper respiratory infection (1, 2 and 2) for placebo, 50 and 100 mg, respectively.

DISCUSSION

In a randomized clinical trial of 64 patients with Alzheimer's disease dementia, simufilam 50 or 100 mg significantly improved multiple biomarkers of Alzheimer's disease, neurodegeneration, neuroinflammation and blood-brain barrier integrity, with no safety issues. Collectively, results of this

randomized controlled trial are consistent with the drug's mechanism of action and replicate a prior, open-label study.²⁰

Increases in A β_{42} and reductions in total tau and p-Tau181 imply reduced Alzheimer's disease pathophysiology. Reduced levels of neurofilament light chain and neurogranin suggest a slower rate of neurodegeneration. The 36% and 43% reductions in neurogranin, considered specific to Alzheimer's disease,²⁴ additionally suggest reduced disease pathology. Reductions in neuroinflammatory markers YKL-40, interleukin-6, sTREM2 and HMGB1 indicate suppressed neuroinflammation. Because HMGB1 also damages neurites and furthers neuroinflammation,²⁴ the more than 30% reductions in HMGB1 imply reduced pathogenic drive by this damage associated molecular pattern. Finally, lower CSF albumin and immunoglobulin G suggest improved blood-brain barrier integrity, possibly related to simufilam's suppression of neuroinflammation, as blood-brain barrier breakdown correlates with neuroinflammation and cognitive decline.^{25,26} Restoring $\alpha 7$ nAChR function by displacing A β_{42} may also improve blood-brain barrier integrity.^{27,28}

Robust statistical correlations between biomarkers in changes from baseline within the placebo arm illustrate the interdependency of biomarkers in Alzheimer's disease and validate the study's biomarker assessments. Strong correlations between biomarkers in changes from baseline within simufilam arms suggest that the filamin A proteopathy is a critical, upstream pathogenic event in Alzheimer's disease.

Reductions in filamin A linkages to $\alpha 7$ nAChR and TLR4 in patient lymphocytes, demonstrating target engagement, likely mirror the target engagement of simufilam in brain. Reductions in these filamin A linkages were previously demonstrated in both brain and lymphocytes of simufilam-treated Alzheimer's disease transgenic mice (lymphocytes unpublished), and in postmortem human Alzheimer's disease brain tissue incubated with simufilam.¹⁷

The small dose-response in this study suggests near saturation of the target protein, anticipated because simufilam, a small molecule, binds the altered conformation of filamin A with ultra-high (580 femtomolar) affinity.¹⁷ Illustrating this potency, simufilam reduced A β ₄₂-induced tau hyperphosphorylation in human postmortem brain tissue at concentrations as low as 1 pM.¹⁷ Clean safety, a mild dose-response, high (98%) response rate and clear evidence of target engagement collectively suggest 50-100 mg b.i.d. is an optimal dose range.

The effect sizes of both doses on both tests of memory suggest a drug effect, and the correlation of episodic memory improvement with decrease in CSF P-tau181 is supportive. Because disease progression is not expected to be detectable over 28 days in mild-to-moderate Alzheimer's disease patients, the biomarker changes and potential cognitive enhancement may be best interpreted as a suppression of disease processes and improved neuronal function. If maintained over time, such changes could be expected to slow disease progression and improve brain health.

Simufilam's potential to modify the disease and enhance cognition is supported by preclinical data. In a triple transgenic mouse model of Alzheimer's disease, simufilam improved cognitive behavior and reduced amyloid deposits, tau hyperphosphorylation, neurofibrillary lesions and inflammatory cytokine release.¹⁷ Additionally, in brains of these transgenic mice, and in postmortem human brain tissue, simufilam restored function of α 7nAChR, NMDA receptors and insulin receptors and improved synaptic plasticity (indicated by NMDA-induced activity-dependent expression of the master synaptic plasticity regulator Arc).¹⁷ Improvements in receptor function and synaptic plasticity could underlie the apparent cognitive enhancement in this trial.

FDA Guidance requires clinical trials in Alzheimer's disease to show a clinical benefit on cognitive and functional co-primary endpoints. Meaningful benefits are unlikely to occur without concurrent improvements in a broad panel of disease biomarkers. There are few reports of drug effects on CSF biomarkers, and these effects on one to three markers have not always shown concurrent effects on

cognition or function.²⁹ Drug effects on biomarkers that are compellingly related to the neurobiology of Alzheimer's disease in the pathway(s) affected by a drug candidate can support a regulatory claim for disease modification.³⁰

Simuflam is the first of a new class of drug candidates to target altered filamin A, a proteopathy in Alzheimer's disease. This clinical dataset of CSF biomarker changes offers new insights into the pathophysiology of Alzheimer's disease and a potential new therapeutic strategy. Simuflam's ability to enhance cognition and slow disease progression in Alzheimer's disease patients will need to be evaluated in large, definitive clinical trials.

Acknowledgements

We thank the patients and caregivers, clinical investigators, site staff and monitors involved in this trial. We are grateful for advice of our advisors and the scientific and financial support of the National Institute on Aging (NIA).

Author Contributions

RB, NF and LHB designed the clinical trial with guidance from JC. Biomarker analyses were conducted blind to treatment and time point by H-YW, ZP and K-CL. APOE genotyping was conducted by K-CL. CC oversaw clinical operations and trial monitors. YGR, TAD, JP, BB, PS, ELB and BN were clinical investigators. GBT analyzed lymphocyte assays. LHB wrote the manuscript with help from HYW, RB and JC. All authors have access to the data via an electronic data capture system, except H-YW, ZP and K-CL who remain blinded to treatment.

Conflicts of Interest Disclosures:

Simufilam is the chemical name for a compound owned by Cassava Sciences, Inc. CC, GBT, RB, NF and LHB are Cassava Sciences employees. H-YW and JC are consultants and scientific advisory board members for Cassava Sciences.

Funding: This trial was supported by NIA grant AG050878.

Role of the Funder: NIA personnel approved the clinical trial protocol. NIA personnel also approved the selection of Data and Safety Monitoring Board members and participate in these meetings.

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Figure Legends

Figure 1. Patient Flow Diagram

Figure 2. Spaghetti plots by group for biomarkers measured by ELISA. Plots show individual patient levels (pg/mL) at screening (left) and at Day 28 (right). All patients in simufilam groups show decreases in all biomarkers except one individual in the 50 mg group. By contrast, placebo patients show movement in both directions for each biomarker. **A:** Core AD pathology biomarkers. **B:** Neurogranin, neurofilament light chain (NfL), and YKL-40. **C:** Secondary biomarkers IL-6, sTREM2 and HMGB1. N=22, 20, 19 for placebo, 50 and 100 mg, respectively.

Figure 3. Simufilam improved biomarkers of AD pathology, neurodegeneration, neuroinflammation and BBB integrity. Percent change from baseline of CSF biomarkers (**A**) and lymphocyte target engagement markers (**B**). Reductions in filamin A linkages to $\alpha 7$ nAChR or TLR4 in lymphocytes indicate target engagement. These secondary analyses of percent change from baseline on all biomarkers excluded the 3 patients with no detectable simufilam in plasma at return visits. Data are means \pm SEM. * $p \leq 0.0001$, # $p < 0.001$, † $p < 0.01$ and + $p < 0.05$ versus placebo. N=22, 20, 19 for placebo, 50 and 100 mg, respectively.

Figure 4. Simufilam appeared to improve both episodic memory and spatial working memory. Effect sizes were calculated by Hedge's g . For the episodic memory test (Paired Associates Learning), the least impaired patients (11 or fewer errors, representing a ceiling effect) and patients with 54 or more errors (very poor performance suggesting not understanding the task) were removed from the analysis. Both datasets removed the 3 patients with no detectable drug in plasma, 2 patients with $\geq 25\%$ non-compliance by pill counts, one patient with no baseline test and one who did not understand instructions per rater notes. N=14, 13, 10 for PAL, and N=22, 17, 18 for spatial working memory for placebo, 50 and 100 mg, respectively.

Table 1. Baseline Demographics and Assessments

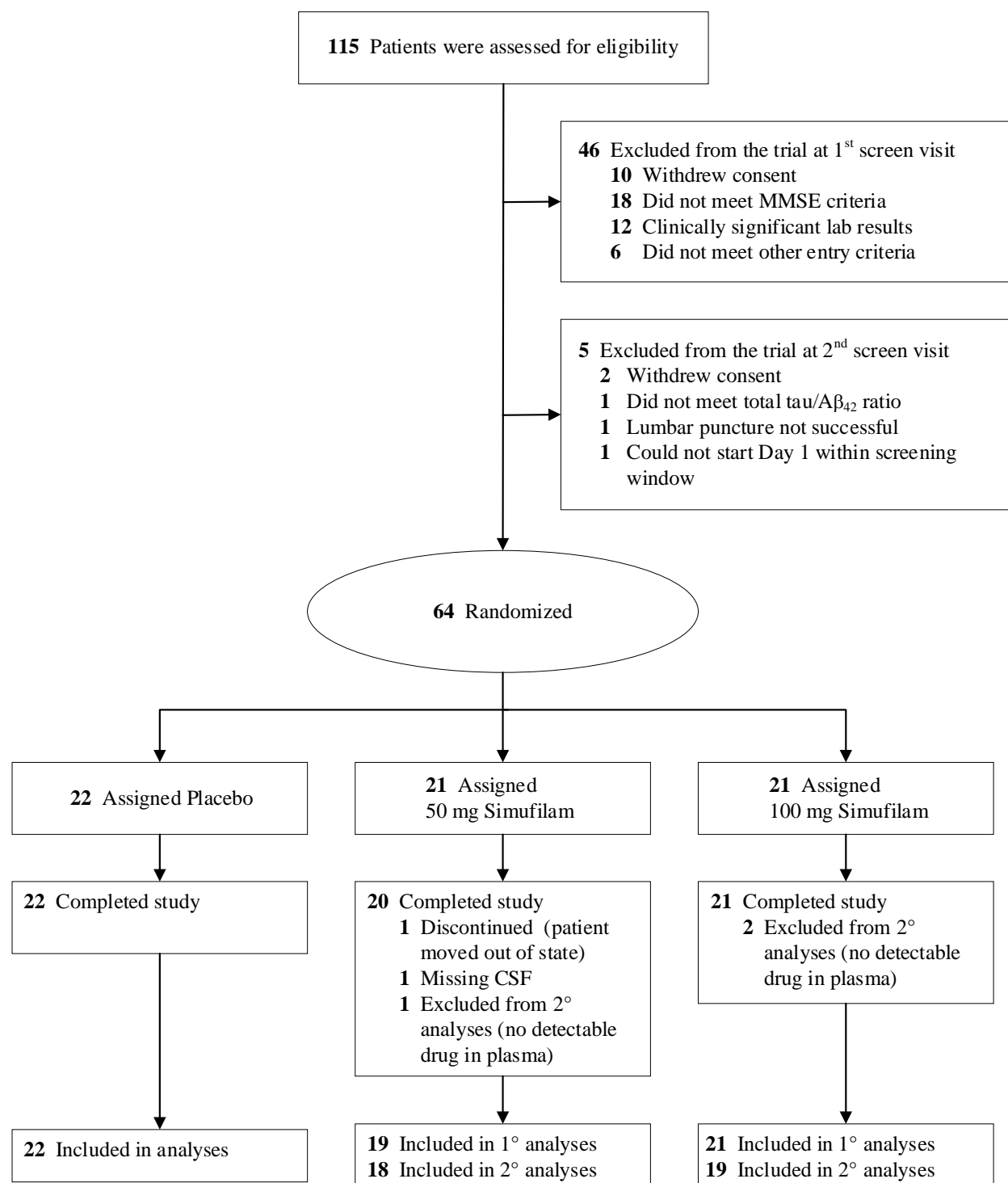
Demographics and Characteristics	Placebo (N=22)	Simufilam 50 mg (N=21)	Simufilam 100 mg (N=21)	p value^a
Age, mean (SD)	71.3 (6.68)	69.3 (5.47)	67.1 (8.76)	0.16
Female sex, No. (%)	11 (50.0)	12 (57.1)	12 (57.1)	n/a
Not white race, No. (%)	3 (13.6)	4 (19.0)	2 (9.5)	n/a
Hispanic or Latino ethnicity, No. (%)	9 (40.9)	11 (52.4)	11 (52.4)	n/a
CSF total tau/A β ₄₂ ratio (SD)	1.20 (0.55)	1.17 (0.58)	1.08 (0.50)	0.75
MMSE, mean (SD)	23.1 (2.78)	22.7 (2.67)	23.0 (2.66)	0.97
Taking cholinesterase inhibitor or memantine, No. (%)	8 (36.4)	5 (23.8)	7 (33.3)	n/a
Heterozygous APOE4	12	14	9	n/a
Homozygous APOE4	1	1	3	n/a
Paired Associates Learning total errors, mean (SD)	35.5 (19.65)	36.1 (18.76)	31.0 (20.74)	0.71
Spatial Working Memory total errors, mean (SD)	19.0 (7.49)	22.3 (6.64)	22.1 (5.88)	0.62
CSF A β ₄₂ pg/mL, mean (SD)	125 (152)	108 (54.8)	117 (51.4)	0.86
CSF total tau pg/mL, mean (SD)	104 (32)	101 (17.6)	106 (27.9)	0.79
CSF P-tau181 pg/mL, mean (SD)	28.5 (0.73)	29.0 (1.0)	29.7 (1.5)	0.01
CSF neurogranin pg/mL, mean (SD)	1200 (365)	1352 (614)	1551 (751)	0.16
CSF NfL pg/mL, mean (SD)	161 (42.8)	181 (64.4)	216 (95.3)	0.06
CSF YKL-40 pg/mL, mean (SD)	206 (29.5)	194 (26.0)	203 (22.7)	0.33
CSF IL-6 pg/mL, mean (SD)	32.5 (1.2)	33.6 (1.7)	33.6 (1.8)	0.03
CSF sTREM2, pg/mL, mean (SD)	878 (435)	882 (476)	861 (421)	0.92
CSF HMGB1, pg/mL, mean (SD)	424 (48.0)	454 (70.6)	446 (67.3)	0.18
CSF/plasma albumin ratio, mean (SD)	0.24 (0.03)	0.25 (0.05)	0.25 (0.08)	0.90
CSF/plasma IgG ratio, mean (SD)	0.200 (0.07)	0.227 (0.07)	0.217 (0.11)	0.61
Lymphocyte filamin A – α 7nAChR, Ratio to total filamin A, mean (SD)	0.59 (0.10)	0.66 (0.12)	0.69 (0.11)	0.05
Lymphocyte filamin A – TLR4, Ratio to total filamin A, mean (SD)	0.55 (0.10)	0.58 (0.11)	0.60 (0.07)	0.25

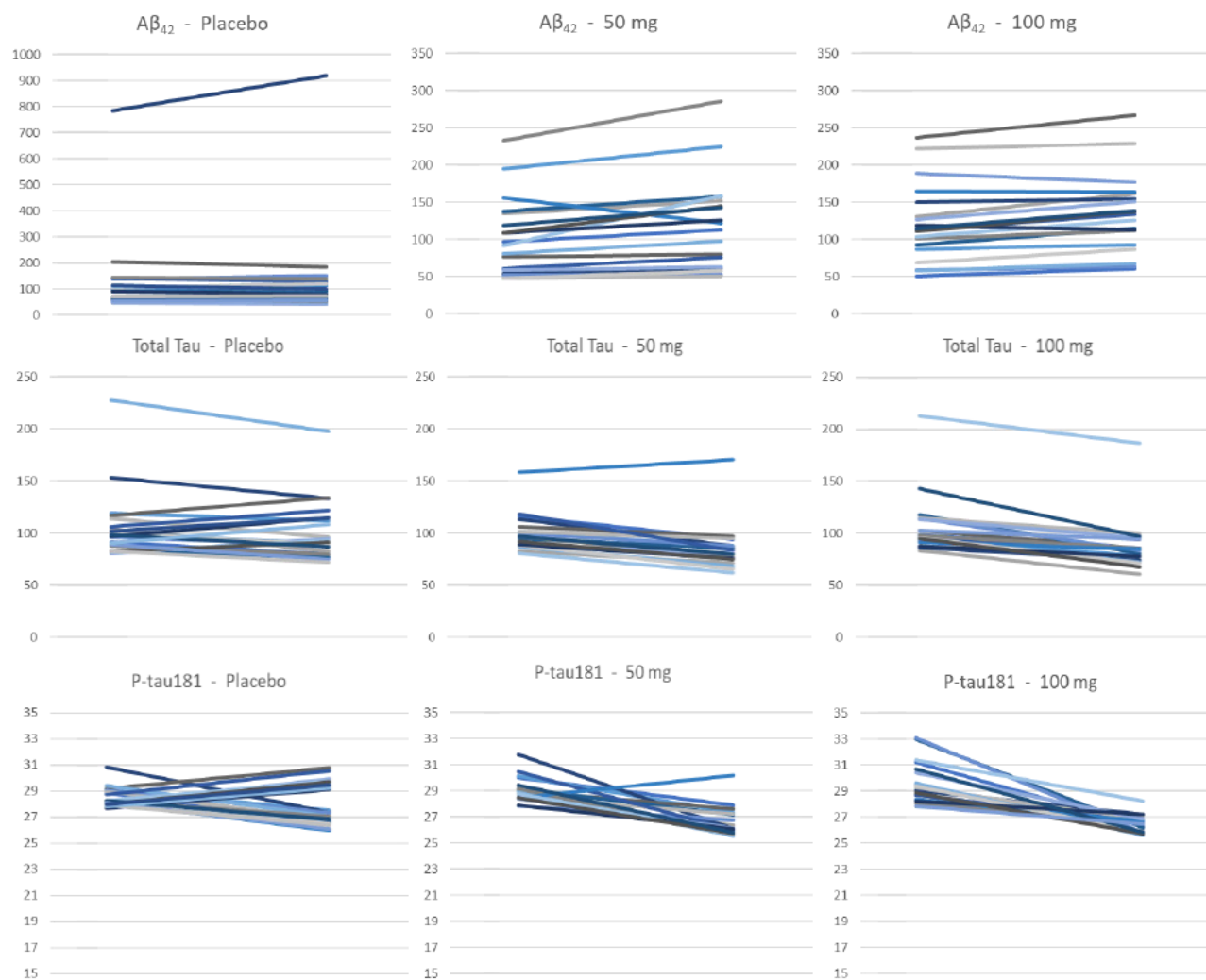
^a p value is for the between groups comparison of the ANOVA. P-tau181 and IL-6 showed p values of 0.01 and 0.03 between groups, due to very low SDs, despite relatively close means. The 0.06 p value for NfL was driven by two extreme values in the high dose group (473 and 390); removing one or both resulted in p=0.16 and p=0.23, respectively.

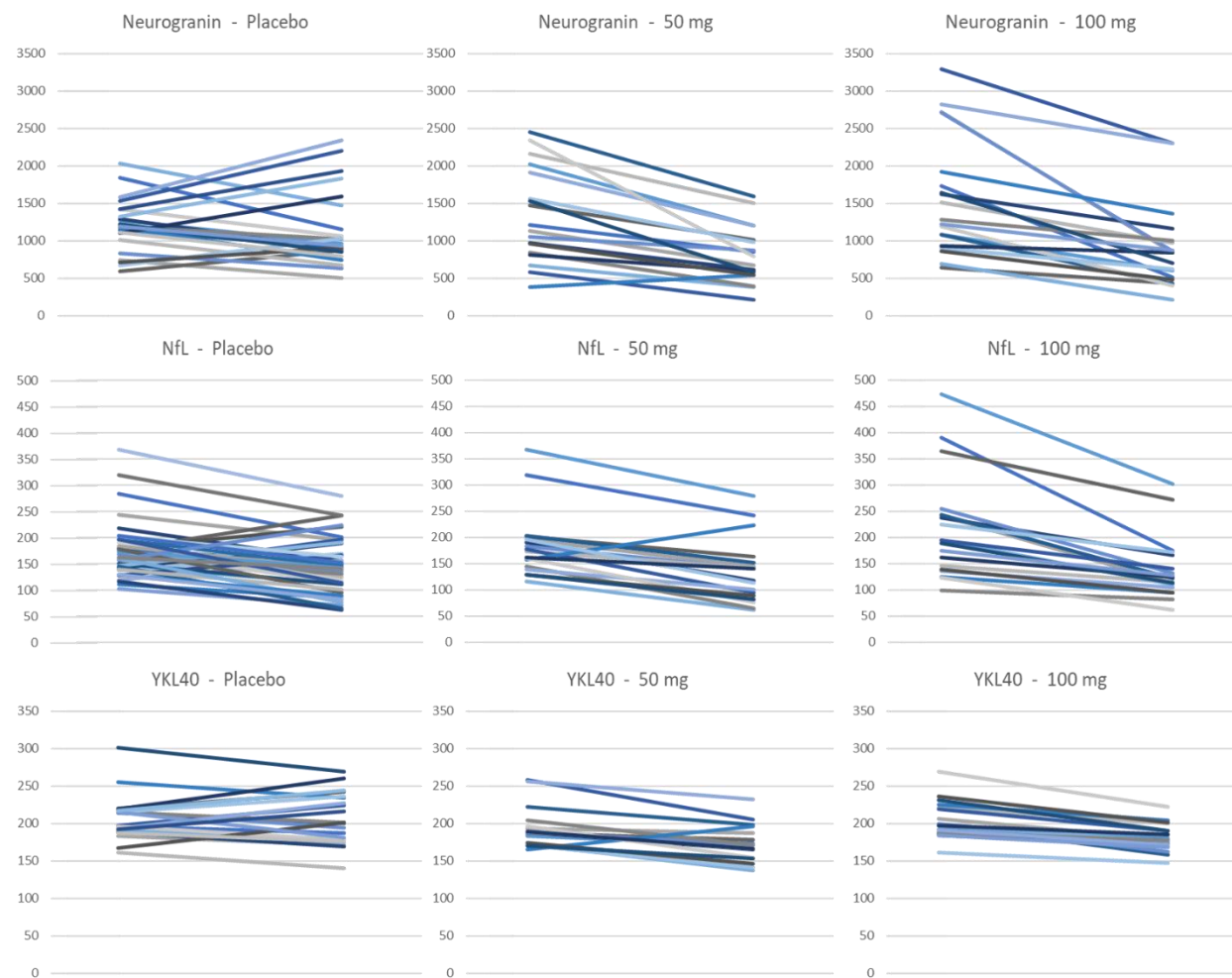
Table 2. Biomarkers Change from Baseline in pg/mL (SD)

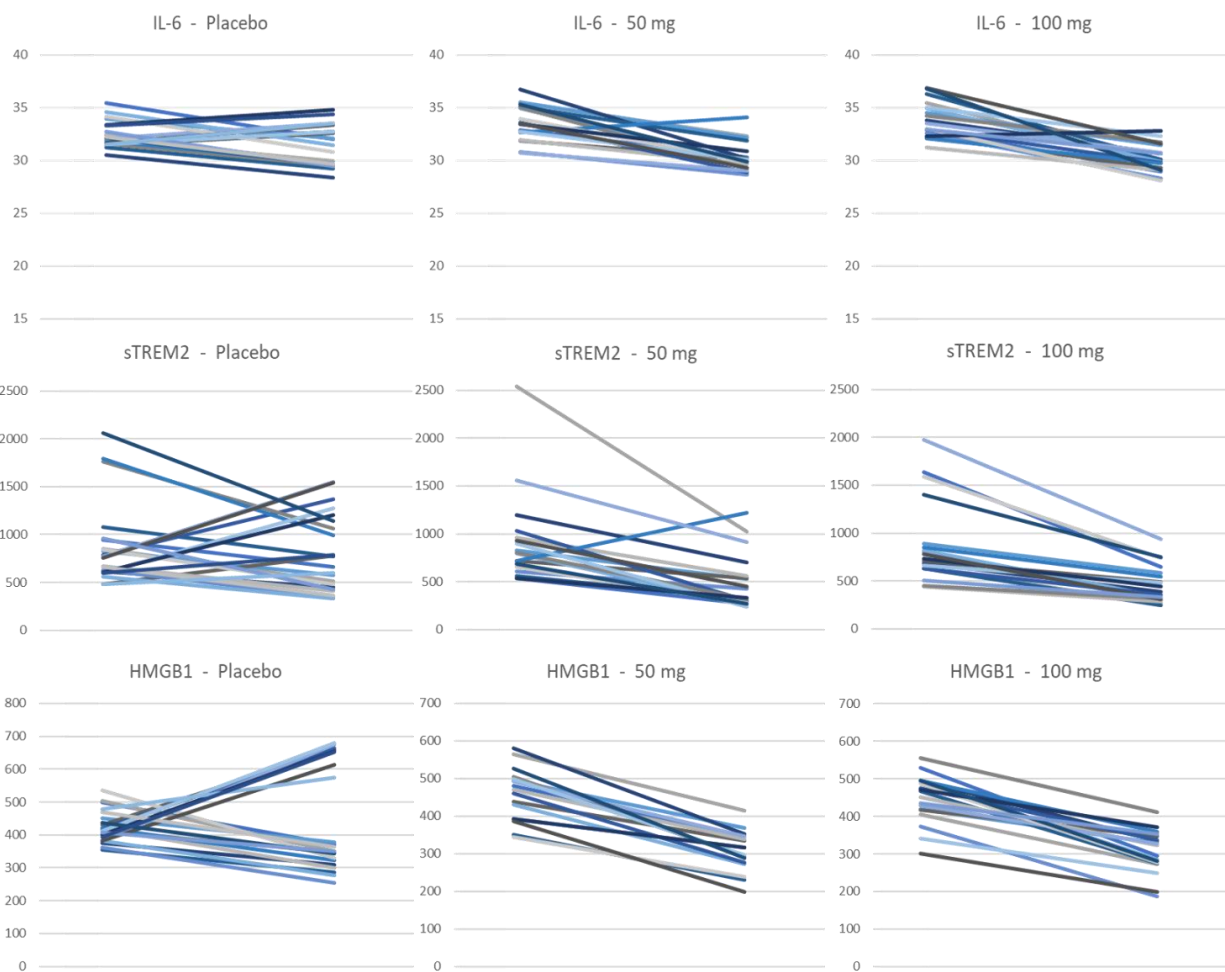
Biomarker	Placebo (N=22)	Simufilam 50 mg		Simufilam 100 mg	
		All Patients N=19	Compliers N=18	All Patients N=21	Compliers N=19
CSF A β ₄₂	4.8 (30.9)	16.2 (21.1) p = 0.01	16.9 (21.5) p = 0.006	12.5 (11.9) p = 0.087	13.4 (11.2) p = 0.088
CSF total tau	-3.2 (14.8)	-14.6 (9.6) p = 0.0012	-14.9 (9.8) p = 0.0014	-18.7 (10.4) p < 0.0001	-19.8 (10.3) p < 0.0001
Total tau/A β ₄₂	-0.029 (0.327)	-0.28 (0.27) p = 0.0006	-0.30 (0.27) p = 0.0008	-0.30 (0.22) p = 0.0001	-0.31 (0.22) p = 0.0001
CSF P-tau181	-0.63 (1.8)	-2.4 (1.6) p = 0.002	-2.5 (1.6) p = 0.003	-3.1 (1.7) p = 0.005	-3.2 (1.7) p = 0.003
CSF neurogranin	-50.5 (434.0)	-527 (361) p = 0.0005	-531 (371) p = 0.0006	-648 (491) p = 0.0002	-681 (505) p = 0.0002
CSF Neurofilament Light Chain	-10.0 (45.0)	-49.7 (35.5) p = 0.0058	-51.0 (36.1) p = 0.0008	-76.3 (50.6) p = 0.0003	-78.5 (52.9) p = 0.0002
CSF YKL-40	-0.96 (24.2)	-20.4 (17.4) p = 0.0001	-20.9 (17.7) p = 0.0002	-22.3 (11.7) p = 0.0001	-23.7 (11.4) p = 0.0001
CSF Interleukin-6	-1.1 (2.0)	-3.3 (1.8) p = 0.011	-3.3 (1.9) p = 0.019	-3.5 (1.8) p = 0.003	-3.7 (1.8) p = 0.0078
CSF sTREM2	-77.3 (510)	-418 (376) p = 0.0005	-424 (386) p = 0.0007	-404 (269) p = 0.0001	-426 (274) p = 0.0002
CSF HMGB1	19.4 (172.3)	-149 (50.3) p = 0.0001	-152 (50.1) p = 0.0001	-140 (51.3) p = 0.0001	-143 (51.3) p = 0.0001
CSF albumin ^a	-240 (1620)	-1184 (1707) p = 0.054	-1245 (1735) p = 0.046	-2103 (1774) p = 0.0001	-2292 (1760) p = 0.0001
CSF IgG ^a	-574.8 (2518.32)	-2269 (2176) p = 0.018	-2444 (2097) p = 0.014	-2253 (2414) p = 0.007	-2350 (2517) p = 0.012
Lymphocyte filamin A – α 7nAChR ^b	-0.07 (0.19)	-0.22 (0.13) p = 0.014	-0.23 (0.13) p = 0.009	-0.22 (0.16) p = 0.008	-0.24 (0.16) p = 0.005
Lymphocyte filamin A – TLR4 ^b	-0.05 (0.18)	-0.19 (0.11) p = 0.011	-0.19 (0.11) p = 0.010	-0.18 (0.13) p = 0.012	-0.19 (0.14) p = 0.010

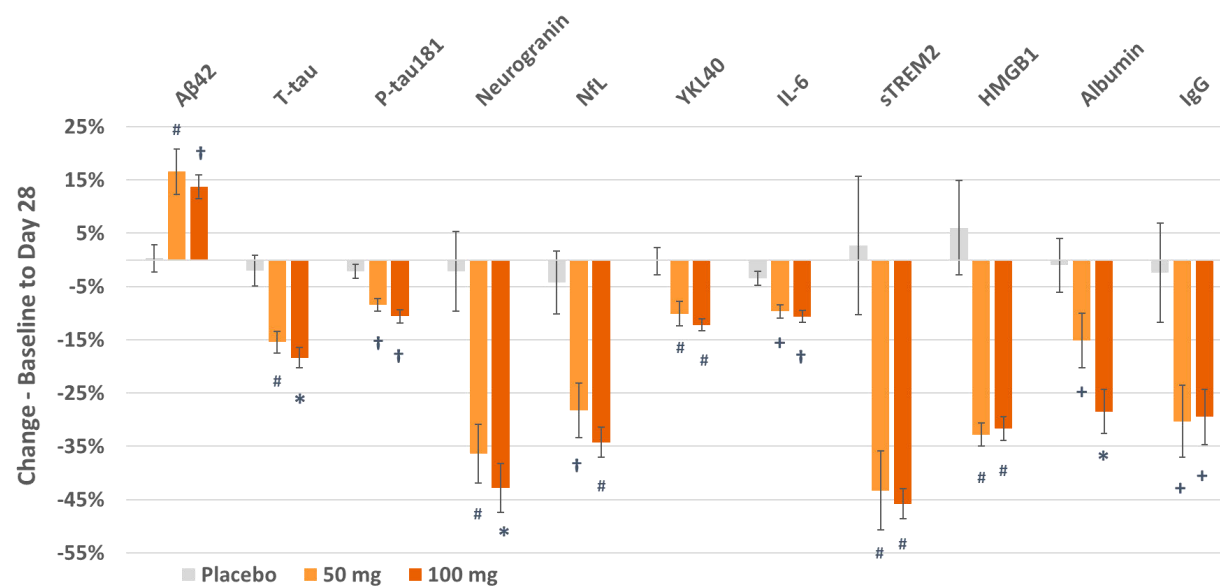
^a Units are optical density units of immunoblot bands.^b Densitometric quantities of α 7nAChR or TLR4 in anti-filamin A precipitates as a ratio to total filamin A. N.B.: p values are compared to placebo for each biomarker.

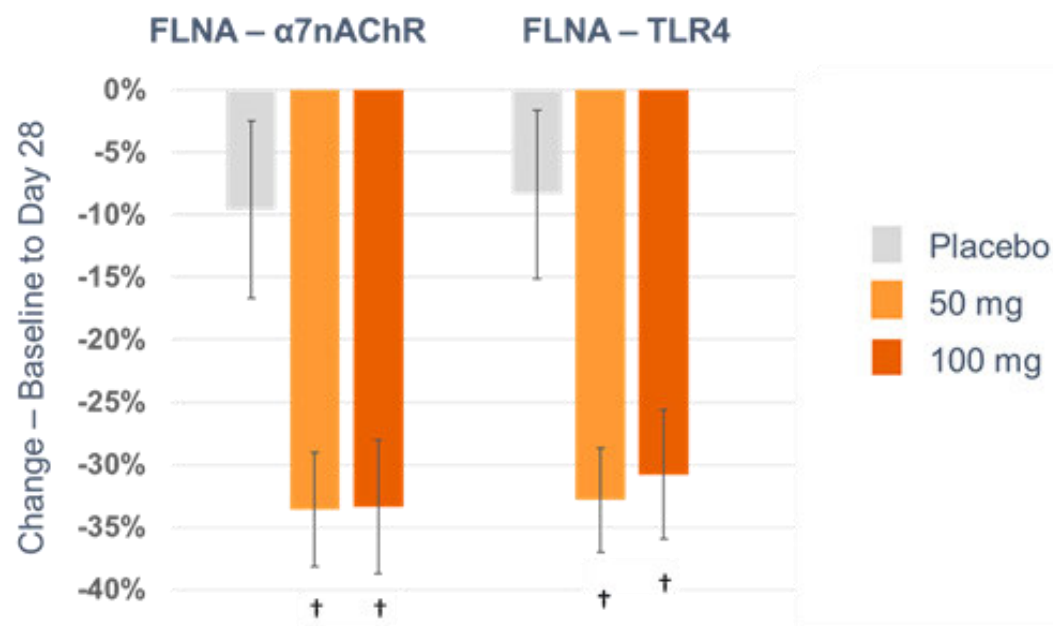


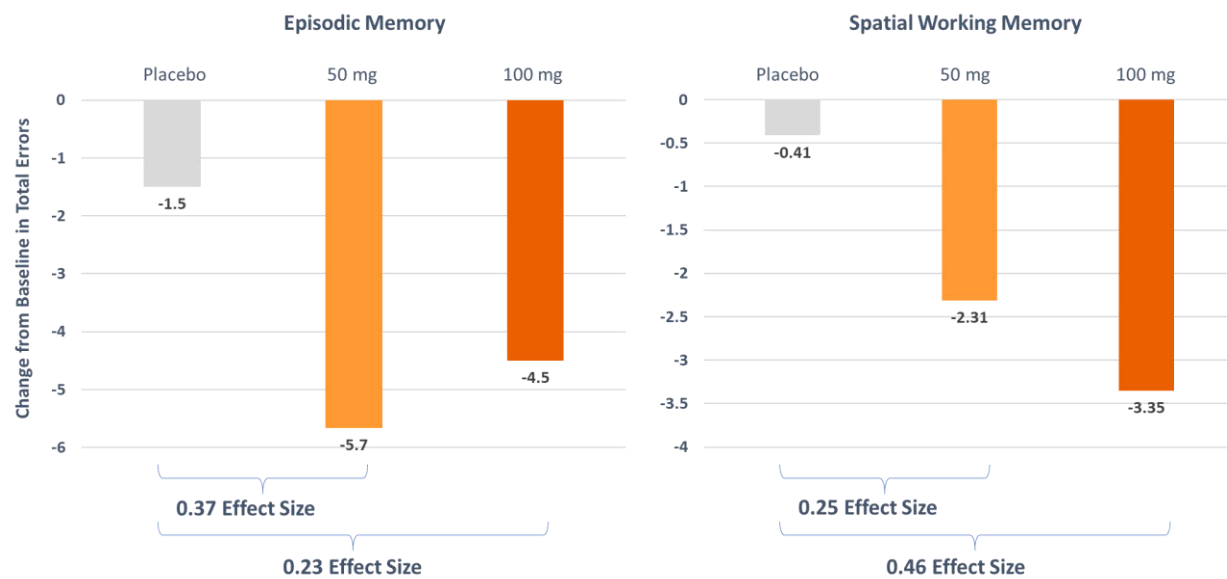












Research in Context (150 words)

1. **Systematic Review:** We searched clinicaltrials.gov and PubMed to determine if randomized controlled trials (RCTs) of other therapeutic candidates for Alzheimer's disease have reported significant treatment effects on multiple cerebrospinal fluid (CSF) biomarkers. A recent review is cited.
2. **Interpretation:** The significant improvements in eleven CSF biomarkers of Alzheimer's disease pathology, neurodegeneration, neuroinflammation and blood-brain barrier integrity in an RCT of mild-to-moderate Alzheimer's disease patients following one-month oral treatment suggests simufilam may slow disease progression.
3. **Future Directions:** Simufilam will be further evaluated in large, definitive clinical trials of Alzheimer's disease dementia.

From: Hoau-yan Wang
Sent time: 06/29/2021 12:46:12 PM
To: Sharki Ahmed
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)
Attachments: Budget justification - CASSAVA -CUNY SOM.docx Statement of Work-PDD.docx

Hi Sharki,

Enclosed are the budget justification and a statement of work you requested.

Thanks.

Best,

Hoau-Yan Wang

*Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY SOM*

From: Sharki Ahmed
Sent: Tuesday, June 29, 2021 11:02 AM
To: Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Prof. Wang,

Please send us the budget justification and a statement of work so I can close out the PARS request on the pre-award side.

Also, please fill out and return the attached FCOI form(s).

Lastly,

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Lindsay Burns <lburns@cassavasciences.com>
Sent: Tuesday, June 29, 2021 10:50 AM
To: Sharki Ahmed; Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Sharki,

What we really need is agreement on the contract terms. The budget is fine from our perspective. We have seen the justification.

Thank you!
Lindsay

From: Sharki Ahmed <sahmed9@ccny.cuny.edu>
Sent: Tuesday, June 29, 2021 9:48 AM
To: Hoau-yan Wang <hywang@med.cuny.edu>
Cc: Marc Scullin <msscullin@med.cuny.edu>; Lindsay Burns <lburns@cassavasciences.com>
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Hi Prof. Wang,

Just wanted to touch base on this proposal. I have listed a deadline for tomorrow. Since we have finalized the budget, please provide us with a budget justification (in Word format).

Dr. Burns- What is needed for this submission? A letter of commitment? CV? Budget? Budget justification?

Best,

Sharki Ahmed
Grants Associate

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160 Convent Avenue SH-Room 16
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sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Wednesday, June 9, 2021 3:06 PM
To: Lindsay Burns; Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Lindsay,

Noted. Thank you for the explanation and clarification.

Best,

Sharki Ahmed
Grants Associate

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GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Lindsay Burns <lburns@cassavasciences.com>
Sent: Wednesday, June 9, 2021 11:03 AM
To: Sharki Ahmed; Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Sharki,

We were planning to submit to an RFA from the Michael J Fox Foundation, but it won't be released now until August 9.

So instead, we are suggesting that Cassava Sciences fund this work so that it can start this summer. Dr. Wang and I have worked on many projects together, and he has been a sub-awardee on multiple Cassava Sciences NIH grants, where the 57% has been used. Because we are proposing that Cassava Sciences fund this work directly, I proposed a lower overhead rate that is in line with what we used in earlier agreements for research conducted by Dr. Wang several years ago.

Kind regards,
Lindsay

From: Sharki Ahmed <sahmed9@ccny.cuny.edu>
Sent: Wednesday, June 9, 2021 8:51 AM
To: Hoau-yan Wang <hywang@med.cuny.edu>
Cc: Marc Scullin <msscullin@med.cuny.edu>; Lindsay Burns <lburns@cassavasciences.com>
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Hi Prof. Wang,

Is there a specific solicitation(RFP) to which you are applying to? If in that solicitation the IDC rate stated is 25%, then that is fine.

Best,

Sharki Ahmed
Grants Associate

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GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-yan Wang
Sent: Monday, June 7, 2021 4:06 PM
To: Sharki Ahmed
Cc: Marc Scullin; Afrodita Feratovic; Lindsay Burns
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Sharki,

Thanks for the budget, I don't see anything in need to be modified.

Regarding the 25% indirect cost, this is from the sponsor, Cassava Sciences (Dr. Lindsay Burns copied here) set the indirect cost rate of 25%. This is a 10% increase from our original plan to submit the grant to Michael J Fox foundation (15% indirect). Since I think it is advantageous to Research foundation (I get the same budget from either sources). If this is not agreeable, we can then in turn submit via Michael J. Fox Foundation. Any question regarding indirect, please communicate with Dr. Burns.

Thanks again.

Best,

Hoau-Yan Wang

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY SOM

From: Sharki Ahmed
Sent: Monday, June 7, 2021 10:46 AM
To: Hoau-yan Wang
Cc: Marc Scullin; Afrodita Feratovic
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Prof. Wang,

As Afrodita mentioned, I will be assisting you on this proposal. Please find attached the draft budget and let me know if there are any changes needed.

Please provide us the solicitation/guidelines for this proposal. Also, you indicated the 25% IDC rate. I have included it as is, but please provide me with the appropriate source for the reduced rate (must be stated in the solicitation). Otherwise, the 57% IDC rate must be used.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Afrodita Feratovic
Sent: Monday, June 7, 2021 9:45 AM
To: Hoau-yan Wang
Cc: Sharki Ahmed; Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Prof. Wang,

Sharki Ahmed is assigned to work with you on this proposal and will follow up with you directly concerning the preparation for this proposal.

IMPORTANT NOTE:

The CUNY Financial Conflict of Interest Form is required. Please complete and return the attached FCOI form by the date indicated below. This form **MUST be completed by all CUNY investigators identified** on the project. While this disclosure form is not required at this application stage for investigators who have not yet been named in this proposal, please keep in mind that once the project is funded and such investigators are identified to be involved in your project activities, **You should notify them that they are required to submit the CUNY Financial Conflict of Interest at that time.**

Please log into **Cayuse SP** now to complete these required sections:

- **Regulatory Compliance** - regarding human and animal subjects
- **Export Control**
- **Intellectual Property**
- **Proposal Abstract** - a draft version is fine

Your SP number is 21-0505

Please finalize your submission according to this timeline:

- **Cayuse SP:** Complete required sections (see above) as soon as possible, no later than **9 am on Monday, June 21st.**
- **Budget:** Finalize with GA by **9 am on Wednesday, June 23rd.**
- **CUNY Conflict of Interest Forms:** Complete and return by **12 pm on Wednesday, June 23rd.**
- **Departmental Approval:** GA initiates approval routing by **3 pm on Wednesday, June 23rd.**

· **Final proposal review:** Provide all proposal documents for GA review by **5 pm on Monday, June 28th.**

Please note that any requests for proposal assistance (PARS) received within 10 business days of scheduled submission, will not be reviewed for full compliance of the sponsor's guidelines. In such cases, the proposal will be submitted as is.

Logging into Cayuse SP: for tutorial and links, visit CCNY's Cayuse website
at: <https://www.ccnycuny.edu/research/cayuse>

RF APPS Peer Review: The RF APPS team has established a proposal peer review system to provide constructive feedback from colleagues to improve the competitiveness of your proposal. For more details, please contact apps@rfccny.org

Best,

Afrodita Feratovic

Grants Associate | Pre-Award

Grants and Sponsored Programs

The City College of New York

160 Convent Avenue | SH – Room 16

New York, NY 10031-9101

(E): aferatovic@ccny.cuny.edu

GSP - <https://www.ccnycuny.edu/research/gsp>

PARS - <https://www.ccnycuny.edu/research/pars>

CCNY - Grants and Sponsored Programs

Proposal Assistance Request Summary

Budget

Request # 4073

Number

Proposal Title Effects of simufilam on pathogenesis associated with Parkinson's disease dementia using postmortem brain tissue

PI Name Hoau-Yan Wang

Department Physiology & Pharmacology

E-mail hywang@med.cuny.edu

Phone Number (212) 6508813

Co-PIs -
-
-

Is CCNY the lead? Yes

Grant
Announcement
Number

Agency AGENCY NOT LISTED
CASSAVA Sciences

Submission
Due Date 06-30-2021

Project Start
Date 08-01-2021

of years for
the budget? 1

Mandatory
Cost Sharing No

Subcontract
Information N/A

Budget
Limitations Yes

Salary & fringe benefit:

Principal Investigator:
\$11,041 (\$7,312 + \$3,729)

Professor Hoau-Yan Wang, Ph.D. requests 5% effort (1.10 Academic months per year). He will design and execute the assays using postmortem brain. He will oversee the data collection and analysis.

Post-doctoral research associate:
Zhe Pei, Ph.D. (1 Calendar months per year) will assist PI in running Immunoprecipitation and Western blotting.
\$ 7,747 (\$ 5,600 + \$ 2,147)

Technician:
Kuo-Chieh Lee, M.S. (2.4 Calendar months per year) will assist PI in tissue processing, cell isolation and myriad of experimental procedures and reagent preparation.

\$ 14,388 (\$ 10,400 + \$ 3,988)

Fringe Benefit
RFCUNY maintains its own fringe benefits program for employees (comparable to those of other academic and non-profit institutions). The cost of providing benefits to employees is included in grants as a direct charge.

To simplify both pre-award budget preparation and post-award accounting procedures, RFCUNY developed a system of Multiple Fringe Benefits Pools. Each grant is charged a flat percentage of each employee's gross annual wages, based on their classification. The percentages represent the best estimate of the actual costs of providing benefits to each employee.

Released Time Faculty:
CUNY Faculty released to work on a grant or contract a rate of 51% is applied to the requested salary support.

A rate of 38% is applied to Full Time/Part Time A employees with an additional .34% of MTA tax.

Specific
Budget Needs

Expendable Supplies:
Antibodies and immunoprecipitation agents
Primary antibodies \$350 x 14 \$ 4,900
protein A/G-conjugated agarose beads x2 \$ 3,224
HRP-secondary antibodies-\$156 x 3 \$ 468

\$ 8,592

Drugs and Chemicals
Phosphatase inhibitor tablets @ \$245 x 2 \$ 490
Protease inhibitor tablets@ \$225 x 2 \$ 450
Digitonin @ \$186/ 500 mg x 2 \$ 372
NP-40 @ \$64/250 ml \$ 64
Bradford reagent \$ 156
\$ 1,532

Electrophoresis and Western blotting equipment and supplies, ECL reagents, Film and Immunohistochemistry
ECL reagent \$490 \$ 490
Methanol \$ 120
Buffer reagents \$ 350
\$ 960

Supplies
Ependoff tubes \$ 250
Pipette tips \$ 200

Cuvettes \$ 100

Gloves \$ 190

\$ 740

Research materials & supplies \$ 11,824

Direct cost \$ 45,000.00

Indirect Costs (25%) \$ 11,250.00

Total \$ 56,250.00

Additional
Comments

Draft Budget
Upload

Grant
Announcement
Upload

RCR
Certificate citiCompletionReport713185 (1)-RCR certificate.pdf

Statement of Work

Dementia and mild cognitive impairment are prevalent in advanced stages of Parkinson disease (PD). Similar to Alzheimer's disease (AD) dementia, there is no effective treatment for dementia associated with PD. In addition to Lewy pathology in the limbic and cortical regions, the molecular mechanisms contributing to cognitive decline in PD remain elusive. We propose to test a novel therapeutic agent, simufilam that binds pathological form of filamin A (FLNA) to reduce A β ₄₂ toxic signaling to hyper-phosphorylation of tau via α 7nAChR, neuroinflammation by TLR4 and brain insulin resistance. This study will use 8 sets of postmortem posterior parietal cortices (PPCs) from matched control, Parkinson's disease, Parkinson's disease with mild cognitive impairment (MCI), and Parkinson's disease with dementia cases. Specifically, we aim to use an established *ex vivo* stimulation method in postmortem brains to assess the effects of simufilam on (1) **FLNA- α 7nAChR/TLR4 and A β ₄₂ - α -synuclein complex levels**. The α 7nAChR and TLR4 levels in the anti-FLNA immunoprecipitates will be measured by immunoblotting with specific antibodies, and the levels of α -synuclein in the anti-A β ₄₂ immunoprecipitates will be measured with an α -synuclein specific antibody. (2) **NMDAR signaling**: The levels of pY⁴¹⁶Src, pY⁴⁰²PyK2, nNOS, PLC- γ , and PKC γ in the anti-NR1 immunoprecipitate by immunoblotting with specific antibodies. The levels of pY¹²⁴⁶-NR2A will also be determined. (3) **Insulin signaling**: The levels of pY^{1150/1151}IR β and IRS-1 will be measured by coimmunoprecipitation and detection with specific antibodies. Improvements in these measures by simufilam *in vitro* treatment would add support to the rationale for testing simufilam in patients with Parkinson's disease dementia.

Title: Preclinical assessing the effectiveness of Simufilam on cognitively impaired Parkinson's disease cases using postmortem brains

BUDGET JUSTIFICATION

Salary & fringe benefit:

Principal Investigator:

\$11,041 (\$7,312 + \$3,729)

Professor Hoau-Yan Wang, Ph.D. requests 5% effort (1.10 Academic months per year). He will design and execute the assays using postmortem brain. He will oversee the data collection and analysis.

Post-doctoral research associate:

Zhe Pei, Ph.D. (1 Calendar months per year) will assist PI in running Immunoprecipitation and Western blotting.

\$ 7,747 (\$ 5,600 + \$ 2,147)

Technician:

Kuo-Chieh Lee, M.S. (2.4 Calendar months per year) will assist PI in tissue processing, cell isolation and myriad of experimental procedures and reagent preparation.

\$ 14,388 (\$ 10,400 + \$ 3,988)

Fringe Benefit

RFCUNY maintains its own fringe benefits program for employees (comparable to those of other academic and non-profit institutions). The cost of providing benefits to employees is included in grants as a direct charge.

To simplify both pre-award budget preparation and post-award accounting procedures, RFCUNY developed a system of Multiple Fringe Benefits Pools. Each grant is charged a flat percentage of each employee's gross annual wages, based on their classification. The percentages represent the best estimate of the actual costs of providing benefits to each employee.

Released Time Faculty:

CUNY Faculty released to work on a grant or contract a rate of 51% is applied to the requested salary support.

A rate of 38% is applied to Full Time/Part Time A employees with an additional .34% of MTA tax.

Expendable Supplies:

Antibodies and immunoprecipitation agents

Primary antibodies \$350 x 14	\$ 4,900
protein A/G-conjugated agarose beads x2	\$ 3,224
HRP-secondary antibodies-\$156 x 3	\$ 468

\$ 8,592

Drugs and Chemicals

Phosphatase inhibitor tablets @ \$245 x 2	\$ 490
Protease inhibitor tablets @ \$225 x 2	\$ 450
Digitonin @ \$186/ 500 mg x 2	\$ 372
NP-40 @ \$64/250 ml	\$ 64
Bradford reagent	\$ 156

\$ 1,532

Electrophoresis and Western blotting equipment and supplies, ECL reagents, Film and Immunohistochemistry

ECL reagent \$490	\$ 490
Methanol	\$ 120
Buffer reagents	\$ 350

\$ 960

Supplies

Ependoff tubes	\$ 250
Pipette tips	\$ 200
Cuvettes	\$ 100
Gloves	\$ 190

\$ 740

Research materials & supplies

\$ 11,824

Direct cost

\$ 45,000.00

Indirect Costs (25%)

\$ 11,250.00

Total

\$ 56,250.00

From: Holli-Anne S Tai
Sent time: 06/29/2021 04:15:33 PM
To: Tricia Mayhew-Noel
Cc: Awards; Hoau-yan Wang
Subject: FCOI Determination -- PI: Hoau-Yan Wang (Cassava Sciences)
Attachments: FCOI_Wang_Cassava Sciences_Form2.pdf FCOI_Wang_Cassava Sciences_Form1.pdf NoA 1_Investigational Research Contract CUNY 17 June 2021.docx

Dear Tricia,

Please see attached FCOI supplement for Professor Wang's new project with Cassava Sciences. May you please let me know if a management plan will be required or if anything else is needed for further determination?

Thank you,

Holli-Anne Tai
Grants Associate
Grants and Sponsored Programs
The City College of New York
160 Convent Avenue | SH – Room 16
New York, NY 10031
Ph: 212-650-5418 | F: 212-650-7906
GSP - <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <http://www.ccny.cuny.edu/research/pars.cfm>

CUNY Significant Financial Interest (SFI) Disclosure Form For Sponsored Projects NOT Funded by the Public Health Service

* to be completed by each investigator on the project

Name of Investigator¹: **Hoau-Yan Wang**

Role of Investigator (project director / **PI** / co-PI / consultant / etc.):

Phone: **212-650-8813**

Email: **hywang@med.cuny.edu**

CUNY College/Site of Research: **CDI-3211**

Title of Sponsored Project²: **Preclinical assessing the effectiveness of Simufilam on cognitively impaired Parkinson's disease cases using postmortem brains**

Cassava Sciences

Funding Source:

Disclosure submission for:

☒ New funding proposal or application

☐ Annual progress report

☐ Material change in a previously disclosed SFI

☐ Discovery or acquisition of a new SFI

☐ New investigator joining an ongoing sponsored project at CUNY

Please indicate whether **you, your spouse, or your dependent children** have any of the following financial interests that may reasonably be related to your institutional responsibilities³:

Please note that this form must be completed by all individuals responsible for the design, conduct, or reporting of sponsored project.

¹ **Investigator:** The project director, principal investigator, co-principal investigators, and any other person, regardless of title of position, who is responsible for the design, conduct, or reporting of a University Sponsored Project, which may include, for example, collaborators or consultants, whether or not such individual is employed by the University or the Research Foundation.

² **Sponsored Project:** Projects or activities involving research, creative activity, training, instruction or service undertaken within or on behalf of the University pursuant to funding or other support from an External Sponsor.

³ **Institutional Responsibilities:** An investigator's professional responsibilities on behalf of the University, performed in the course of and within the scope of the Investigator's appointment or employment by the University, which may include, for example, activities such as research, research consultation, teaching, professional practice, institutional administration, committee memberships, and service on panels such as Institutional Review Boards, Institutional Animal Care and Use Committees or Institutional Biosafety Committees.

1. A total of salary, any other payment for services (for example, consulting fees or honoraria), and royalties expected to be received in the next 12 months that exceeds \$10,000, when aggregated for you, your spouse, and your dependent children, excluding any salary, royalties, or other remuneration from CUNY and income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities or from service on advisory committees or review panels for such entities.	Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
2. An equity interest (for example, stocks, stock options, or other ownership interests) in any single entity that, when aggregated for you, your spouse, and your dependent children, exceeds \$10,000 in value, as determined through reference to public prices or other reasonable measures of fair market value, <u>AND</u> represents more than a five percent (5%) ownership interest in the entity.	Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
3. Intellectual property rights and interests (for example, patents, copyrights).	Yes <input type="checkbox"/> No <input type="checkbox"/>

For yourself ONLY:

4. If you are responsible for developing, discovering, or creating CUNY-owned intellectual property, are you aware of the acquisition or intention to acquire ownership of, or a license to, that intellectual property by any corporation, partnership, or other legal entity (excluding entities controlled by the U.S. government, the State or City of New York, or CUNY) in or from which you have a financial interest described in any of Items 1 or 2 above? NOTE: If you answered "Yes" to this question you must also complete the CUNY Acquisition of or License to CUNY Intellectual Property (CALCIP) form and submit it to your College Conflicts Officer and the Director of the CUNY Technology Commercialization Office (TCO).	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A <input type="checkbox"/>
5. Do you teach, supervise, or otherwise have control over any student or postdoctoral associate at CUNY who might be involved in work for any corporation, partnership, or other legal entity (excluding entities controlled by the U.S. government, the State or City of New York, or CUNY) in or from which you have a financial interest described in any of Items 1 or 2 above?	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>

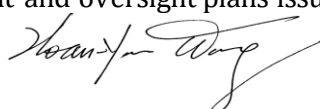
If you responded "yes" to any of the questions above, you must also complete a CUNY Significant Financial Interest Supplement Form. This Form, and the Supplement Form if required, should be submitted to your College Conflicts Officer, with a copy to your Grants Officer.

If you have any questions about this Form or the information it seeks, please refer to the [sponsored projects conflict of interest web site](#) or contact your [College Conflicts Officer](#).

Agreement & Signature:

By signing this form, I certify the following:

- The above statements are complete, true and accurate.
- I will submit an updated Form annually, prior to submission of annual progress reports; and also within 30 days of any material change to the above-disclosed Significant Financial Interest(s) or discovering or acquiring a new Significant Financial Interest.
- I will comply with all applicable regulations, CUNY policies, sponsor requirements, and any conflict of interest management and oversight plans issued by CUNY.



6/29/2021

Signature

Date

CUNY Significant Financial Interest Supplement Form for Sponsored Projects NOT Funded by the Public Health Service

Name of Investigator: **Hoau-Yan Wang**

Role of Investigator (project director / **PI** / co-PI / consultant / etc.):

CUNY College/Site of Research: **CDI-3211**

Title of Sponsored Project: **Preclinical assessing the effectiveness of Simufilam on cognitively impaired Parkinson's disease cases using postmortem brains.**

Funding Source: **Cassava Sciences**

Does this project involve human subject research? Yes ☐ No ☒

Please provide requested details regarding your positive responses made on the CUNY Significant Financial Interest Disclosure Form and, if necessary, use additional Supplement Forms:

1. A total of salary, any other payment for services (for example, consulting fees or honoraria), and royalties expected to be received in the next 12 months that exceeds \$10,000, when aggregated for you, your spouse, and your dependent children, excluding any remuneration from CUNY and income from engagements sponsored by public or nonprofit entities or from service on advisory committees or review panels for such entities:

i) Name of person or persons (and relationship to self) to whom the salary or payment is expected to be made:

Hoau-Yan Wang (self)

Name of entity:

Cassava Sciences

Nature of salary, payment for other services, or royalties (description of work performed for remuneration):

Consultancy

Amount of salary, payment for other services, or royalties expected to be received in the next 12 months:

\$24,000

Relationship to your institutional responsibilities:

NONE

ii) Name of person or persons (and relationship to self) to whom the salary or payment is expected to be made:

Name of entity:

Nature of salary, payment for other services, or royalties:

Amount of salary, payment for other services, or royalties expected to be received in the next 12 months:

Relationship to your institutional responsibilities:

2. An equity interest (for example, stocks, stock options, or other ownership interests) in any single entity that, when aggregated for you, your spouse, and your dependent children, exceeds \$10,000 in value, as determined through reference to public prices or other reasonable measures of fair market value, AND represents more than a five percent (5%) ownership interest in the entity:

Name of person or persons (and relationship to self) who hold(s) the equity interest:

Hoau-Yan Wang (Self)

Name of entity:

Cassava Sciences

Type of equity interest:

Stock & Stock options

Current value of equity interest and/or percentage of ownership interest in the entity, as applicable:

\$125,000

Relationship to your institutional responsibilities:

NONE

3. Intellectual property rights and interests (for example, patents, copyrights):

Owner(s) of the intellectual property:

N/A

Description of the intellectual property:

Description of any royalties or income you currently receive or may receive in the future:

Relationship to your institutional responsibilities:

4. Acquisition or intention to acquire ownership of, or a license to, CUNY-owned intellectual property by an entity in which you have a financial interest described in items 1 or 2 above:

Name of entity: **N/A**

Description of CUNY-owned intellectual property and your role in developing, discovering, or creating it:

Description of the interest that the entity has acquired or is intending to acquire:

5. Teaching, supervision, or otherwise having control over any student or postdoctoral associate at CUNY who might be involved in work for an entity in which you have a financial interest described in items 1 or 2 above:

Name of entity: **NONE**

Name of the student(s) or post doctoral associate(s) (please specify whether these are graduate students or post-docs):

Planned involvement of the student(s) or post-doctoral associate(s):

State your specific relationship with the student(s) involved in the project, (e.g. instructor, faculty advisor, thesis supervision, etc.):

Agreement & Signature:

By signing this form, I certify to the following:

- **All of the information contained herein is true, accurate and complete.**
- **As required, I will submit an updated Form annually, prior to submission of annual progress reports; and also within 30 days of any material change to the above-disclosed Significant Financial Interest(s) or discovering or acquiring a new Significant Financial Interest.**
- **I will comply with all applicable regulations, CUNY policies, sponsor requirements and any conflict of interest management and oversight plans issued by CUNY.**



6/29/2021

Signature

Date

From: Lindsay Burns <lburns@cassavasciences.com>
Sent time: 06/29/2021 04:35:00 PM
To: Holli-Anne S Tai; Sharki Ahmed; Awards
Cc: Marc Scullin; Hoau-yan Wang
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)
Attachments: Investigational Research Contract CUNY 17 June 2021.docx

All,

I am sending the contract again with the payment schedule section complete (in Attachment A). The detailed budget was always there in the Attachment B. If your contracts people would like the contract amount listed elsewhere, please ask them to insert it in the appropriate place.

Thanks,
Lindsay

From: Holli-Anne S Tai <htai@ccny.cuny.edu>
Sent: Tuesday, June 29, 2021 3:15 PM
To: Sharki Ahmed <sahmed9@ccny.cuny.edu>; Lindsay Burns <lburns@cassavasciences.com>; Awards <awards@ccny.cuny.edu>
Cc: Marc Scullin <msscullin@med.cuny.edu>; Hoau-yan Wang <hywang@med.cuny.edu>
Subject: RE: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Thank you Sharki,

Dr. Burns, we have received the contract, but before we can route it to our Legal team for review, we required a line item budget to be completed.

Professor Wang: Per CUNY policy, Your FCOI supplement form will also need to be sent to the College Conflicts Office for further review and determination. I will copy you on the email.

Best,

Holli-Anne Tai
Grants Associate
Grants and Sponsored Programs
The City College of New York
160 Convent Avenue | SH – Room 16
New York, NY 10031
Ph: 212-650-5418 | F: 212-650-7906
GSP - <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <http://www.ccny.cuny.edu/research/pars.cfm>

From: Sharki Ahmed <sahmed9@ccny.cuny.edu>
Sent: Tuesday, June 29, 2021 3:38 PM
To: Lindsay Burns <lburns@cassavasciences.com>; Awards <awards@ccny.cuny.edu>
Cc: Marc Scullin <msscullin@med.cuny.edu>; Hoau-yan Wang <hywang@med.cuny.edu>
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Dr. Burns,

I am looping in the awards team for information on that.

Awards Team- Do you have the contract? And has it been reviewed as per Dr. Burns' email? (We have finished on the Pre-award side).

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs

The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Lindsay Burns <lburns@cassavasciences.com>
Sent: Tuesday, June 29, 2021 3:35 PM
To: Sharki Ahmed
Cc: Marc Scullin; Hoau-yan Wang
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Sharki,

Has the contract been reviewed? Is it ready to sign? Did you pass it on or are you asking me to do that? I thought it would have been there when I sent it over. I'm just confused.

Thanks,
Lindsay

From: Sharki Ahmed <sahmed9@ccny.cuny.edu>
Sent: Tuesday, June 29, 2021 2:15 PM
To: Lindsay Burns <lburns@cassavasciences.com>
Cc: Marc Scullin <mscullin@med.cuny.edu>; Hoau-yan Wang <hywang@med.cuny.edu>
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Hi Dr. Burns,

Below is the email address for our post-award team.

awards@ccny.cuny.edu

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Tuesday, June 29, 2021 3:13 PM
To: Lindsay Burns
Cc: Marc Scullin; Grants Preaward; Hoau-yan Wang
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Dr. Burns,

Please find attached the documents for Prof. Wang.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Tuesday, June 29, 2021 10:59 AM
To: Lindsay Burns; Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Dr. Burns,

Noted. So I will provide you with the budget, budget justification and a letter. The agreements on the contract terms would be a post-award function, I will send you the appropriate email once I send you the above mentioned documents.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Lindsay Burns <lburns@cassavasciences.com>
Sent: Tuesday, June 29, 2021 10:50 AM
To: Sharki Ahmed; Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Sharki,

What we really need is agreement on the contract terms. The budget is fine from our perspective. We have seen the justification.

Thank you!
Lindsay

From: Sharki Ahmed <sahmed9@ccny.cuny.edu>
Sent: Tuesday, June 29, 2021 9:48 AM
To: Hoau-yan Wang <hywang@med.cuny.edu>
Cc: Marc Scullin <mscullin@med.cuny.edu>; Lindsay Burns <lburns@cassavasciences.com>
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Hi Prof. Wang,

Just wanted to touch base on this proposal. I have listed a deadline for tomorrow. Since we have finalized the budget, please provide us with a budget justification (in Word format).

Dr. Burns- What is needed for this submission? A letter of commitment? CV? Budget? Budget justification?

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Wednesday, June 9, 2021 3:06 PM
To: Lindsay Burns; Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Lindsay,

Noted. Thank you for the explanation and clarification.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Lindsay Burns <lburns@cassavasciences.com>
Sent: Wednesday, June 9, 2021 11:03 AM
To: Sharki Ahmed; Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Sharki,

We were planning to submit to an RFA from the Michael J Fox Foundation, but it won't be released now until August 9. So instead, we are suggesting that Cassava Sciences fund this work so that it can start this summer. Dr. Wang and I have worked on many projects together, and he has been a sub-awardee on multiple Cassava Sciences NIH grants, where the 57% has been used. Because we are proposing that Cassava Sciences fund this work directly, I proposed a lower overhead rate that is in line with what we used in earlier agreements for research conducted by Dr. Wang several years ago.

Kind regards,
Lindsay

From: Sharki Ahmed <sahmed9@ccny.cuny.edu>

Sent: Wednesday, June 9, 2021 8:51 AM

To: Hoau-yan Wang <hywang@med.cuny.edu>

Cc: Marc Scullin <mscullin@med.cuny.edu>; Lindsay Burns <lburns@cassavasciences.com>

Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Hi Prof. Wang,

Is there a specific solicitation(RFP) to which you are applying to? If in that solicitation the IDC rate stated is 25%, then that is fine.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>

PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-yan Wang

Sent: Monday, June 7, 2021 4:06 PM

To: Sharki Ahmed

Cc: Marc Scullin; Afrodita Feratovic; Lindsay Burns

Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Sharki,

Thanks for the budget, I don't see anything in need to be modified.

Regarding the 25% indirect cost, this is from the sponsor, Cassava Sciences (Dr. Lindsay Burns copied here) set the indirect cost rate of 25%. This is a 10% increase from our original plan to submit the grant to Michael J Fox foundation (15% indirect). Since I think it is advantageous to Research foundation (I get the same budget from either sources). If this is not agreeable, we can then in turn submit via Michael J. Fox Foundation. Any question regarding indirect, please communicate with Dr. Burns.

Thanks again.

Best,

Hoau-Yan Wang

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY SOM

From: Sharki Ahmed

Sent: Monday, June 7, 2021 10:46 AM

To: Hoau-yan Wang

Cc: Marc Scullin; Afrodita Feratovic

Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Prof. Wang,

As Afrodita mentioned, I will be assisting you on this proposal. Please find attached the draft budget and let me know if there are any changes needed.

Please provide us the solicitation/guidelines for this proposal. Also, you indicated the 25% IDC rate. I have included it as is, but please provide me with the appropriate source for the reduced rate (must be stated in the solicitation). Otherwise, the 57% IDC rate must be used.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Afrodita Feratovic
Sent: Monday, June 7, 2021 9:45 AM
To: Hoau-yan Wang
Cc: Sharki Ahmed; Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Prof. Wang,

Sharki Ahmed is assigned to work with you on this proposal and will follow up with you directly concerning the preparation for this proposal.

IMPORTANT NOTE:

The CUNY Financial Conflict of Interest Form is required. Please complete and return the attached FCOI form by the date indicated below. This form **MUST be completed by all CUNY investigators identified** on the project. While this disclosure form is not required at this application stage for investigators who have not yet been named in this proposal, please keep in mind that once the project is funded and such investigators are identified to be involved in your project activities, **You should notify them that they are required to submit the CUNY Financial Conflict of Interest at that time.**

Please log into **Cayuse SP** now to complete these required sections:

- **Regulatory Compliance** - regarding human and animal subjects
- **Export Control**
- **Intellectual Property**
- **Proposal Abstract** - a draft version is fine

Your SP number is 21-0505

Please finalize your submission according to this timeline:

- **Cayuse SP:** Complete required sections (see above) as soon as possible, no later than **9 am on Monday, June 21st.**
- **Budget:** Finalize with GA by **9 am on Wednesday, June 23rd.**
- **CUNY Conflict of Interest Forms:** Complete and return by **12 pm on Wednesday, June 23rd.**
- **Departmental Approval:** GA initiates approval routing by **3 pm on Wednesday, June 23rd.**
- **Final proposal review:** Provide all proposal documents for GA review by **5 pm on Monday, June 28th.**

Please note that any requests for proposal assistance (PARS) received within 10 business days of scheduled submission, will not be reviewed for full compliance of the sponsor's guidelines. In such cases, the proposal will be submitted as is.

Logging into Cayuse SP: for tutorial and links, visit CCNY's Cayuse website at: <https://www.ccny.cuny.edu/research/cayuse>

RF APPS Peer Review: The RF APPS team has established a proposal peer review system to provide constructive feedback from colleagues to improve the competitiveness of your proposal. For more details, please contact apps@rfcuny.org

Best,

Afrodita Feratovic

Grants Associate | Pre-Award

Grants and Sponsored Programs 

The City College of New York

160 Convent Avenue | SH – Room 16

New York, NY 10031-9101

(E): aferatovic@ccny.cuny.edu

GSP - <https://www.ccny.cuny.edu/research/gsp>

PARS - <https://www.ccny.cuny.edu/research/pars>

CCNY - Grants and Sponsored Programs

Proposal Assistance Request Summary

Budget Request Number	# 4073
Proposal Title	Effects of simufilam on pathogenesis associated with Parkinson's disease dementia using postmortem brain tissue
PI Name	Hoau-Yan Wang
Department	Physiology & Pharmacology
E-mail	hywang@med.cuny.edu
Phone Number	(212) 6508813
Co-PIs	- - -
Is CCNY the lead?	Yes
Grant Announcement Number	
Agency	AGENCY NOT LISTED CASSAVA Sciences
Submission Due Date	06-30-2021
Project Start Date	08-01-2021
# of years for the budget?	1
Mandatory Cost Sharing	No
Subcontract Information	N/A
Budget Limitations	Yes
	Salary & fringe benefit:
	Principal Investigator:
	\$11,041 (\$7,312 + \$3,729)

Professor Hoau-Yan Wang, Ph.D. requests 5% effort (1.10 Academic months per year). He will design and execute the assays using postmortem brain. He will oversee the data collection and analysis.

Post-doctoral research associate:

Zhe Pei, Ph.D. (1 Calendar months per year) will assist PI in running Immunoprecipitation and Western blotting.

\$ 7,747 (\$ 5,600 + \$ 2,147)

Technician:

Kuo-Chieh Lee, M.S. (2.4 Calendar months per year) will assist PI in tissue processing, cell isolation and myriad of experimental procedures and reagent preparation.

\$ 14,388 (\$ 10,400 + \$ 3,988)

Fringe Benefit

RFCUNY maintains its own fringe benefits program for employees (comparable to those of other academic and non-profit institutions). The cost of providing benefits to employees is included in grants as a direct charge.

To simplify both pre-award budget preparation and post-award accounting procedures, RFCUNY developed a system of Multiple Fringe Benefits Pools. Each grant is charged a flat percentage of each employee's gross annual wages, based on their classification. The percentages represent the best estimate of the actual costs of providing benefits to each employee.

Released Time Faculty:

CUNY Faculty released to work on a grant or contract a rate of 51% is applied to the requested salary support.

A rate of 38% is applied to Full Time/Part Time A employees with an additional .34% of MTA tax.

Specific Budget
Needs

Expendable Supplies:

Antibodies and immunoprecipitation agents

Primary antibodies \$350 x 14 \$ 4,900

protein A/G-conjugated agarose beads x2 \$ 3,224

HRP-secondary antibodies-\$156 x 3 \$ 468

\$ 8,592

Drugs and Chemicals

Phosphatase inhibitor tablets @ \$245 x 2 \$ 490

Protease inhibitor tablets@ \$225 x 2 \$ 450

Digitonin @ \$186/ 500 mg x 2 \$ 372

NP-40 @ \$64/250 ml \$ 64

Bradford reagent \$ 156

\$ 1,532

Electrophoresis and Western blotting equipment and supplies, ECL reagents, Film and Immunohistochemistry

ECL reagent \$490 \$ 490

Methanol \$ 120

Buffer reagents \$ 350

\$ 960

Supplies

Ependoff tubes \$ 250

Pipette tips \$ 200

Cuvettes \$ 100

Gloves \$ 190

\$ 740

Research materials & supplies \$ 11,824

Direct cost \$ 45,000.00

Indirect Costs (25%) \$ 11,250.00

Total \$ 56,250.00

Additional
Comments

Draft Budget
Upload

Grant
Announcement
Upload

RCR Certificate citiCompletionReport713185 (1)-RCR certificate.pdf

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INVESTIGATIONAL RESEARCH AGREEMENT

This Investigational Research Agreement ("Agreement"), effective as of **June 15, 2021**, is entered into by and between Cassava Sciences, Inc. ("Cassava"), a Delaware CUNY whose principal business address is 7801 N. Capital of Texas Highway, Suite 260, Austin, TX 78731 ("Cassava"), and **Hoau-Yan Wang, Ph.D.** located at the **Research Foundation of CUNY (RFCUNY)** of the City College of New York, each a "Party" or collectively, the "Parties."

WHEREAS, Cassava has developed proprietary technology and desires to fund the investigational research of Hoau-Yan Wang, Ph.D., Medical Professor, Physiology & Pharmacology, RFCUNY Medical School ("Researcher") under this Agreement ("Research") in the evaluation of the Cassava's proprietary molecule 'simufilam' ("Research Drug") in accordance with the research entitled: **Effects of simufilam on pathogenesis associated with Parkinson's disease dementia using postmortem brain tissue** ("Protocol"), which is incorporated herein by reference as Attachment A.

WHEREAS, Cassava desires to have such Research conducted by RFCUNY and Researcher in accordance with the terms and conditions of this Agreement; and

NOW, THEREFORE, in consideration of the mutual covenants contained herein, and intending to be legally bound hereby, the Parties hereto agree as follows:

ARTICLE 1: DEFINITIONS

1.1 Confidential Information means and includes all technical information, inventions, software, know-how, methods, techniques, patient records, data and other legally protected or proprietary ideas or materials, whether or not patentable or copyrightable, involving Research Drug or Research that is identified as confidential or proprietary at the time it is delivered or communicated or where Confidential Information is not designated as confidential or confirmed in writing to be confidential, it will still be deemed to be Confidential Information if a person, familiar with the industry, would reasonably believe the information to be confidential in nature based on the circumstances. Any obligation to maintain the confidentiality of Confidential Information will not apply to information that: (a) was known to the receiving Party before receipt from the disclosing Party as evidenced by the receiving Party's written records; (b) is or becomes available to the public through no fault of the receiving Party; (c) is received in good faith by the receiving Party from a third party and is not subject to an obligation of confidentiality owed by the third party to the disclosing Party, or (d) is required to be disclosed by order of governmental authority or a court of

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competent jurisdiction, provided that the receiving Party shall use its best efforts to obtain confidential treatment of such information by the agency or court.

1.2 Intellectual Property means and includes all technical information, inventions, discoveries, software, know-how, methods, techniques, formulae, data, processes and other proprietary ideas, whether or not patentable or copyrightable, that are conceived, discovered, developed or reduced to practice in the conduct of Research.

ARTICLE 2: PERFORMANCE

2.1 RFCUNY and Researcher will perform all the services described herein, or incidental to those described herein, in accordance with the highest standards of clinical research practice. The Research will be conducted in full compliance with this Agreement and in accordance with the Protocol, any Protocol amendments mutually agreed to by the Parties, and all applicable laws and regulations. For clarity it is agreed that RFCUNY and Researcher will only use Cassava's test compounds for the work set forth in the Protocol, unless specifically agreed in writing by Cassava, and Researcher and RFCUNY will return any unused test compounds to the Cassava at the conclusion of the Protocol.

2.2 Performance of the Research under this Agreement shall commence no later than **August 1st, 2021** and Research activities shall be completed on or before **January 31st, 2022**. In case of delayed performance, this Agreement may, at Cassava's option, be extended for subsequent one-month periods until the Research is completed. Cassava shall, in any case, have the option to terminate this Agreement by giving written notice of termination in accordance with Article 7.

The Parties acknowledge that the Researcher will utilize RFCUNY's facilities for this Research.

ARTICLE 3: PAYMENT

3.1 Cassava shall make payments to RFCUNY in accordance with the payment schedule and to the payee as set forth in Attachment B.

3.2 Cassava shall reimburse RFCUNY for all direct and indirect costs incurred by CUNY in connection with the Research up to the amount in Attachment B. Cassava will not be liable for any payment in excess of the amount set forth in Attachment B except upon Cassava's written agreement.

ARTICLE 4: RECORDS AND REPORTS AND CONFIDENTIAL INFORMATION

4.1 All data generated in the Research, including all information required in the Protocol, records, reports, and other work product generated by or on behalf of Researcher in the course of performance of the Research ("Data") shall be the sole and exclusive property of Cassava. The RFCUNY and Researcher may use such Data for their own non-commercial research, publication (subject to article 6) and education purposes in accordance with this Agreement, but will not disclose or transfer any such Data collected under the Protocol to any third party, without the prior written permission of Cassava. All Data collected under the Protocol shall be delivered to Cassava

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by Investigator in a timely manner throughout the performance of this Research, as provided in the Protocol, and in no event later than ten (10) working days after the date of termination of this Agreement or on which Cassava otherwise requests delivery of the Data. Cassava shall have the right to review, publish, disclose and use, any Data developed during the course of this Research as Cassava, in its sole discretion, deems appropriate, including, without limitation, in submission to FDA and other regulatory authorities.

4.2 RFCUNY and Researcher shall not disclose to any other party or use for any purpose other than performance of Research, Cassava's Confidential Information.

ARTICLE 5: INTELLECTUAL PROPERTY

5.1 Title to any Intellectual Property generated in the Research by RFCUNY or Researcher, including but not limited to Intellectual Property relating to Research or use of the Research Drug, or variants thereof, whether or not contemplated by the written description or Protocol of Research ("Research Drug Use"), shall vest exclusively in Cassava. Title to any Intellectual Property developed solely by Cassava shall vest exclusively in Cassava. All rights, title and interests to Intellectual Property developed in the performance of Research shall at all times be owned exclusively and throughout the world by Cassava without demand for further payment by RFCUNY or Researcher. RFCUNY and Researcher agrees that whenever requested to do so by Cassava, it shall, at Cassava's sole cost and expense: give testimony; execute all registrations, applications, assignments, renewals, extensions or other instruments; or take other steps that Cassava shall deem necessary to secure, maintain and protect the intellectual property rights in the services in the United States or any foreign country or to otherwise protect Cassava's interests therein.

The Parties intend and consider the services and intellectual property provided by RFCUNY and Researcher under this Agreement to be works made for hire for Cassava. If for any reason the services are not considered works made for hire under applicable law, RFCUNY and Researcher hereby sells, assigns and transfers exclusively to Cassava and its successors and assigns all rights, title and interest, including goodwill, in and to the intellectual property, including registrations and applications, in all services, and all works based upon, derived from or incorporating all or part of services, and all rights corresponding to the forgoing throughout the world.

5.2 RFCUNY shall promptly report to Cassava in writing any Intellectual Property developed in the performance of Research.

Researcher and all other study personnel are bound or shall have agreed: (a) to comply with the terms of this Agreement; and (b) not to enter into agreements with third parties which would impair their ability to perform Research.

5.3 Nothing in this Agreement shall be interpreted as giving RFCUNY any rights under any intellectual property rights now, or hereafter, owned by Cassava prior to the effective date of this Agreement. Nothing in this Agreement shall be interpreted as giving Cassava any rights under any intellectual property rights now, or hereafter, owned by RFCUNY prior to the effective date of this Agreement.

CONFIDENTIAL**ARTICLE 6: PUBLICATION**

6. It is understood and mutually agreed upon that the study design and Research proposed herein are a collaborative effort by Cassava and RFCUNY and, if appropriate, that both Parties will share in Publication authorship commensurate with intellectual contribution. RFCUNY and Researcher shall be free to publish, present or use any results arising out of the performance of this Agreement ("Publication") for their own instructional, research or publication objectives, provided that such Publication does not disclose any Confidential Information. At least forty-five (45) days prior to submission for publication, presentation or use, RFCUNY and Researcher shall submit to Cassava for review and comment any proposed oral, written, or electronic Publication, which period may be extended for an additional thirty (30) days if requested in writing by Cassava in the event that Cassava provides reasonable need for such extension. Expedited reviews for abstracts or poster presentations may be arranged if mutually agreeable to Cassava, RFCUNY and Researcher. In the event that any proposed Publication contains Confidential Information of Cassava, at the request of Cassava, such information shall be removed. Upon notice to RFCUNY that Cassava reasonably believes that one or more patent applications relating to an Invention (as defined in Article 1.2 hereof) should be filed prior to any Publication, then such Publication will be delayed until such patent application(s) have been filed, provided that RFCUNY and Researcher and Cassava shall cooperate in expeditiously filing any such patent application(s).

ARTICLE 7: TERMINATION

7.1 In addition to termination upon the conclusion of Research as provided in Article 2, either Party may terminate this Agreement effective upon written notice to the other Party, if the other Party breaches any of the terms or conditions of this Agreement and fails to cure such breach within thirty (30) days after receiving written notice thereof. In the event of an incurable breach, the non-breaching Party may terminate this Agreement effective immediately upon written notice to the breaching Party.

7.2 In addition, either Party may terminate this Agreement for any reason upon thirty (30) days prior written notice to the other Party. In such event, RFCUNY and Researcher shall immediately take proper steps to terminate activities in a cost-effective manner.

7.3 In the event of termination of this Agreement prior to its stated term whether for breach or for any other reason whatsoever, RFCUNY shall be entitled to retain from the payments made by Cassava prior to termination RFCUNY's reasonable costs of concluding the work in progress. Allowable costs include, without limitation, all costs or non-cancelable commitments incurred prior to the receipt or issuance, by RFCUNY, of the notice of termination. In the event of termination, RFCUNY and Researcher shall submit a final report of all costs incurred and all funds received under this Agreement within thirty (30) days after the effective termination date. The report shall be accompanied by a check in the amount of any excess of funds advanced over costs and allowable commitments incurred.

7.4 Termination of this Agreement shall not affect the rights and obligations of the Parties accrued prior to the date of termination. The provisions of Article 5, entitled Intellectual Property, Article 6, entitled Publication, Article 8, entitled Disclaimer of Warranties, Indemnification and Article

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11 entitled Miscellaneous, shall survive such termination. Section 4.1 shall survive termination for a period of five (5) years.

ARTICLE 8: REPRESENTATIONS AND WARRANTIES, INDEMNIFICATION

8.1 RFCUNY and Researcher each represent and warrant that:

- (i) they have the legal authority and right to enter into this Agreement;
- (ii) they have no obligations to any other Party which is in conflict with their obligations under this Agreement;
- (iii) they will conduct the Research in accordance with the Protocol in full compliance with all applicable laws and regulations;
- (iv) The Research will be conducted solely at RFCUNY's facilities;
- (v) All representations made, directly or indirectly, by RFCUNY and Researcher to Cassava related to RFCUNY and Researcher qualifications, ability and competence to perform the Services or as set forth in any document or as a part of any other understanding by Cassava in relation thereto, are true and correct to the best of RFCUNY and Researcher knowledge at the time of RFCUNY's execution of this Agreement;
- (vi) they acknowledge that (i) Cassava's Confidential Information may represent material, non-public information of the Cassava, (ii) federal securities laws prohibit anyone who is in possession of material, non-public information of Cassava from purchasing or selling Cassava's securities on the basis of material, non-public information of Cassava and (iii) neither it, its affiliates nor its representatives in possession of material, non-public information of Cassava shall purchase or sell securities of Cassava on the basis of material, non-public information of Cassava during the Agreement Term and for one (1) year thereafter;

8.2 Cassava represents and warrants that: (i) Cassava has the legal authority and right to enter into this Agreement; and (ii) Cassava has no obligation to any other Party which is in conflict with Cassava's obligation under this Agreement.

8.3 Cassava agrees to indemnify RFCUNY and Researcher from any and all liability, loss, or damage they might suffer as a result of claims, demands, costs or judgment against them arising out of or relating to a breach by Cassava of any of its representations, warranties or obligations under this Agreement except to the extent that the RFCUNY's or Researcher's negligent actions or gross omissions contributed to the liability, loss or damage.

8.4 RFCUNY and Researcher agree to indemnify and hold Cassava harmless from any and all liability, loss, or damage it might suffer as a result of claims, demands, costs or judgment which are or alleged to be arising solely out of:

Gross negligence or willful misconduct on the part of RFCUNY or Researcher; or

A breach of its representations, warranties or obligations under this Agreement; or

Services and any other materials or information provided by RFCUNY and Researcher to Cassava, arising from the actual or alleged infringement by the services or software products used by RFCUNY and Researcher in connection with the services of any third-

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party's intellectual property rights including, but not limited to, copyrights, trademarks, trade names, service marks or patent rights.

8.5 Each Party's agreement to indemnify and hold the other harmless is conditioned on the indemnified Party:

Providing written notice to the indemnifying Party of any claim, demand or action arising out of the Indemnified activities within thirty (30) days after the indemnified Party has knowledge of such claim, demand or action;

Permitting the indemnifying Party to assume full responsibility to investigate, prepare for and defend against any such claim or demand;

Assisting the indemnifying Party, at the indemnifying Party's reasonable expense, in the investigation of preparation for and defense of any such claim or demand;

Not compromising or settling such claim or demand without the indemnifying Party's written consent.

ARTICLE 9: NOTICES

9.1 Notices under this Agreement shall be in writing and sent only by prepaid, recognized public courier and addressed as follows:

If to RFCUNY:

<**CONTACT INFORMATION**>

If to Cassava:

Cassava Sciences, Inc.
Attention President and CEO
7801 N. Capital of Texas Highway, Suite 260
Austin, TX 78731
512-501-2480

ARTICLE 10: PUBLICITY

10.1 Neither Party will issue a press release or make any other public statement that references this Agreement or identify the other in any promotional advertising or other promotional materials to be disseminated to the public or use the name of Researcher, employee of RFCUNY, or any trademark, service mark, trade name, or symbol of the other without the other's prior written consent, except to the extent required by law or federal agencies.

CONFIDENTIAL**ARTICLE 11: MISCELLANEOUS**

11.1 This Agreement shall in all respects be governed by and construed in accordance with the laws in force in the State of New York.

11.2 Neither RFCUNY nor Researcher may assign this Agreement without the prior written consent of Cassava. Cassava may assign this Agreement with written notice to the RFCUNY.

11.3 If any provision of this Agreement becomes or is declared illegal, invalid, or unenforceable, such provision will be divisible from this Agreement and will be deemed to be deleted from this Agreement. If such deletion substantially alters the basis of this Agreement the Parties will negotiate in good faith to amend the provisions of this Agreement to give effect to the original intent of the Parties.

11.4 RFCUNY and Cassava are independent contractors and neither is an agent, joint venturer, or partner of the other.

11.5 In the event of any inconsistencies between the terms of this Agreement and the documents referenced or incorporated herein, the terms of this Agreement will prevail.

11.6 This Agreement represents the entire agreement and understanding between the Parties with respect to its subject matter and supersedes any prior and/or contemporaneous discussions, representations, or agreements, whether written or oral, of the Parties regarding this subject matter.

11.7 Amendments or changes to this Agreement must be in writing and signed by duly authorized representatives of the Parties.

11.8 Cassava and its designated representatives shall have the right, upon reasonable notice, to audit all applicable records of RFCUNY for the purpose of determining RFCUNY's compliance with the obligations set forth in this Section. This right to audit shall extend throughout the Agreement Term and for one (1) year after the (i) expiration or termination of this Agreement or (ii) resolution of any dispute between Cassava and RFCUNY hereunder.

11.9 Each Party may sign this Agreement via electronic signature or deliver a signed copy by electronic mail. Signatures obtained in this manner shall be legally binding.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be signed as of the dates entered below.

[SIGNATURE PAGE FOLLOWS]

CONFIDENTIAL

RFCUNY:

Signature:

Date:

Name:

Title:

RESEARCHER:

Signature:

Date:

Name: Hoau-Yan Wang, Ph.D.,
Title: Medical Professor, CUNY

CASSAVA SCIENCES, Inc:

Signature:

Date:

Remi Barbier
President & CEO, Cassava Sciences, Inc.

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ATTACHMENTS:

Attachment A – Protocol

Study Title: **Effects of simufilam on pathogenesis associated with Parkinson's disease dementia using postmortem brain tissue**

1. Executive Summary

Dementia and mild cognitive impairment are prevalent in advanced stages of Parkinson disease (PD). Similar to Alzheimer's disease (AD) dementia, there is no effective treatment for dementia associated with PD. In addition to Lewy pathology in the limbic and cortical regions, the molecular mechanisms contributing to cognitive decline in PD remain elusive. Despite with overlapping symptoms, AD and PD appear to differentially affect cognitive domains, although, as in AD, low CSF amyloid- β 42 (A β 42) also predicts future cognitive decline and dementia in PD. We propose to test a novel therapeutic agent, simufilam that binds pathological form of filamin A (FLNA) to reduce A β 42 toxic signaling to hyper-phosphorylation of tau via α 7nAChR, neuroinflammation by TLR4 and brain insulin resistance. Specifically, we aim to use an established ex vivo stimulation method in postmortem brains from PD without and with dementia as well as neurologically normal controls to assess the effects of simufilam on (1) A β 42-induced FLNA association with α 7nAChRs and TLR4, (2) A β 42- α 7nAChR linkage, (3) insulin signaling, (4) A β 42-associated α -synuclein levels, (5) phosphorylated tau, and (6) inflammatory cytokine levels (TNF α , IL-6 and IL-1 β). Improvements in these measures by simufilam in vitro treatment would add support to the rationale for testing simufilam in patients with Parkinson's disease dementia.

2. Plan of Work

This study will use 8 sets of posterior parietal cortices (PPCs) from matched control, Parkinson's disease, Parkinson's disease with mild cognitive impairment (MCI), and Parkinson's disease with dementia cases. Approximately 20 mg of postmortem brain tissues will be prepared to 100 μ m x 100 μ m x 3 mm prisms using a chilled McIlwain tissue chopper. PPC prisms will be washed with oxygenated 0.3 mM Mg²⁺-containing Krebs' Ringer (LMKB) 3 times and incubated with 1 nM Simufilam containing LMKB for 1 hour and oxygenated with 95% O₂/5% CO₂ for 1 min every 15 min as described previously (Wang et al., 2017). The treated PPC tissues will be used to assess: (1) **FLNA- α 7nAChR/TLR4 and A β 42 - α -synuclein complex levels.** The α 7nAChR and TLR4 levels in the anti-FLNA immunoprecipitates will be measured by immunoblotting with specific antibodies, and the levels of α -synuclein in the anti-A β 42 immunoprecipitates will be measured with an α -synuclein specific antibody. Each will be quantified by densitometric quantitation.

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Equally divided tissue will be incubated with 10 μ M NMDA/ 1 μ M glycine to assess
(2) **NMDAR signaling**: The levels of pY⁴¹⁶Src, pY⁴⁰²PyK2, nNOS, PLC- γ , and PKC γ in the anti-NR1 immunoprecipitate by immunoblotting with specific antibodies. The levels of pY¹²⁴⁶-NR2A will also be determined.

The other portions of divided tissue will be incubated with 1 nM insulin to examine
(3) **Insulin signaling**: The levels of pY^{1150/1151}IR β and IRS-1 will be measured by coimmunoprecipitation and detection with specific antibodies.

3. Quality Statement

It is understood that this work is not subject to GLP requirements, but will be performed according to sound scientific principles, in compliance with City University of New York Medical School standard operating procedures, and with review by supervisory technical staff.

4. Timing

The project can be started in August 1st, 2021 and is expected to finish before January 31st, 2022.

Summary of Costs and Payment Schedule

A summary of costs and payment schedule is listed in Attachment B.

Wet lab and statistical analyses work will be performed at:

Department of Molecular, Cellular & Biomedical Sciences
Center for Discovery and Innovation
CDI-3370 85 St. Nicholas Terrace,
New York, NY 10031

All accounting activities will be processed at:

Department of Molecular, Cellular & Biomedical Sciences
City University of New York School of Medicine
160 Convent Avenue
New York, NY 10031

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3. Summary of Costs and Payment Schedule

Cassava will pay RFCUNY 25% upon signing of this contract, 50% upon completion of the experiments, and the final 25% upon receipt of draft report. Payments will be made within 30 days of invoice.

Total contract amount: **\$56,250**

CONFIDENTIAL**ATTACHMENTS:****Attachment B – Payment and Budget****Detailed Budget:****Salary & fringe benefit:**

Principal Investigator:

\$11,041 (\$7,312 + \$3,729)

Professor Hoau-Yan Wang, Ph.D. requests 5% effort (1.10 Academic months per year). He will design and execute the assays using postmortem brain. He will oversee the data collection and analysis.

Post-doctoral research associate:

Zhe Pei, Ph.D. (1 Calendar months per year) will assist PI in running Immunoprecipitation and Western blotting.

\$ 7,747 (\$ 5,600 + \$ 2,147)

Technician:

Kuo-Chieh Lee, M.S. (2.4 Calendar months per year) will assist PI in tissue processing, cell isolation and myriad of experimental procedures and reagent preparation.

\$ 14,388 (\$ 10,400 + \$ 3,988)***Fringe Benefit***

RFCUNY maintains its own fringe benefits program for employees (comparable to those of other academic and non-profit institutions). The cost of providing benefits to employees is included in grants as a direct charge.

To simplify both pre-award budget preparation and post-award accounting procedures, RFCUNY developed a system of Multiple Fringe Benefits Pools. Each grant is charged a flat percentage of each employee's gross annual wages, based on their classification. The percentages represent the best estimate of the actual costs of providing benefits to each employee.

Released Time Faculty:

CUNY Faculty released to work on a grant or contract a rate of 51% is applied to the requested salary support.

A rate of 38% is applied to Full Time/Part Time A employees with an additional .34% of MTA tax.

Expendable Supplies:

Antibodies and immunoprecipitation agents

Primary antibodies \$350 x 14	\$ 4,900
protein A/G-conjugated agarose beads x2	\$ 3,224
HRP-secondary antibodies-\$156 x 3	\$ 468

\$ 8,592

Drugs and Chemicals

Phosphatase inhibitor tablets @ \$245 x 2	\$ 490
Protease inhibitor tablets@ \$225 x 2	\$ 450
Digitonin @ \$186/ 500 mg x 2	\$ 372
NP-40 @ \$64/250 ml	\$ 64
Bradford reagent	\$ 156

\$ 1,532

Electrophoresis and Western blotting equipment and supplies, ECL reagents, Film and Immunohistochemistry

ECL reagent \$490	\$ 490
Methanol	\$ 120
Buffer reagents	\$ 350

\$ 960

Supplies

Ependoff tubes	\$ 250
Pipette tips	\$ 200
Cuvettes	\$ 100
Gloves	\$ 190

\$ 740

Research materials & supplies

\$ 11,824

Direct cost

\$ 45,000.00

Indirect Costs (25%)

\$ 11,250.00

Total

\$ 56,250.00

From: Tricia Mayhew-Noel
Sent time: 07/27/2021 01:16:42 PM
To: Hoau-yan Wang
Cc: Maria D Lima; Holli-Anne S Tai; Alexander King
Subject: Fw: FCOI Determination -- PI: Hoau-Yan Wang (Cassava Sciences)
Attachments: FCOI_Wang_Cassava Sciences_Form2.pdf FCOI_Wang_Cassava Sciences_Form1.pdf NoA 1_Investigational Research Contract CUNY 17 June 2021.docx

Dear Professor Wang,

On a previous Conflict of Interest application, titled, "Linking peripheral and brain insulin resistance to AD neuropathology and cognition", which was funded by National Institute of Aging NIH/Rush University Medical Center, you stated the following to Dr. Lima, CCNY's College Conflicts Officer, which was indicated in her review of your application and in the determination of a COI. Please confirm whether this information is still applicable or whether it should be updated for this new grant being funded by Cassava.

"The PI serves as a consultant and a member of the scientific advisory board of CASSAVA for preclinical development and clinical trials of their proprietary drug and diagnostic (biomarker) candidates in central nervous diseases, especially the Alzheimer's disease . Together with other experts in the field, he answers their scientific questions to facilitate CASSAVA's drug and diagnostic development in preclinical testing and clinical trial design. He also functions as CASSAVA's academic collaborator in which he participates as a co-PI or co-investigator in ongoing NIH-funded SBIR and STTR (R41, R42, R44) clinical trial projects. In these projects, he is responsible for analyzing patient samples for CASSAVA. CASSAVA owns the intellectual properties (patents) of all the small molecule drug and diagnostic candidates.

Thanks for your response.

Best Regards,
Tricia

Tricia Mayhew-Noel, MS

Director, Research Compliance & Ethics
Division for Research
Shepard Hall Room 108B
160 Convent Ave
New York, NY 10031
1-212-650-7902 (phone)
1-212-650-8344 (fax)
tmayhewnoel@ccny.cuny.edu (email)
Zoom link: <https://ccny.zoom.us/my/tmayhewnoel>
<http://www.ccny.cuny.edu/irb/> (website)

From: Holli-Anne S Tai
Sent: Tuesday, June 29, 2021 4:15 PM
To: Tricia Mayhew-Noel
Cc: Awards; Hoau-yan Wang
Subject: FCOI Determination -- PI: Hoau-Yan Wang (Cassava Sciences)

Dear Tricia,

Please see attached FCOI supplement for Professor Wang's new project with Cassava Sciences. May you please let me know if a management plan will be required or if anything else is needed for further determination?

Thank you,

Holli-Anne Tai
Grants Associate
Grants and Sponsored Programs
The City College of New York
160 Convent Avenue | SH - Room 16
New York, NY 10031
Ph: 212-650-5418 | F: 212-650-7906
GSP - <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <http://www.ccny.cuny.edu/research/pars.cfm>

CUNY Significant Financial Interest (SFI) Disclosure Form For Sponsored Projects NOT Funded by the Public Health Service

* to be completed by each investigator on the project

Name of Investigator¹: **Hoau-Yan Wang**

Role of Investigator (project director / **PI** / co-PI / consultant / etc.):

Phone: **212-650-8813**

Email: **hywang@med.cuny.edu**

CUNY College/Site of Research: **CDI-3211**

Title of Sponsored Project²: **Preclinical assessing the effectiveness of Simufilam on cognitively impaired Parkinson's disease cases using postmortem brains**

Cassava Sciences

Funding Source:

Disclosure submission for:

☒ New funding proposal or application

☐ Annual progress report

☐ Material change in a previously disclosed SFI

☐ Discovery or acquisition of a new SFI

☐ New investigator joining an ongoing sponsored project at CUNY

Please indicate whether **you, your spouse, or your dependent children** have any of the following financial interests that may reasonably be related to your institutional responsibilities³:

Please note that this form must be completed by all individuals responsible for the design, conduct, or reporting of sponsored project.

¹ **Investigator:** The project director, principal investigator, co-principal investigators, and any other person, regardless of title of position, who is responsible for the design, conduct, or reporting of a University Sponsored Project, which may include, for example, collaborators or consultants, whether or not such individual is employed by the University or the Research Foundation.

² **Sponsored Project:** Projects or activities involving research, creative activity, training, instruction or service undertaken within or on behalf of the University pursuant to funding or other support from an External Sponsor.

³ **Institutional Responsibilities:** An investigator's professional responsibilities on behalf of the University, performed in the course of and within the scope of the Investigator's appointment or employment by the University, which may include, for example, activities such as research, research consultation, teaching, professional practice, institutional administration, committee memberships, and service on panels such as Institutional Review Boards, Institutional Animal Care and Use Committees or Institutional Biosafety Committees.

1. A total of salary, any other payment for services (for example, consulting fees or honoraria), and royalties expected to be received in the next 12 months that exceeds \$10,000, when aggregated for you, your spouse, and your dependent children, excluding any salary, royalties, or other remuneration from CUNY and income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities or from service on advisory committees or review panels for such entities.	YesX No <input type="checkbox"/>
2. An equity interest (for example, stocks, stock options, or other ownership interests) in any single entity that, when aggregated for you, your spouse, and your dependent children, exceeds \$10,000 in value, as determined through reference to public prices or other reasonable measures of fair market value, <u>AND</u> represents more than a five percent (5%) ownership interest in the entity.	YesX No <input type="checkbox"/>
3. Intellectual property rights and interests (for example, patents, copyrights).	Yes <input type="checkbox"/> No <input type="checkbox"/>

For yourself ONLY:

4. If you are responsible for developing, discovering, or creating CUNY-owned intellectual property, are you aware of the acquisition or intention to acquire ownership of, or a license to, that intellectual property by any corporation, partnership, or other legal entity (excluding entities controlled by the U.S. government, the State or City of New York, or CUNY) in or from which you have a financial interest described in any of Items 1 or 2 above? NOTE: If you answered "Yes" to this question you must also complete the CUNY Acquisition of or License to CUNY Intellectual Property (CALCIP) form and submit it to your College Conflicts Officer and the Director of the CUNY Technology Commercialization Office (TCO).	Yes <input type="checkbox"/> No X N/A <input type="checkbox"/>
5. Do you teach, supervise, or otherwise have control over any student or postdoctoral associate at CUNY who might be involved in work for any corporation, partnership, or other legal entity (excluding entities controlled by the U.S. government, the State or City of New York, or CUNY) in or from which you have a financial interest described in any of Items 1 or 2 above?	Yes <input type="checkbox"/> No X

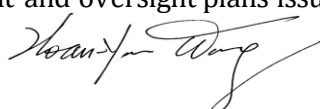
If you responded "yes" to any of the questions above, you must also complete a CUNY Significant Financial Interest Supplement Form. This Form, and the Supplement Form if required, should be submitted to your College Conflicts Officer, with a copy to your Grants Officer.

If you have any questions about this Form or the information it seeks, please refer to the [sponsored projects conflict of interest web site](#) or contact your [College Conflicts Officer](#).

Agreement & Signature:

By signing this form, I certify the following:

- The above statements are complete, true and accurate.
- I will submit an updated Form annually, prior to submission of annual progress reports; and also within 30 days of any material change to the above-disclosed Significant Financial Interest(s) or discovering or acquiring a new Significant Financial Interest.
- I will comply with all applicable regulations, CUNY policies, sponsor requirements, and any conflict of interest management and oversight plans issued by CUNY.



6/29/2021

Signature

Date

CUNY Significant Financial Interest Supplement Form for Sponsored Projects NOT Funded by the Public Health Service

Name of Investigator: **Hoau-Yan Wang**

Role of Investigator (project director / **PI** / co-PI / consultant / etc.):

CUNY College/Site of Research: **CDI-3211**

Title of Sponsored Project: **Preclinical assessing the effectiveness of Simufilam on cognitively impaired Parkinson's disease cases using postmortem brains.**

Funding Source: **Cassava Sciences**

Does this project involve human subject research? Yes ☐ No ☒

Please provide requested details regarding your positive responses made on the CUNY Significant Financial Interest Disclosure Form and, if necessary, use additional Supplement Forms:

1. A total of salary, any other payment for services (for example, consulting fees or honoraria), and royalties expected to be received in the next 12 months that exceeds \$10,000, when aggregated for you, your spouse, and your dependent children, excluding any remuneration from CUNY and income from engagements sponsored by public or nonprofit entities or from service on advisory committees or review panels for such entities:

i) Name of person or persons (and relationship to self) to whom the salary or payment is expected to be made:

Hoau-Yan Wang (self)

Name of entity:

Cassava Sciences

Nature of salary, payment for other services, or royalties (description of work performed for remuneration):

Consultancy

Amount of salary, payment for other services, or royalties expected to be received in the next 12 months:

\$24,000

Relationship to your institutional responsibilities:

NONE

ii) Name of person or persons (and relationship to self) to whom the salary or payment is expected to be made:

Name of entity:

Nature of salary, payment for other services, or royalties:

Amount of salary, payment for other services, or royalties expected to be received in the next 12 months:

Relationship to your institutional responsibilities:

2. An equity interest (for example, stocks, stock options, or other ownership interests) in any single entity that, when aggregated for you, your spouse, and your dependent children, exceeds \$10,000 in value, as determined through reference to public prices or other reasonable measures of fair market value, AND represents more than a five percent (5%) ownership interest in the entity:

Name of person or persons (and relationship to self) who hold(s) the equity interest:

Hoau-Yan Wang (Self)

Name of entity:

Cassava Sciences

Type of equity interest:

Stock & Stock options

Current value of equity interest and/or percentage of ownership interest in the entity, as applicable:

\$125,000

Relationship to your institutional responsibilities:

NONE

3. Intellectual property rights and interests (for example, patents, copyrights):

Owner(s) of the intellectual property:

N/A

Description of the intellectual property:

Description of any royalties or income you currently receive or may receive in the future:

Relationship to your institutional responsibilities:

4. Acquisition or intention to acquire ownership of, or a license to, CUNY-owned intellectual property by an entity in which you have a financial interest described in items 1 or 2 above:

Name of entity: **N/A**

Description of CUNY-owned intellectual property and your role in developing, discovering, or creating it:

Description of the interest that the entity has acquired or is intending to acquire:

5. Teaching, supervision, or otherwise having control over any student or postdoctoral associate at CUNY who might be involved in work for an entity in which you have a financial interest described in items 1 or 2 above:

Name of entity: **NONE**

Name of the student(s) or post doctoral associate(s) (please specify whether these are graduate students or post-docs):

Planned involvement of the student(s) or post-doctoral associate(s):

State your specific relationship with the student(s) involved in the project, (e.g. instructor, faculty advisor, thesis supervision, etc.):

Agreement & Signature:

By signing this form, I certify to the following:

- **All of the information contained herein is true, accurate and complete.**
- **As required, I will submit an updated Form annually, prior to submission of annual progress reports; and also within 30 days of any material change to the above-disclosed Significant Financial Interest(s) or discovering or acquiring a new Significant Financial Interest.**
- **I will comply with all applicable regulations, CUNY policies, sponsor requirements and any conflict of interest management and oversight plans issued by CUNY.**



6/29/2021

Signature

Date

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INVESTIGATIONAL RESEARCH AGREEMENT

This Investigational Research Agreement ("Agreement"), effective as of **June 15, 2021**, is entered into by and between Cassava Sciences, Inc. ("Cassava"), a Delaware CUNY whose principal business address is 7801 N. Capital of Texas Highway, Suite 260, Austin, TX 78731 ("Cassava"), and **Hoau-Yan Wang, Ph.D.** located at the **Research Foundation of CUNY (RFCUNY)** of the City College of New York, each a "Party" or collectively, the "Parties."

WHEREAS, Cassava has developed proprietary technology and desires to fund the investigational research of Hoau-Yan Wang, Ph.D., Medical Professor, Physiology & Pharmacology, RFCUNY Medical School ("Researcher") under this Agreement ("Research") in the evaluation of the Cassava's proprietary molecule 'simufilam' ("Research Drug") in accordance with the research entitled: **Effects of simufilam on pathogenesis associated with Parkinson's disease dementia using postmortem brain tissue** ("Protocol"), which is incorporated herein by reference as Attachment A.

WHEREAS, Cassava desires to have such Research conducted by RFCUNY and Researcher in accordance with the terms and conditions of this Agreement; and

NOW, THEREFORE, in consideration of the mutual covenants contained herein, and intending to be legally bound hereby, the Parties hereto agree as follows:

ARTICLE 1: DEFINITIONS

1.1 Confidential Information means and includes all technical information, inventions, software, know-how, methods, techniques, patient records, data and other legally protected or proprietary ideas or materials, whether or not patentable or copyrightable, involving Research Drug or Research that is identified as confidential or proprietary at the time it is delivered or communicated or where Confidential Information is not designated as confidential or confirmed in writing to be confidential, it will still be deemed to be Confidential Information if a person, familiar with the industry, would reasonably believe the information to be confidential in nature based on the circumstances. Any obligation to maintain the confidentiality of Confidential Information will not apply to information that: (a) was known to the receiving Party before receipt from the disclosing Party as evidenced by the receiving Party's written records; (b) is or becomes available to the public through no fault of the receiving Party; (c) is received in good faith by the receiving Party from a third party and is not subject to an obligation of confidentiality owed by the third party to the disclosing Party, or (d) is required to be disclosed by order of governmental authority or a court of

competent jurisdiction, provided that the receiving Party shall use its best efforts to obtain confidential treatment of such information by the agency or court.

1.2 Intellectual Property means and includes all technical information, inventions, discoveries, software, know-how, methods, techniques, formulae, data, processes and other proprietary ideas, whether or not patentable or copyrightable, that are conceived, discovered, developed or reduced to practice in the conduct of Research.

ARTICLE 2: PERFORMANCE

2.1 RFCUNY and Researcher will perform all the services described herein, or incidental to those described herein, in accordance with the highest standards of clinical research practice. The Research will be conducted in full compliance with this Agreement and in accordance with the Protocol, any Protocol amendments mutually agreed to by the Parties, and all applicable laws and regulations. For clarity it is agreed that RFCUNY and Researcher will only use Cassava's test compounds for the work set forth in the Protocol, unless specifically agreed in writing by Cassava, and Researcher and RFCUNY will return any unused test compounds to the Cassava at the conclusion of the Protocol.

2.2 Performance of the Research under this Agreement shall commence no later than **August 1st, 2021** and Research activities shall be completed on or before **January 31st, 2022**. In case of delayed performance, this Agreement may, at Cassava's option, be extended for subsequent one-month periods until the Research is completed. Cassava shall, in any case, have the option to terminate this Agreement by giving written notice of termination in accordance with Article 7.

The Parties acknowledge that the Researcher will utilize RFCUNY's facilities for this Research.

ARTICLE 3: PAYMENT

3.1 Cassava shall make payments to RFCUNY in accordance with the payment schedule and to the payee as set forth in Attachment B.

3.2 Cassava shall reimburse RFCUNY for all direct and indirect costs incurred by CUNY in connection with the Research up to the amount in Attachment B. Cassava will not be liable for any payment in excess of the amount set forth in Attachment B except upon Cassava's written agreement.

ARTICLE 4: RECORDS AND REPORTS AND CONFIDENTIAL INFORMATION

4.1 All data generated in the Research, including all information required in the Protocol, records, reports, and other work product generated by or on behalf of Researcher in the course of performance of the Research ("Data") shall be the sole and exclusive property of Cassava. The RFCUNY and Researcher may use such Data for their own non-commercial research, publication (subject to article 6) and education purposes in accordance with this Agreement, but will not disclose or transfer any such Data collected under the Protocol to any third party, without the prior written permission of Cassava. All Data collected under the Protocol shall be delivered to Cassava

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by Investigator in a timely manner throughout the performance of this Research, as provided in the Protocol, and in no event later than ten (10) working days after the date of termination of this Agreement or on which Cassava otherwise requests delivery of the Data. Cassava shall have the right to review, publish, disclose and use, any Data developed during the course of this Research as Cassava, in its sole discretion, deems appropriate, including, without limitation, in submission to FDA and other regulatory authorities.

4.2 RFCUNY and Researcher shall not disclose to any other party or use for any purpose other than performance of Research, Cassava's Confidential Information.

ARTICLE 5: INTELLECTUAL PROPERTY

5.1 Title to any Intellectual Property generated in the Research by RFCUNY or Researcher, including but not limited to Intellectual Property relating to Research or use of the Research Drug, or variants thereof, whether or not contemplated by the written description or Protocol of Research ("Research Drug Use"), shall vest exclusively in Cassava. Title to any Intellectual Property developed solely by Cassava shall vest exclusively in Cassava. All rights, title and interests to Intellectual Property developed in the performance of Research shall at all times be owned exclusively and throughout the world by Cassava without demand for further payment by RFCUNY or Researcher. RFCUNY and Researcher agrees that whenever requested to do so by Cassava, it shall, at Cassava's sole cost and expense: give testimony; execute all registrations, applications, assignments, renewals, extensions or other instruments; or take other steps that Cassava shall deem necessary to secure, maintain and protect the intellectual property rights in the services in the United States or any foreign country or to otherwise protect Cassava's interests therein.

The Parties intend and consider the services and intellectual property provided by RFCUNY and Researcher under this Agreement to be works made for hire for Cassava. If for any reason the services are not considered works made for hire under applicable law, RFCUNY and Researcher hereby sells, assigns and transfers exclusively to Cassava and its successors and assigns all rights, title and interest, including goodwill, in and to the intellectual property, including registrations and applications, in all services, and all works based upon, derived from or incorporating all or part of services, and all rights corresponding to the forgoing throughout the world.

5.2 RFCUNY shall promptly report to Cassava in writing any Intellectual Property developed in the performance of Research.

Researcher and all other study personnel are bound or shall have agreed: (a) to comply with the terms of this Agreement; and (b) not to enter into agreements with third parties which would impair their ability to perform Research.

5.3 Nothing in this Agreement shall be interpreted as giving RFCUNY any rights under any intellectual property rights now, or hereafter, owned by Cassava prior to the effective date of this Agreement. Nothing in this Agreement shall be interpreted as giving Cassava any rights under any intellectual property rights now, or hereafter, owned by RFCUNY prior to the effective date of this Agreement.

ARTICLE 6: PUBLICATION

6. It is understood and mutually agreed upon that the study design and Research proposed herein are a collaborative effort by Cassava and RFCUNY and, if appropriate, that both Parties will share in Publication authorship commensurate with intellectual contribution. RFCUNY and Researcher shall be free to publish, present or use any results arising out of the performance of this Agreement ("Publication") for their own instructional, research or publication objectives, provided that such Publication does not disclose any Confidential Information. At least forty-five (45) days prior to submission for publication, presentation or use, RFCUNY and Researcher shall submit to Cassava for review and comment any proposed oral, written, or electronic Publication, which period may be extended for an additional thirty (30) days if requested in writing by Cassava in the event that Cassava provides reasonable need for such extension. Expedited reviews for abstracts or poster presentations may be arranged if mutually agreeable to Cassava, RFCUNY and Researcher. In the event that any proposed Publication contains Confidential Information of Cassava, at the request of Cassava, such information shall be removed. Upon notice to RFCUNY that Cassava reasonably believes that one or more patent applications relating to an Invention (as defined in Article 1.2 hereof) should be filed prior to any Publication, then such Publication will be delayed until such patent application(s) have been filed, provided that RFCUNY and Researcher and Cassava shall cooperate in expeditiously filing any such patent application(s).

ARTICLE 7: TERMINATION

7.1 In addition to termination upon the conclusion of Research as provided in Article 2, either Party may terminate this Agreement effective upon written notice to the other Party, if the other Party breaches any of the terms or conditions of this Agreement and fails to cure such breach within thirty (30) days after receiving written notice thereof. In the event of an incurable breach, the non-breaching Party may terminate this Agreement effective immediately upon written notice to the breaching Party.

7.2 In addition, either Party may terminate this Agreement for any reason upon thirty (30) days prior written notice to the other Party. In such event, RFCUNY and Researcher shall immediately take proper steps to terminate activities in a cost-effective manner.

7.3 In the event of termination of this Agreement prior to its stated term whether for breach or for any other reason whatsoever, RFCUNY shall be entitled to retain from the payments made by Cassava prior to termination RFCUNY's reasonable costs of concluding the work in progress. Allowable costs include, without limitation, all costs or non-cancelable commitments incurred prior to the receipt or issuance, by RFCUNY, of the notice of termination. In the event of termination, RFCUNY and Researcher shall submit a final report of all costs incurred and all funds received under this Agreement within thirty (30) days after the effective termination date. The report shall be accompanied by a check in the amount of any excess of funds advanced over costs and allowable commitments incurred.

7.4 Termination of this Agreement shall not affect the rights and obligations of the Parties accrued prior to the date of termination. The provisions of Article 5, entitled Intellectual Property, Article 6, entitled Publication, Article 8, entitled Disclaimer of Warranties, Indemnification and Article

11 entitled Miscellaneous, shall survive such termination. Section 4.1 shall survive termination for a period of five (5) years.

ARTICLE 8: REPRESENTATIONS AND WARRANTIES, INDEMNIFICATION

8.1 RFCUNY and Researcher each represent and warrant that:

- (i) they have the legal authority and right to enter into this Agreement;
- (ii) they have no obligations to any other Party which is in conflict with their obligations under this Agreement;
- (iii) they will conduct the Research in accordance with the Protocol in full compliance with all applicable laws and regulations;
- (iv) The Research will be conducted solely at RFCUNY's facilities;
- (v) All representations made, directly or indirectly, by RFCUNY and Researcher to Cassava related to RFCUNY and Researcher qualifications, ability and competence to perform the Services or as set forth in any document or as a part of any other understanding by Cassava in relation thereto, are true and correct to the best of RFCUNY and Researcher knowledge at the time of RFCUNY's execution of this Agreement;
- (vi) they acknowledge that (i) Cassava's Confidential Information may represent material, non-public information of the Cassava, (ii) federal securities laws prohibit anyone who is in possession of material, non-public information of Cassava from purchasing or selling Cassava's securities on the basis of material, non-public information of Cassava and (iii) neither it, its affiliates nor its representatives in possession of material, non-public information of Cassava shall purchase or sell securities of Cassava on the basis of material, non-public information of Cassava during the Agreement Term and for one (1) year thereafter;

8.2 Cassava represents and warrants that: (i) Cassava has the legal authority and right to enter into this Agreement; and (ii) Cassava has no obligation to any other Party which is in conflict with Cassava's obligation under this Agreement.

8.3 Cassava agrees to indemnify RFCUNY and Researcher from any and all liability, loss, or damage they might suffer as a result of claims, demands, costs or judgment against them arising out of or relating to a breach by Cassava of any of its representations, warranties or obligations under this Agreement except to the extent that the RFCUNY's or Researcher's negligent actions or gross omissions contributed to the liability, loss or damage.

8.4 RFCUNY and Researcher agree to indemnify and hold Cassava harmless from any and all liability, loss, or damage it might suffer as a result of claims, demands, costs or judgment which are or alleged to be arising solely out of:

Gross negligence or willful misconduct on the part of RFCUNY or Researcher; or

A breach of its representations, warranties or obligations under this Agreement; or

Services and any other materials or information provided by RFCUNY and Researcher to Cassava, arising from the actual or alleged infringement by the services or software products used by RFCUNY and Researcher in connection with the services of any third-

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party's intellectual property rights including, but not limited to, copyrights, trademarks, trade names, service marks or patent rights.

8.5 Each Party's agreement to indemnify and hold the other harmless is conditioned on the indemnified Party:

Providing written notice to the indemnifying Party of any claim, demand or action arising out of the Indemnified activities within thirty (30) days after the indemnified Party has knowledge of such claim, demand or action;

Permitting the indemnifying Party to assume full responsibility to investigate, prepare for and defend against any such claim or demand;

Assisting the indemnifying Party, at the indemnifying Party's reasonable expense, in the investigation of preparation for and defense of any such claim or demand;

Not compromising or settling such claim or demand without the indemnifying Party's written consent.

ARTICLE 9: NOTICES

9.1 Notices under this Agreement shall be in writing and sent only by prepaid, recognized public courier and addressed as follows:

If to RFCUNY:

<**CONTACT INFORMATION**>

If to Cassava:

Cassava Sciences, Inc.
Attention President and CEO
7801 N. Capital of Texas Highway, Suite 260
Austin, TX 78731
512-501-2480

ARTICLE 10: PUBLICITY

10.1 Neither Party will issue a press release or make any other public statement that references this Agreement or identify the other in any promotional advertising or other promotional materials to be disseminated to the public or use the name of Researcher, employee of RFCUNY, or any trademark, service mark, trade name, or symbol of the other without the other's prior written consent, except to the extent required by law or federal agencies.

CONFIDENTIAL**ARTICLE 11: MISCELLANEOUS**

11.1 This Agreement shall in all respects be governed by and construed in accordance with the laws in force in the State of New York.

11.2 Neither RFCUNY nor Researcher may assign this Agreement without the prior written consent of Cassava. Cassava may assign this Agreement with written notice to the RFCUNY.

11.3 If any provision of this Agreement becomes or is declared illegal, invalid, or unenforceable, such provision will be divisible from this Agreement and will be deemed to be deleted from this Agreement. If such deletion substantially alters the basis of this Agreement the Parties will negotiate in good faith to amend the provisions of this Agreement to give effect to the original intent of the Parties.

11.4 RFCUNY and Cassava are independent contractors and neither is an agent, joint venturer, or partner of the other.

11.5 In the event of any inconsistencies between the terms of this Agreement and the documents referenced or incorporated herein, the terms of this Agreement will prevail.

11.6 This Agreement represents the entire agreement and understanding between the Parties with respect to its subject matter and supersedes any prior and/or contemporaneous discussions, representations, or agreements, whether written or oral, of the Parties regarding this subject matter.

11.7 Amendments or changes to this Agreement must be in writing and signed by duly authorized representatives of the Parties.

11.8 Cassava and its designated representatives shall have the right, upon reasonable notice, to audit all applicable records of RFCUNY for the purpose of determining RFCUNY's compliance with the obligations set forth in this Section. This right to audit shall extend throughout the Agreement Term and for one (1) year after the (i) expiration or termination of this Agreement or (ii) resolution of any dispute between Cassava and RFCUNY hereunder.

11.9 Each Party may sign this Agreement via electronic signature or deliver a signed copy by electronic mail. Signatures obtained in this manner shall be legally binding.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be signed as of the dates entered below.

[SIGNATURE PAGE FOLLOWS]

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RFCUNY:

Signature:

Date:

Name:

Title:

RESEARCHER:

Signature:

Date:

Name: Hoau-Yan Wang, Ph.D.,
Title: Medical Professor, CUNY

CASSAVA SCIENCES, Inc:

Signature:

Date:

Remi Barbier
President & CEO, Cassava Sciences, Inc.

ATTACHMENTS:

Attachment A – Protocol

Study Title: **Effects of simufilam on pathogenesis associated with Parkinson's disease dementia using postmortem brain tissue**

1. Executive Summary

Dementia and mild cognitive impairment are prevalent in advanced stages of Parkinson disease (PD). Similar to Alzheimer's disease (AD) dementia, there is no effective treatment for dementia associated with PD. In addition to Lewy pathology in the limbic and cortical regions, the molecular mechanisms contributing to cognitive decline in PD remain elusive. Despite with overlapping symptoms, AD and PD appear to differentially affect cognitive domains, although, as in AD, low CSF amyloid- β 42 (A β 42) also predicts future cognitive decline and dementia in PD. We propose to test a novel therapeutic agent, simufilam that binds pathological form of filamin A (FLNA) to reduce A β 42 toxic signaling to hyper-phosphorylation of tau via α 7nAChR, neuroinflammation by TLR4 and brain insulin resistance. Specifically, we aim to use an established ex vivo stimulation method in postmortem brains from PD without and with dementia as well as neurologically normal controls to assess the effects of simufilam on (1) A β 42-induced FLNA association with α 7nAChRs and TLR4, (2) A β 42- α 7nAChR linkage, (3) insulin signaling, (4) A β 42-associated α -synuclein levels, (5) phosphorylated tau, and (6) inflammatory cytokine levels (TNF α , IL-6 and IL-1 β). Improvements in these measures by simufilam in vitro treatment would add support to the rationale for testing simufilam in patients with Parkinson's disease dementia.

2. Plan of Work

This study will use 8 sets of posterior parietal cortices (PPCs) from matched control, Parkinson's disease, Parkinson's disease with mild cognitive impairment (MCI), and Parkinson's disease with dementia cases. Approximately 20 mg of postmortem brain tissues will be prepared to 100 μ m x 100 μ m x 3 mm prisms using a chilled McIlwain tissue chopper. PPC prisms will be washed with oxygenated 0.3 mM Mg²⁺-containing Krebs' Ringer (LMKB) 3 times and incubated with 1 nM Simufilam containing LMKB for 1 hour and oxygenated with 95% O₂/5% CO₂ for 1 min every 15 min as described previously (Wang et al., 2017). The treated PPC tissues will be used to assess: (1) **FLNA- α 7nAChR/TLR4 and A β 42 - α -synuclein complex levels.** The α 7nAChR and TLR4 levels in the anti-FLNA immunoprecipitates will be measured by immunoblotting with specific antibodies, and the levels of α -synuclein in the anti-A β 42 immunoprecipitates will be measured with an α -synuclein specific antibody. Each will be quantified by densitometric quantitation.

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Equally divided tissue will be incubated with 10 μ M NMDA/ 1 μ M glycine to assess
(2) **NMDAR signaling**: The levels of pY⁴¹⁶Src, pY⁴⁰²PyK2, nNOS, PLC- γ , and PKC γ in the anti-NR1 immunoprecipitate by immunoblotting with specific antibodies. The levels of pY¹²⁴⁶-NR2A will also be determined.

The other portions of divided tissue will be incubated with 1 nM insulin to examine
(3) **Insulin signaling**: The levels of pY^{1150/1151}IR β and IRS-1 will be measured by coimmunoprecipitation and detection with specific antibodies.

3. Quality Statement

It is understood that this work is not subject to GLP requirements, but will be performed according to sound scientific principles, in compliance with City University of New York Medical School standard operating procedures, and with review by supervisory technical staff.

4. Timing

The project can be started in August 1st, 2021 and is expected to finish before January 31st, 2022.

Summary of Costs and Payment Schedule

A summary of costs and payment schedule is listed in Attachment B.

Wet lab and statistical analyses work will be performed at:

Department of Molecular, Cellular & Biomedical Sciences
Center for Discovery and Innovation
CDI-3370 85 St. Nicholas Terrace,
New York, NY 10031

All accounting activities will be processed at:

Department of Molecular, Cellular & Biomedical Sciences
City University of New York School of Medicine
160 Convent Avenue
New York, NY 10031

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3. Summary of Costs and Payment Schedule

ATTACHMENTS:

Attachment B – Payment and Budget

Detailed Budget:

Salary & fringe benefit:

Principal Investigator:

\$11,041 (\$7,312 + \$3,729)

Professor Hoau-Yan Wang, Ph.D. requests 5% effort (1.10 Academic months per year). He will design and execute the assays using postmortem brain. He will oversee the data collection and analysis.

Post-doctoral research associate:

Zhe Pei, Ph.D. (1 Calendar months per year) will assist PI in running Immunoprecipitation and Western blotting.

\$ 7,747 (\$ 5,600 + \$ 2,147)

Technician:

Kuo-Chieh Lee, M.S. (2.4 Calendar months per year) will assist PI in tissue processing, cell isolation and myriad of experimental procedures and reagent preparation.

\$ 14,388 (\$ 10,400 + \$ 3,988)

Fringe Benefit

RFCUNY maintains its own fringe benefits program for employees (comparable to those of other academic and non-profit institutions). The cost of providing benefits to employees is included in grants as a direct charge.

To simplify both pre-award budget preparation and post-award accounting procedures, RFCUNY developed a system of Multiple Fringe Benefits Pools. Each grant is charged a flat percentage of each employee's gross annual wages, based on their classification. The percentages represent the best estimate of the actual costs of providing benefits to each employee.

Released Time Faculty:

CUNY Faculty released to work on a grant or contract a rate of 51% is applied to the requested salary support.

A rate of 38% is applied to Full Time/Part Time A employees with an additional .34% of MTA tax.

Expendable Supplies:

Antibodies and immunoprecipitation agents

Primary antibodies \$350 x 14	\$ 4,900
protein A/G-conjugated agarose beads x2	\$ 3,224
HRP-secondary antibodies-\$156 x 3	\$ 468

\$ 8,592

Drugs and Chemicals

Phosphatase inhibitor tablets @ \$245 x 2	\$ 490
Protease inhibitor tablets@ \$225 x 2	\$ 450
Digitonin @ \$186/ 500 mg x 2	\$ 372
NP-40 @ \$64/250 ml	\$ 64
Bradford reagent	\$ 156

\$ 1,532

Electrophoresis and Western blotting equipment and supplies, ECL reagents, Film and Immunohistochemistry

ECL reagent \$490	\$ 490
Methanol	\$ 120
Buffer reagents	\$ 350

\$ 960

Supplies

Ependoff tubes	\$ 250
Pipette tips	\$ 200
Cuvettes	\$ 100
Gloves	\$ 190

\$ 740

Research materials & supplies

\$ 11,824

Direct cost

\$ 45,000.00

Indirect Costs (25%)

\$ 11,250.00

Total

\$ 56,250.00

From: Hoau-yan Wang
Sent time: 07/30/2021 01:38:31 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your encouragements always and giving your opinions and questions as I need such reminders to keep my comments plain and understandable.

I will **answer your questions directly underneath each query you posted**. Since I am blind to all patient related info, I can only answer in general terms.

Hope all is well with you and your family.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Thursday, July 29, 2021 10:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Congratulation to your researches going with a gigantic step forward. After reading updated PTI-125 related papers in CCAI 2021, I had a feeling that your lab works have gradually verified the MOA of Filamin A with abnormal conformation. There are thoughts with results of SavaDx and 9-month data as follows :

- 1) Correlation studies of Abnormal Filamin A in phase 2b patients is a positive step. That is a great findings and direction in the framework of diagnosis tool. However, taking Abnormal Filamin A as a biomarker needs more works to establish that which level of Abnormal Filamin A should be detected as an early sign of AD. I am wondering if a totally new or compatible antibody in your earlier works of SavaDx is employed in this study.
- Indeed, this is just the initial steps. The antibodies used obviously required constant verifications using that was used earlier. It is a tedious work but there are no short cuts. We need to define the timeline when the abnormal FLNA can be detected (not an easy task because we don't even know when is early).
- 2) Cognition Improvement of 3.0 Points on ADAS-Cog at 9 Months ($p < 0.001$) is great for patients as a process of Filamin A normalization. However, most people are wondering why NPI score in 9 month improved less than in 6 month by 0.6 points. All tested biomarkers are consistent with improvements which relieved lots of overhangs.
- People forget Alzheimer's disease is a progressive neurodegenerative disease with multiple factors at play. As patients deteriorate cognitively due to brain function declines, there are added factors hence the magnitude of improvements become less comparing the the baseline. The 0.6 points less at 9 month reflects just that (obviously it also depends on the stage of disease when patients first enrolled) but the curve will be stabilize for period of time.
- 3) 22% of patients declined less than reported in the science literature at 9 months. Why these patients are so hard to respond to treatment of simufilam ? Any other upstream catalyst for these patients ?
- Well, we don't actually know but my guess is that these patients have other issues or they were selected at later stage of the disease even though their MMSE or ADAS-Cog when enrolled were not bad. While we like to have 100% responsive rate, it is an unrealistic expectation. This drive home the importance of early diagnosis. I am sure if we treat earlier, we will see a better result.
- 4) As reported earlier, Evonik will supply Cassava Sciences with large-scale, clinical-grade quantities of simufilam. I am wondering if Evonik will produce good qualities of simufilam as in phase 2b study and it should be carefully verified before entering phase 3.
- Clearly, QC will be done carefully.
- 5) Finally, is abnormal filamin A responsible for the symptom or modifying answer to AD ?
- While we all want to find the "bad" guy (abnormal FLNA is a critical but one of the bad guys I am sure there are many others). Fortunately, fixing abnormal FLNA promotes healthier and more resilient brain but unfortunately can't fix anything already beyond repairs or dead. I am a realistic person by showing people what I saw but I don't want to give a wrong impression that fixing abnormal FLNA can bring back what have already damaged.

I am honored to be with your ongoing researches and contributions to AD patients. Thanks for your hard works.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, June 30, 2021 8:29 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Sorry for my late reply. I often just get occupied by too many tasks in hand and consequently delay in my response to you and many.

Yes, lots efforts had been on the multiple fronts and there should be an update in phase 2b study. I will be interest in learning of your comments.

I watch the COVID-19 situation in Taiwan closely. It is most unfortunately some careless acts led to such a spread. Even though it is pale by comparison to US and EU, it is still very concerning especially in Taipei (the worst in transparency) and New Taipei. A solution to this monumental disaster must include understand the pathogen (virus) so that more effective medications together with vaccination can put this pandemic out for good.

Best wishes to you and your family, it is looking better recently so that normalcy is near.

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, June 22, 2021 12:18 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After reading a recent news from Cassava Sciences, I realized that there will be a presentation at AAIC during the week of July 26-30th about SavaDx clinical dataset from PTI-125's Phase 2b study of 64 patients. Look forward to seeing more updates of SavaDx developments which you must devote lots of time and energy.

Affected by recent COVID-19 impacts in Taiwan, I have been working from home more than 1 month. Hope that this history-making pandemics will be alleviated or solved by pharmaceutical solutions. The same goes to PTI-125 to help patients in need. Thanks.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 23, 2021 10:26 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

The MOA for PTI-125 is very different from that of ANVS401. PTI-125 reverses an abnormal filamin A thereby reducing the toxic signaling pathways that drive neurodegeneration and inflammation. ANVS401 functions as a translational blockers that presumably (based on cell and transgenic models) to reduce toxic substances such as amyloid beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. The major problem is that reducing those "toxic" substances do not work in humans. In fact, ANVS401 blocks APP (amyloid precursor protein) to reduce amyloid beta. APP is a known trophic factor whose expression increases when brain is injured. More of the problem, we know reduction in amyloid beta by beta or gamma secretase inhibitors do not stop Alzheimer's disease progression and in some cases actually worsen cognitive impairments. Hence, I don't predict any synergy between PTI-125 and ANVS401.

Postmortem brains are not suitable to study metabolic dysfunction because one can only show there is metabolic disturbance but can not conclusively show the source, when and how the metabolic dysfunction occur. Transgenic animal models are partial models at best and are very different from actual disease, therefore they are inheritably insufficient to any pathogenic pathway questions just about any diseases.

I hope my explanations help answering your questions.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, February 21, 2021 3:05 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

I had some thoughts again regarding to the upstream causes of Alzheimer disease and MOA of PTI-125.

As you mentioned earlier, there were complicated lab works deriving chemical compounds of PTI-125 to restore of Filamin A with abnormal conformation. I am curious to know what is the chemical MOA of PTI-125 which differentiates from other approaches such as ANVS401 of Annovis Bio Inc. to decrease multiple neurotoxic in Cerebrospinal Fluid (CSF) and improve axonal transport of nerve cell. Their therapeutic target also aims for reductions of neuroinflammation and neurodegeneration. Is there any synergetic effect to combine PTI-125 and ANVS401 ?

As in previous email, I am skeptical about causes of metabolic dysfunction related to Alzheimer disease. Is there any direct proof from human postmortem model instead of mouse model ?
Thanks again for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 16, 2021 1:08 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

First, Happy Lunar New Year. Wishing you and your family a happy, healthy and prosperous year of Ox.

Regarding your question, Donepezil's ADAS-cog score you are referring to are raw score. Once taking placebo control into consideration, the improvement achieved by 24 months of 5 mg and 10 mg daily dose of donepezil were around 0.35 and 0.39 (page 16 stat significant). By now we know donepezil's clinical effectiveness eventually diminished as disease progresses. Obviously, we hope the cognitive benefit of PTI-125 continues based on the biomarker data. The improvement in cognition is depending on the baseline state of the patients (how severe the dementia and obviously the accuracy of diagnosis). I can't say too much and frankly nobody is all that certain.

Based on the mechanism of action, we predict the therapeutic effects of PTI-125 are applicable to a broad range of Alzheimer's disease patients. Again, the magnitude of benefits depend on the severity of dementia - the earlier the better. Hence, it is important to have a reliable early diagnosis tool though we still not entirely sure how to define "early".

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, February 15, 2021 10:32 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After some thoughts and review of data during Chinese New Year, I have some questions needed for your comments as follows :

1. ADAS-Cog Improvement between ARICEPT and PTI-125 : In

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively after 24 weeks of treatment. These differences were statistically significant for 473 patients. Compared with baseline, 5 mg/day and 10 mg/day treatments of donepezil at 24 weeks showed 1.06 and 1.6 benefits in a controlled study. However, the press release of Cassava Sciences on Feb. 2, 2021 mentioned that six months of PTI-125 treatment improved cognition scores by 1.6 points on ADAS-Cog11.

These comparative improvements did not clearly distinguish the therapeutic advantage of PTI-125 compared with ARICEPT in 24 weeks of treatment. Is it true for this simple observation as above? Is there any indication that PTI-125 will have better effects after prolonged period of time (such as 1 year) by restoring of Filamin A with abnormal conformation?

2. You mentioned that collective efforts try to bring some solutions for Alzheimer's disease patients. Does it mean that a subset of Alzheimer patients would be appropriate for therapeutic effects of PTI-125 and diagnosis tool of SavaDx? While other patients are not ideal enough?

Thanks so much for your insights again.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, February 4, 2021 4:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thank you for your well wishes and positive comments. Your continued interests in finding solutions for Alzheimer's disease research motivate us and I can truly say I am trying my very best. I thank you for keeping me informed and discussions on the findings from other investigators. We will keep moving forward and hope our collective efforts can bring some solutions for Alzheimer's disease patients.

Will keep safe the best I can as the COVID pandemic is still very bad here. Hopefully, with vaccination the situation improves in the coming months.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, February 2, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

Nice to know that the interim result of PTI-125 is positive and brings lights to the Alzheimer community. Congratulation to your continued efforts. There must be lots of persons sending emails to you regarding to this matter. To continue your clinical endeavors, I truly wish you to keep safe in this covid-19 epidemics. Your academic and real-word contributions are very much appreciated.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, January 21, 2021 11:55 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for keeping me informed of the recent development. I am all tied up by my extensive teaching load and research activities (this pandemic has caused tremendous pain with limited access).

Regarding the levels of N-terminal fragment of tau in the blood as a predictor of cognitive decline, this is really nothing new because we know the levels of tau in the CSF and blood positively correlate with the extent of neuronal damage (tau exist exclusively in neurons). The question is the sensitivity of detection that allow us to sound the alarm. With the more sensitive mass spectrometry we obviously are better equipped than before.

Thanks again. I will find time to answer your earlier queries.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 20, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] some development of diagnosis tool for reference

Dear Hoau :

There is some development of blood test for Alzheimer's disease to predict future cognitive decline in healthy people with levels of N-terminal fragment of tau (NT1). Data link is as <https://www.sciencedaily.com/releases/2020/12/201209115147.htm>. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, January 16, 2021 3:44 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks always for your info that keeping me in the loop of current Alzheimer's disease findings.

The problem is that this type of academic research using (genetically modified) rodent models that bear little resemblance to human Alzheimer's disease lead us to nowhere and frankly confuse & dilute our efforts. Hydrogen sulfide is no doubt playing a regulatory role in many physiological activities. Just because it is decreased with aging and replacing it can improve cognition in rodents doesn't mean it is therapeutically possible. Don't forget the hydrogen sulfide is quite toxic one should worry the accumulation can severely hurt the brain function. Most importantly, there is no evidence rodent models have neurodegeneration (unlike brains in humans with Alzheimer's disease). GSK3a/b is one of the hubs in metabolism/energy regulation and as one of the tau kinases that have a sophisticate feed forward and feedback regulators. There is no evidence there is anything change in GSK3a/b in Alzheimer's disease. In general, kinases and phosphatases are terrible targets because they all have tons of regulators once activated or inhibited in a progressively changing brain like in Alzheimer's disease is predictably short-lived and ineffective especially when the disease becomes symptomatic (much too late).

Thanks. Have a good weekend.

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 13, 2021 10:36 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

It seems to me more and more researches trying to target early pathogenesis of Alzheimer's disease which might be

inspired by evidences of many clinical results. There is a recent research from John Hopkins Medicine working with University of Exeter concerning with effects of hydrogen sulfide, GSK3 β and other proteins involved in the pathogenesis of Alzheimer's disease. Their data link is https://medicalxpress.com/news/2021-01-hydrogen-sulfide-alzheimer-disease.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter. Hope that this information would be interesting to you. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 13, 2021 2:13 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Sorry for my late reply, sometimes I made a mental note to reply but I got busy and kind of putting it off. The impacts of concussion obviously vary according to the severity and frequency (multiple mild concussions can be quite damaging). It sounds like your father had a severe concussion that resulted in motor/sensory imbalance and dementia. I understand how hard it is to see your father suffer but unable to help.

There is no doubt vascular dysfunction is a risk factor and often accompanies Alzheimer's disease (cerebral amyloid angiopathy). That said, the cause-effect relationship between vascular dysfunction and Alzheimer's disease is not straight forward.

Indeed, upstream is a relative term. Abnormal filamin A can be induced by sub-chronic amyloid (soluble) infusion into brains. If abnormality in filamin A is blocked (by PTI-125), there is significant reduction in amyloid plaques (dead neurons) and neurofibrillary tangles. More importantly, brain activities with higher receptor and synaptic activities and function improve at least in mouse model of Alzheimer's disease. These data indicate reversing abnormality of filamin A especially when at the stage when mild clinical dementia is detected may be a promising way to treatment Alzheimer's disease.

Hope I answer your questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, January 4, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your comments. After two decades of researches, your important findings have a step forward which is a remarkable achievement. I do admire your courage and patience with regard to this tough disease in which early detections are probably with both natures of science and art. My father was in a healthy condition before concussion and developed with signs of body imbalance and occurrence of Alzheimer disease. It was heartbreaking without ways to lessen his burden.

My assumption of root occurrence from vascular dysfunction might be wrong. It seems to me that finding a solution with very early detection before massive degeneration occurs is more than challenging. I am wondering which events trigger the formation of abnormal filamin A. If you could come up with a diagnosis tool tracing up the root cause of abnormal filamin A, it might be a better start than random guesses. I am not sure if I am right in this direction.

BTW, you mentioned that abnormal filamin A is an upstream event. Would you shed some lights on which upstream events are already verified up to now since upstream is a relative word ? Thanks so much for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, January 5, 2021 1:07 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

There is no doubt vascular dysfunction is an important part of the Alzheimer's disease (AD) pathology. Filamin A with abnormal conformation is found in plasma from AD patients doesn't necessary mean abnormal filamin A from platelets is resulted from vascular pathology including amyloid angiopathy, infarcts. More importantly, the abnormal filamin A in peripheral may be the result of brain pathogenic changes (occurs later).

Our data indicate abnormal filamin A is an upstream event. However, AD treatment effects are better if starts earlier (hence early detection before massive degeneration occurs is the key). I always think multiple therapeutic agents may be synergistic or additive. Again, if all the treatments administered after massive degeneration there is no treatments strong enough.

Thanks.

All the best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, January 3, 2021 7:50 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks for your kindly reply. Happy New Year !

Since conformational filamin A is structurally found in palates, I therefore assume that vascular pathologies are related to this disease. Your researches in various aspects of insulin resistances were published and your comments really show how hard it is to trace pathogenic events.

I really appreciate your continued research and endeavor to find more upstream targets treating Alzheimer disease effectively. It seems to me in your comments that restoration of conformational filamin A is not strong enough to show disease modifying effects. Is it true ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Monday, January 4, 2021 3:14 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Happy New Year. Wishing you and your family a healthy and prosperous year 2021.

It is my life time goal to help bring effective treatments and early diagnosis of the Alzheimer's disease (and other diseases with cognitive impairments). For the last two decades, I worked to identify possible drug and diagnostic targets. I'm mindful of the burden of the Alzheimer's disease caregivers, especially the potential of depression.

Regarding your question, there is no concrete data to show the function of blood platelet had changed in Alzheimer's disease (plausible of course). There are diverse pathogenic mechanisms and of course diseases such as diabetes (causes vascular pathologies) and history of concussion (multiple) had been suspected to be culprits to promote Alzheimer's disease. Surely, prevent such problems is useful but whether such measurements can reverse the damages that already done is everyone's guess. We had tried to control insulin resistance for years but the results thus far showed not much of effects. This may indicate that brain insulin resistance is not an early pathogenic event. We will do more to find more upstream targets so that we can more effective to treat Alzheimer's disease.

Thanks for your continuing interests and communications.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, December 29, 2020 7:38 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your kindly reply. For my father, a better treatment of Alzheimer disease is motivated and caregivers deserve to be with less burden. Regarding to the timing of conformational changes, I am curious to know if this is related to conditional changes of palates which caused by blood clotting, vascular abnormality or concussion, etc. Your endeavor of this tough disease is really appreciated.

Please be safe since pandemic and cold weather persist in northern atmosphere. Have a wonderful and peaceful New Year to you and your family.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, December 30, 2020 6:56 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks for your email.

Your friend is correct regarding the difficulty of finding specific antibodies for the filamin A with altered conformation in Alzheimer's disease. Indeed, the epitope of the altered filamin A may be hidden or had been processed. Obviously, computational approaches had been used to help us find viable antibodies. We still don't know when the conformational changes occur during the Alzheimer's disease pathogenesis even though we think this event occur early. But, what is early? This timing issue also requires some attention.

Yes, one-year extension of the open-label study is well under the way. Obviously, we will be looking for cognitive improvement and reduction in pathogenic drives such as reduction in inflammatory markers and degeneration.

Thanks again for your continued interests in getting the Alzheimer's disease treatment. I am working hard to get to this goal.

Happy New Year to you and your family.

Best regards,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Monday, December 28, 2020 4:58 AM

To: Hoau-yan Wang

Subject: [EXTERNAL] Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Wish you a happy holiday and healthy new year, too. Regarding to the issue of diagnosis, my friend specialized in chemistry of antibody suggested to me recently that an exhaustive search of appropriate antibody to be connected with conformational filamin A in human palates might be required to have a solution of universal antibody for different races. A modern equipment with computerized tools would be helpful in this exhaustive search process. Since the epitope of

conformational filamin A might be structurally hidden, an appropriate antibody might be sensitively or selectively enough to be effective. Hope that this information is useful.

A one-year, open label study of PTI-125 was initiated in March 2020 and enrolled over 60% of patients as mentioned in public. Supposedly, safety issues are not a big concern since expanded clinical trials still proceed. How about attributes of reduced inflammatory cytokine levels and improved cognition/behavior in this perspective since earlier enrolled patients had been treated with more than 6 months ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 23, 2020 4:03 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Season Greetings

Dear 宜明,

Sorry for my late reply as I am deep in the semester end exam and grading.

Wow, time flies by so quickly. It has been more than a year already since we started our communication. It is my pleasure to discuss the field of neuroscience even though we actually are learning on the way. I am thankful for the opportunities you have given me to think about the questions you have posted in different angles. Truly, we all hope we have grown some in knowledge and get effective Alzheimer's disease treatments forward to contain this terrible disease. I am for one will do everything I can and work tireless toward this goal. It takes collective efforts to get this under control so that I am collaborating with academic and industrial partners to look into as many ways we can investigate and test the effectiveness. Thanks to you for keeping me informed of many new strategies other have come up with in Alzheimer's disease diagnosis and treatments.

We all hope we can better handle this COVID pandemic. With the approval of 2 vaccines, I am hopeful we are better equipped to start limiting the death tolls and eventually control this horrific virus. I sincerely hope people learn from this as we all have to play a part (wearing mask, wash hands frequently etc). This experience certainly humbles us as we humans appear more vulnerable (at least not as invincible) than we think. The fact Taiwan has done so well in controlling COVID makes me proud to be a Taiwanese.

Wishing you and your family happy holidays and a healthy, peaceful and prosperous year 2021.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, December 20, 2020 8:43 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Season Greetings

Dear Hoau-Yan :

It's been more than 1 year since I have this particular opportunity to know you. Your in-depth and insightful knowledge has given me more understandings in this tough field of neuroscience. Your assistances and comments are really appreciated. Hopefully, we will be better off with more solutions of pandemics and preventive measures next year. At this time of season, I truly wish you a Merry Christmas and happy New Year !

Best Regards,
宜明



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鄭宜明 Eddy Jeng - CDIB's email address has been changed from @cdibh.com to yiming_j@cdibcapital.com, please update your contact information.

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From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent time: 07/31/2021 02:49:37 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Thanks for your kindly reply during busy hours as always. Knocking off hard nuts is especially tough especially there was no precedent before. Your persistence and genuine contributions to global AD community is obvious. I am happy that your finding of the bad guy will eventually be a history of AD and even mankind. Your family and friends will be certainly proud of you after so many tough years spent in lab and related researches.

Your answers to my naïve questions are plain and understandable. To my personal curiosity which might be common to most people, I have additional questions as below.

1. Is there any plateau effect after months of oral treatment of PTI-125 since biomarkers of neuroinflammation and neurodegeneration will eventually reach their peaks ? Will responded patients need to take oral treatments of PTI-125 in their lifetime ?
2. When temporal changes of individual patient during the span of treatments will be revealed ? This information might show more consistent and clearer trend of treatment effects.
3. For neurons already beyond repairs or dead, is there any viable therapeutic or complimentary solution ?
4. Would mental or physical rehabilitations for patients during or after treatments add more values to their health ?

There must be lots of works needed to be done after this stage. For all your dedication, I believe that all time spent in search of better treatments will be meaningful and greatly appreciated. Thanks again in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, July 31, 2021 1:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your encouragements always and giving your opinions and questions as I need such reminders to keep my comments plain and understandable.

I will **answer your questions directly underneath each query you posted**. Since I am blind to all patient related info, I can only answer in general terms.

Hope all is well with you and your family.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Thursday, July 29, 2021 10:49 AM
To: Hoau-yan Wang

Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Congratulation to your researches going with a gigantic step forward. After reading updated PTI-125 related papers in CCAI 2021, I had a feeling that your lab works have gradually verified the MOA of Filamin A with abnormal conformation. There are thoughts with results of SavaDx and 9-month data as follows :

- 1) Correlation studies of Abnormal Filamin A in phase 2b patients is a positive step. That is a great findings and direction in the framework of diagnosis tool. However, taking Abnormal Filamin A as a biomarker needs more works to establish that which level of Abnormal Filamin A should be detected as an early sign of AD. I am wondering if a totally new or compatible antibody in your earlier works of SavaDx is employed in this study.
- Indeed, this is just the initial steps. The antibodies used obviously required constant verifications using that was used earlier. It is a tedious work but there are no short cuts. We need to define the timeline when the abnormal FLNA can be detected (not an easy task because we don't even know when is early).
- 2) Cognition Improvement of 3.0 Points on ADAS-Cog at 9 Months ($p < 0.001$) is great for patients as a process of Filamin A normalization. However, most people are wondering why NPI score in 9 month improved less than in 6 month by 0.6 points. All tested biomarkers are consistent with improvements which relieved lots of overhangs.
- People forget Alzheimer's disease is a progressive neurodegenerative disease with multiple factors at play. As patients deteriorate cognitively due to brain function declines, there are added factors hence the magnitude of improvements become less comparing the the baseline. The 0.6 points less at 9 month reflects just that (obviously it also depends on the stage of disease when patients first enrolled) but the curve will be stabilize for period of time.
- 3) 22% of patients declined less than reported in the science literature at 9 months. Why these patients are so hard to respond to treatment of simufilam ? Any other upstream catalyst for these patients ?
- Well, we don't actually know but my guess is that these patients have other issues or they were selected at later stage of the disease even though their MMSE or ADAS-Cog when enrolled were not bad. While we like to have 100% responsive rate, it is an unrealistic expectation. This drive home the importance of early diagnosis. I am sure if we treat earlier, we will see a better result.
- 4) As reported earlier, Evonik will supply Cassava Sciences with large-scale, clinical-grade quantities of simufilam. I am wondering if Evonik will produce good qualities of simufilam as in phase 2b study and it should be carefully verified before entering phase 3.
- Clearly, QC will be done carefully.
- 5) Finally, is abnormal filamin A responsible for the symptom or modifying answer to AD ?
- While we all want to find the "bad" guy (abnormal FLNA is a critical but one of the bad guys I am sure there are many others). Fortunately, fixing abnormal FLNA promotes healthier and more resilient brain but unfortunately can't fix anything already beyond repairs or dead. I am a realistic person by showing people what I saw but I don't want to give a wrong impression that fixing abnormal FLNA can bring back what have already damaged.

I am honored to be with your ongoing researches and contributions to AD patients. Thanks for your hard works.

Best Regards,

宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, June 30, 2021 8:29 PM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Sorry for my late reply. I often just get occupied by too many tasks in hand and consequently delay in my response to you and many.

Yes, lots efforts had been on the multiple fronts and there should be an update in phase 2b study. I will be interest in learning of your comments.

I watch the COVID-19 situation in Taiwan closely. It is most unfortunately some careless acts led to such a spread. Even though it is pale by comparison to US and EU, it is still very concerning especially in Taipei (the worst in

transparency) and New Taipei. A solution to this monumental disaster must include understanding the pathogen (virus) so that more effective medications together with vaccination can put this pandemic out for good.

Best wishes to you and your family, it is looking better recently so that normalcy is near.

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, June 22, 2021 12:18 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After reading a recent news from Cassava Sciences, I realized that there will be a presentation at AAIC during the week of July 26-30th about SavaDx clinical dataset from PTI-125's Phase 2b study of 64 patients. Look forward to seeing more updates of SavaDx developments which you must devote lots of time and energy.

Affected by recent COVID-19 impacts in Taiwan, I have been working from home more than 1 month. Hope that this history-making pandemics will be alleviated or solved by pharmaceutical solutions. The same goes to PTI-125 to help patients in need. Thanks.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 23, 2021 10:26 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

The MOA for PTI-125 is very different from that of ANVS401. PTI-125 reverses an abnormal filamin A thereby reducing the toxic signaling pathways that drive neurodegeneration and inflammation. ANVS401 functions as a translational blockers that presumably (based on cell and transgenic models) to reduce toxic substances such as amyloid beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. The major problem is that reducing those "toxic" substances do not work in humans. In fact, ANVS401 blocks APP (amyloid precursor protein) to reduce amyloid beta. APP is a known trophic factor whose expression increases when brain is injured. More of the problem, we know reduction in amyloid beta by beta or gamma secretase inhibitors do not stop Alzheimer's disease progression and in some cases actually worsen cognitive impairments. Hence, I don't predict any synergy between PTI-125 and ANVS401.

Postmortem brains are not suitable to study metabolic dysfunction because one can only show there is metabolic disturbance but can not conclusively show the source, when and how the metabolic dysfunction occur. Transgenic animal models are partial models at best and are very different from actual disease, therefore they are inheritably insufficient to any pathogenic pathway questions just about any diseases.

I hope my explanations help answering your questions.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, February 21, 2021 3:05 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

I had some thoughts again regarding to the upstream causes of Alzheimer disease and MOA of PTI-125.

As you mentioned earlier, there were complicated lab works deriving chemical compounds of PTI-125 to restore of Filamin A with abnormal conformation. I am curious to know what is the chemical MOA of PTI-125 which differentiates from other approaches such as ANVS401 of Annovis Bio Inc. to decrease multiple neurotoxic in Cerebrospinal Fluid (CSF) and improve axonal transport of nerve cell. Their therapeutic target also aims for reductions of neuroinflammation and neurodegeneration. Is there any synergetic effect to combine PTI-125 and ANVS401 ?

As in previous email, I am skeptical about causes of metabolic dysfunction related to Alzheimer disease. Is there any direct proof from human postmortem model instead of mouse model ?
Thanks again for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 16, 2021 1:08 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

First, Happy Lunar New Year. Wishing you and your family a happy, healthy and prosperous year of Ox.

Regarding your question, Donepezil's ADAS-cog score you are referring to are raw score. Once taking placebo control into consideration, the improvement achieved by 24 months of 5 mg and 10 mg daily dose of donepezil were around 0.35 and 0.39 (page 16 stat significant). By now we know donepezil's clinical effectiveness eventually diminished as disease progresses. Obviously, we hope the cognitive benefit of PTI-125 continues based on the biomarker data. The improvement in cognition is depending on the baseline state of the patients (how severe the dementia and obviously the accuracy of diagnosis). I can't say too much and frankly nobody is all that certain.

Based on the mechanism of action, we predict the therapeutic effects of PTI-125 are applicable to a broad range of Alzheimer's disease patients. Again, the magnitude of benefits depend on the severity of dementia - the earlier the better. Hence, it is important to have a reliable early diagnosis tool though we still not entirely sure how to define "early".

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, February 15, 2021 10:32 AM
To: Hoau-yan Wang

Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After some thoughts and review of data during Chinese New Year, I have some questions needed for your comments as follows :

1. ADAS-Cog Improvement between ARICEPT and PTI-125 : In https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively after 24 weeks of treatment. These differences were statistically significant for 473 patients. Compared with baseline, 5 mg/day and 10 mg/day treatments of donepezil at 24 weeks showed 1.06 and 1.6 benefits in a controlled study. However, the press release of Cassava Sciences on Feb. 2, 2021 mentioned that six months of PTI-125 treatment improved cognition scores by 1.6 points on ADAS-Cog11.

These comparative improvements did not clearly distinguish the therapeutic advantage of PTI-125 compared with ARICEPT in 24 weeks of treatment. Is it true for this simple observation as above ? Is there any indication that PTI-125 will have better effects after prolonged period of time (such as 1 year) by restoring of Filamin A with abnormal conformation ?

2. You mentioned that collective efforts try to bring some solutions for Alzheimer's disease patients. Does it mean that a subset of Alzheimer patients would be appropriate for therapeutic effects of PTI-125 and diagnosis tool of SavaDx ? While other patients are not ideal enough ?

Thanks so much for your insights again.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, February 4, 2021 4:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thank you for your well wishes and positive comments. Your continued interests in finding solutions for Alzheimer's disease research motivate us and I can truly say I am trying my very best . I thank you for keeping me informed and discussions on the findings from other investigators. We will keep moving forward and hope our collective efforts can bring some solutions for Alzheimer's disease patients.

Will keep safe the best I can as the COVID pandemic is still very bad here. Hopefully, with vaccination the situation improves in the coming months.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, February 2, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

Nice to know that the interim result of PTI-125 is positive and brings lights to the Alzheimer community. Congratulation to your continued efforts. There must be lots of persons sending emails to you regarding to this matter. To continue your clinical endeavors, I truly wish you to keep safe in this covid-19 epidemics. Your academic and real-word contributions are very much appreciated.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, January 21, 2021 11:55 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for keeping me informed of the recent development. I am all tied up by my extensive teaching load and research activities (this pandemic has caused tremendous pain with limited access).

Regarding the levels of N-terminal fragment of tau in the blood as a predictor of cognitive decline, this is really nothing new because we know the levels of tau in the CSF and blood positively correlate with the extent of neuronal damage (tau exist exclusively in neurons). The question is the sensitivity of detection that allow us to sound the alarm. With the more sensitive mass spectrometry we obviously are better equipped than before.

Thanks again. I will find time to answer your earlier queries.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 20, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] some development of diagnosis tool for reference

Dear Hoau :

There is some development of blood test for Alzheimer's disease to predicte future cognitive decline in healthy people with levels of N-terminal fragment of tau (NT1). Data link is as <https://www.sciencedaily.com/releases/2020/12/201209115147.htm>. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, January 16, 2021 3:44 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks always for your info that keeping me in the loop of current Alzheimer's disease findings.

The problem is that this type of academic research using (genetically modified) rodent models that bear little resemblance to human Alzheimer's disease lead us to nowhere and frankly confuse & dilute our efforts. Hydrogen sulfide is no doubt playing a regulatory role in many physiological activities. Just because it is decreased with aging and replacing it can improve cognition in rodents doesn't mean it is therapeutically possible. Don't forget the hydrogen sulfide is quite toxic one should worry the accumulation can severely hurt the brain function. Most importantly, there is no evidence rodent models have neurodegeneration (unlike brains in humans with Alzheimer's disease). GSK3a/b is one of the hubs in metabolism/energy regulation and as one of the tau kinases that have a sophisticated feed forward and feedback regulators. There is no evidence there is anything change in GSK3a/b in Alzheimer's disease. In general, kinases and phosphatases are terrible targets because they all have tons of regulators once activated or inhibited in a progressively changing brain like in Alzheimer's disease is predictably short-lived and ineffective especially when the disease becomes symptomatic (much too late).

Thanks. Have a good weekend.

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 13, 2021 10:36 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

It seems to me more and more researches trying to target early pathogenesis of Alzheimer's disease which might be inspired by evidences of many clinical results. There is a recent research from John Hopkins Medicine working with University of Exeter concerning with effects of hydrogen sulfide, GSK3 β and other proteins involved in the pathogenesis of Alzheimer's disease. Their data link is https://medicalxpress.com/news/2021-01-hydrogen-sulfide-alzheimer-disease.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter. Hope that this information would be interesting to you. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 13, 2021 2:13 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Sorry for my late reply, sometimes I made a mental note to reply but I got busy and kind of putting it off. The impacts of concussion obviously vary according to the severity and frequency (multiple mild concussions can be quite damaging). It sounds like your father had a severe concussion that resulted in motor/sensory imbalance and dementia. I understand how hard it is to see your father suffer but unable to help.

There is no doubt vascular dysfunction is a risk factor and often accompanies Alzheimer's disease (cerebral amyloid angiopathy). That said, the cause-effect relationship between vascular dysfunction and Alzheimer's disease is not straight forward.

Indeed, upstream is a relative term. Abnormal filamin A can be induced by sub-chronic amyloid (soluble) infusion into brains. If abnormality in filamin A is blocked (by PTI-125), there is significant reduction in amyloid plaques (dead neurons) and neurofibrillary tangles. More importantly, brain activities with higher receptor and synaptic activities and function improve at least in mouse model of Alzheimer's disease. These data indicate reversing abnormality of filamin A especially when at the stage when mild clinical dementia is detected may be a promising way to treatment Alzheimer's disease.

Hope I answer your questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, January 4, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your comments. After two decades of researches, your important findings have a step forward which is a remarkable achievement. I do admire your courage and patience with regard to this tough disease in which early detections are probably with both natures of science and art. My father was in a healthy condition before concussion and developed with signs of body imbalance and occurrence of Alzheimer disease. It was heartbreaking without ways to lessen his burden.

My assumption of root occurrence from vascular dysfunction might be wrong. It seems to me that finding a solution with very early detection before massive degeneration occurs is more than challenging. I am wondering which events trigger the formation of abnormal filamin A. If you could come up with a diagnosis tool tracing up the root cause of abnormal filamin A, it might be a better start than random guesses. I am not sure if I am right in this direction.

BTW, you mentioned that abnormal filamin A is an upstream event. Would you shed some lights on which upstream events are already verified up to now since upstream is a relative word ? Thanks so much for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, January 5, 2021 1:07 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

There is no doubt vascular dysfunction is an important part of the Alzheimer's disease (AD) pathology. Filamin A with abnormal conformation is found in plasma from AD patients doesn't necessary mean abnormal filamin A from platelets is resulted from vascular pathology including amyloid angiopathy, infarcts. More importantly, the abnormal filamin A in peripheral may be the result of brain pathogenic changes (occurs later).

Our data indicate abnormal filamin A is an upstream event. However, AD treatment effects are better if starts earlier (hence early detection before massive degeneration occurs is the key). I always think multiple therapeutic agents may be synergistic or additive. Again, if all the treatments administered after massive degeneration there is no treatments strong enough.

Thanks.

All the best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, January 3, 2021 7:50 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks for your kindly reply. Happy New Year !

Since conformational filamin A is structurally found in palates, I therefore assume that vascular pathologies are related to this disease. Your researches in various aspects of insulin resistances were published and your comments really show how hard it is to trace pathogenic events.

I really appreciate your continued research and endeavor to find more upstream targets treating Alzheimer disease effectively. It seems to me in your comments that restoration of conformational filamin A is not strong enough to show disease modifying effects. Is it true ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, January 4, 2021 3:14 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Happy New Year. Wishing you and your family a healthy and prosperous year 2021.

It is my life time goal to help bring effective treatments and early diagnosis of the Alzheimer's disease (and other diseases with cognitive impairments). For the last two decades, I worked to identify possible drug and diagnostic targets. I'm mindful of the burden of the Alzheimer's disease caregivers, especially the potential of depression.

Regarding your question, there is no concrete data to show the function of blood platelet had changed in Alzheimer's disease (plausible of course). There are diverse pathogenic mechanisms and of course diseases such as diabetes (causes vascular pathologies) and history of concussion (multiple) had been suspected to be culprits to promote Alzheimer's disease. Surely, prevent such problems is useful but whether such measurements can reverse the damages that already done is everyone's guess. We had tried to control insulin resistance for years but the results thus far showed not much of effects. This may indicate that brain insulin resistance is not an early pathogenic event. We will do more to find more upstream targets so that we can more effective to treat Alzheimer's disease.

Thanks for your continuing interests and communications.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, December 29, 2020 7:38 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your kindly reply. For my father, a better treatment of Alzheimer disease is motivated and caregivers deserve to be with less burden. Regarding to the timing of conformational changes, I am curious to know if this is related to conditional changes of palates which caused by blood clotting, vascular abnormality or concussion, etc. Your endeavor of this tough disease is really appreciated.

Please be safe since pandemic and cold weather persist in northern atmosphere. Have a wonderful and peaceful New Year to you and your family.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, December 30, 2020 6:56 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks for your email.

Your friend is correct regarding the difficulty of finding specific antibodies for the filamin A with altered conformation in Alzheimer's disease. Indeed, the epitope of the altered filamin A may be hidden or had been processed. Obviously, computational approaches had been used to help us find viable antibodies. We still don't know when the conformational changes occur during the Alzheimer's disease pathogenesis even though we think this event occur early. But, what is early? This timing issue also requires some attention.

Yes, one-year extension of the open-label study is well under the way. Obviously, we will be looking for cognitive improvement and reduction in pathogenic drives such as reduction in inflammatory markers and degeneration.

Thanks again for your continued interests in getting the Alzheimer's disease treatment. I am working hard to get to this goal.

Happy New Year to you and your family.

Best regards,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, December 28, 2020 4:58 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Wish you a happy holiday and healthy new year, too. Regarding to the issue of diagnosis, my friend specialized in chemistry of antibody suggested to me recently that an exhaustive search of appropriate antibody to be connected with conformational filamin A in human palates might be required to have a solution of universal antibody for different races. A modern equipment with computerized tools would be helpful in this exhaustive search process. Since the epitope of conformational filamin A might be structurally hidden, an appropriate antibody might be sensitively or selectively enough to be effective. Hope that this information is useful.

A one-year, open label study of PTI-125 was initiated in March 2020 and enrolled over 60% of patients as mentioned in public. Supposedly, safety issues are not a big concern since expanded clinical trials still proceed. How about attributes of reduced inflammatory cytokine levels and improved cognition/behavior in this perspective since earlier enrolled patients had been treated with more than 6 months ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 23, 2020 4:03 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Season Greetings

Dear 宜明,

Sorry for my late reply as I am deep in the semester end exam and grading.

Wow, time flies by so quickly. It has been more than a year already since we started our communication. It is my pleasure to discuss the field of neuroscience even though we actually are learning on the way. I am thankful for the opportunities you have given me to think about the questions you have posted in different angles. Truly, we all hope we have grown some in knowledge and get effective Alzheimer's disease treatments forward to contain this terrible disease. I am for one will do everything I can and work tireless toward this goal. It takes collective efforts to get this under control so that I am collaborating with academic and industrial partners to look into as many ways we can investigate and test the effectiveness. Thanks to you for keeping me informed of many new strategies other have come up with in Alzheimer's disease diagnosis and treatments.

We all hope we can better handle this COVID pandemic. With the approval of 2 vaccines, I am hopeful we are better equipped to start limiting the death tolls and eventually control this horrific virus. I sincerely hope people learn from this as we all have to play a part (wearing mask, wash hands frequently etc). This experience certainly humbles us as we humans appear more vulnerable (at least not as invincible) than we think. The fact Taiwan has done so well in controlling COVID makes me proud to be a Taiwanese.

Wishing you and your family happy holidays and a healthy, peaceful and prosperous year 2021.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, December 20, 2020 8:43 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] Season Greetings

Dear Hoau-Yan :

It's been more than 1 year since I have this particular opportunity to know you. Your in-depth and insightful knowledge has given me more understandings in this tough field of neuroscience. Your assistances and comments are really appreciated. Hopefully, we will be better off with more solutions of pandemics and preventive measures next year. At this time of season, I truly wish you a Merry Christmas and happy New Year !

Best Regards,
宜明



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Subject: Re: your 2017 paper
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Please find a PDF copy of our 2017 Neurobiol of Aging paper you have requested.

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Best,

Hoau-Yan

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY SOM

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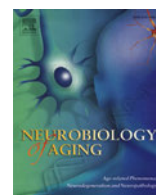
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PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis

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ABSTRACT

We show that amyloid β_{1-42} ($A\beta_{42}$) triggers a conformational change in the scaffolding protein filamin A (FLNA) to induce FLNA associations with $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7nAChR$) and toll like receptor 4 (TLR4). These aberrant associations respectively enable $A\beta_{42}$'s toxic signaling via $\alpha 7nAChR$ to hyperphosphorylate tau protein, and TLR4 activation to release inflammatory cytokines. PTI 125 is a small molecule that preferentially binds altered FLNA and restores its native conformation, restoring receptor and synaptic activities and reducing its $\alpha 7nAChR$ /TLR4 associations and downstream pathologies. Two month oral PTI 125 administration to triple transgenic (3xTg) Alzheimer's disease (AD) mice before or after apparent neuropathology and to 8 month wildtypes with milder neuropathologies reduced receptor dysfunctions and improved synaptic plasticity, with some improvements in nesting behavior and spatial and working memory in 3xTg AD mice. PTI 125 also reduced tau hyperphosphorylation, aggregated $A\beta_{42}$ deposition, neurofibrillary tangles, and neuroinflammation. Efficacy in postmortem AD and $A\beta_{42}$ treated age matched control hippocampal slices was concentration dependent starting at 1 picomolar (pM) concentration. PTI 125 is the first therapeutic candidate to preferentially bind an altered protein conformation and reverse this proteopathy.

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1. Introduction

The most frequent cause of dementia, Alzheimer's disease (AD) is a devastating neurodegenerative disorder with an enormous health care burden and no disease modifying treatment. The worldwide AD incidence was 46.8 million in 2015 and is estimated to double every 20 years to reach 74.7 million in 2030 and 131 million by 2050 (Prince et al., 2015).

Although amyloid β , in particular amyloid β_{1-42} ($A\beta_{42}$), is considered the most causative agent in AD, numerous clinical failures of amyloid targeting antibodies have challenged this thesis. Potential reasons for these failures include the possible protective effect of amyloid (Hefter et al., 2016) and treating too late in disease progression, as neuropathology precedes symptoms by 10–25 years (Bateman et al., 2012; Trojanowski et al., 2010). However, a prominent toxic effect of soluble $A\beta_{42}$ delivers an additional explanation.

Cognitive impairment and the magnitude of synaptic deficit in AD brain are more highly correlated with soluble $A\beta_{42}$ than with the abundance of amyloid plaques (Haass and Selkoe, 2007; Näslund et al., 2000), which are actually the lysis remnants of degenerated and $A\beta_{42}$ overburdened neurons (D'Andrea and Nagele, 2006). Extensive research has elucidated the role of the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7nAChR$) in the toxicity of soluble $A\beta_{42}$ (D'Andrea and Nagele, 2006; Dziewczapolski et al., 2009; Inestrosa et al., 2013; Medeiros et al., 2014; Ni et al., 2013; Ondrejcek et al., 2012). Soluble $A\beta_{42}$ binds and signals via $\alpha 7nAChR$, essentially hijacking this receptor to abnormally activate various kinases (Dineley et al., 2002; Hu et al., 2008; Wang et al., 2003; Zhang et al., 2013) to heighten tau phosphorylation. This hyperphosphorylation of tau alters its normal function and cellular distribution and disrupts axonal/dendritic transport, leading to neurofibrillary lesions, dendritic breakdown, and ultimately neurofibrillary tangles (NFTs) (Wang et al., 2003). Importantly, soluble $A\beta_{42}$ binds $\alpha 7nAChR$ with an extraordinarily high (high femtomolar) affinity (Wang et al., 2000a,b), creating substantial competition for antibodies. Amyloid plaques may be more easily bound by antibodies, though this removal may only increase the pool of soluble $A\beta_{42}$ to bind $\alpha 7nAChR$ and other, lower affinity targets.

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PTI 125 is a novel AD drug candidate that binds the scaffolding protein filamin A (FLNA) to prevent A β ₄₂'s toxic cascade via α 7nAChR (Wang et al., 2012). PTI 125's novel mechanism relies on our discovery that A β ₄₂ signaling via α 7nAChR requires the association of FLNA with α 7nAChR, an otherwise nearly nonexistent interaction (Wang et al., 2012). By binding FLNA, PTI 125 reduces A β ₄₂'s binding affinity for α 7nAChR, thereby preventing A β ₄₂'s signaling and further accumulation on α 7nAChRs. PTI 125 markedly improved the functioning of α 7nAChR, N methyl D aspartate receptor (NMDAR) and insulin receptor (IR) in an intra cerebroventricular (ICV) A β ₄₂ infusion mouse model of AD and in human postmortem AD brain, implying some cognitive recovery. PTI 125 even dissociated α 7nAChR bound A β ₄₂ in postmortem AD brain, accomplished by reducing A β ₄₂'s affinity for α 7nAChR 1000 to 10,000 fold. In this acute mouse model, PTI 125 also markedly reduced the levels of hyperphosphorylated tau, NFTs and amyloid deposits, indicating slowed disease progression. In a second function, PTI 125 reduced inflammatory cytokine release by reducing an A β ₄₂ induced association of FLNA with TLR4. This combination of functional enhancement, slowed disease progression and reduced neuroinflammation demonstrated by PTI 125 preclinical data is unparalleled by other therapeutic candidates.

We now show that PTI 125 preferentially binds a disease associated conformation of FLNA. PTI 125 reverses this FLNA proteopathy to prevent its critical role in A β ₄₂'s toxic effects as well as A β ₄₂'s otherwise femtomolar binding to α 7nAChR. We demonstrate PTI 125's beneficial effects in triple transgenic (3xTg) AD mice, starting 2 month oral administration both before and after established neuropathology and in older wild type mice with substantial A β burden. Additionally, using postmortem AD or A β ₄₂ treated age matched control brain slices, we show efficacy at concentrations as low as 1 picomolar (pM). Importantly, PTI 125 largely restores FLNA to its native conformation in AD brain and in mice but has no effect on native FLNA in controls. This conformation dependent differentiation suggests a safety advantage despite a ubiquitous target.

2. Materials and methods

2.1. Materials and chemicals

Anti pY⁹⁶⁰IRb (44 800G) and A β ₁₋₄₂ were obtained from Invitrogen. Anti PSD 95 (05494), A β ₄₂ (AB5739), and NFTs (AB1518) were from Millipore Bioscience Research Reagents. Anti pY^{1150/1151}IR β (SC 81500), phosphotyrosine (SC 508), α 7nAChR (SC 65844), FLNA (SC 7565 [IP], SC 28284, SC 271440), anti-insulin receptor substrate 1 (IRS 1) (SC 515017), TLR4 (SC 293072), IR β (SC 20739, SC 81465), anti-neuronal nitric oxide synthase (nNOS) (SC 5302), phospholipase C γ 1 (PLC γ 1) (SC 7290), pY⁴⁰²PyK (SC 81512), anti-NMDA receptor subunit 1 (NR1) (SC 1467 [IP], SC 9058 [WB]), anti-NMDA receptor subunit 2A (SC 9056), anti-NMDA receptor subunit 2B (SC 9057), tau (SC 1995 [IP], SC 58860 [WB]), γ protein kinase C (SC 166385), actin (SC 7210), β actin (SC 47778), nitro tyrosine (SC 32757), Arc (SC 15325 [IP], SC 17839 [WB]), anti-tumor necrosis factor α (TNF α) (SC 8301), anti-Interleukin 6 (IL 6) (SC 7920), anti-Interleukin 1 β (IL 1 β) (SC 7884) and tau (SC 1995 [IP], SC 58860 [WB]) were all purchased from Santa Cruz Biotechnology. Anti pY⁴¹⁶Src (#2101) was from Cell Signaling. Anti pSer²⁰²tau (AT 8), anti pThr²³¹tau (AT 180), anti pThr¹⁸¹ (AT 270), Reacti Bind NeutrAvidin high binding capacity coated 96 well plates, covalently conjugated protein A/G agarose beads, antigen elution buffer and chemiluminescent reagents were purchased from Pierce Thermo Scientific. Biotinylated anti IL1 β (13 7016 85), anti TNF α (13 7349 85) and anti-IL 6 (13 7068 85) were purchased from eBioscience. Phosphorstop

phosphatase inhibitors (Roche), Complete mini ethyl enediaminetetraacetic acid (EDTA) –free protease inhibitor tablet (Roche), and alkaline phosphatase were purchased from Sigma. A β derived peptides were dissolved in 50 mM Tris, pH 9.0 containing 10% dimethyl sulfoxide (DMSO) and stored at 80 °C. All test agents were freshly made according to manufacturer's recommendation. If DMSO was used as the solvent, the highest DMSO concentration in the incubation medium was 1%.

2.2. Postmortem human brain tissue study

This study protocol conformed to the Declaration of Helsinki: Ethical Principles for Biomedical Research Involving Human Beings (the 4th amendment) as reflected in a prior approval by the City College of New York and City University of New York School of Medicine human research committee. The participants had a uniform clinical evaluation that included a medical history, complete neurological examination, cognitive testing including Mini-Mental State Examination and other cognitive tests on episodic memory, semantic memory and language, working memory, perceptual speed, and visuospatial ability as well as psychiatric rating. Based on this information, subjects received AD diagnoses based on National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984). Postmortem brain tissues of the frontal cortex (FCX) from patients with clinically diagnosed sporadic AD and control tissues from normal, age matched, and neurologically normal individuals were obtained from the Harvard Brain Tissue Resource Center (HBTRC, Belmont, MA, USA) and UCLA Brain Tissue Resource Center (UBTRC, Los Angeles, CA, USA). Both the HBTRC and UBTRC are supported in part by the National Institute of Health. The postmortem time intervals for collecting these brains were ≤ 13 hours (mean postmortem intervals for collection of AD and control brain samples were 6.0 ± 0.9 hours and 5.8 ± 0.8 hours, respectively). The cases used in this study have 79.4 ± 4.0 and 79.4 ± 3.8 years of age as well as postmortem intervals of 4.6 ± 0.9 and 4.5 ± 1.6 hours for ADs and controls, respectively. Diagnostic neuropathological examination was conducted on fixed sections stained with hematoxylin and eosin stain and with modified Bielschowsky silver staining (Yamamoto and Hirano, 1986) to establish any disease diagnosis according to defined criteria (Hyman and Trojanowski, 1997) and brain tissue from age matched controls was similarly screened. The presence of both neuritic (amyloid) plaques and NFTs in all AD brains was confirmed by Nissl and Bielschowsky staining and characterized immunohistochemically with anti A β ₄₂ and NFT staining in frontal and entorhinal cortex as well as hippocampus as described previously (Wang et al., 2000a). Control tissues exhibited only minimal, localized microscopic neuropathology of AD (0–3 neuritic plaques/10 \times field and 0–6 NFTs/10 \times field in hippocampus). One gram blocks from Brodmann areas 10 and/or 46 of FCX were dissected using a band saw from fresh frozen coronal brain sections maintained at 80 °C. All postmortem tissues were identified by an anonymous identification number, and experiments were performed as a best matched pair without knowledge of clinical information.

2.3. Ex vivo incubation of brain slices

For in vitro assessments, postmortem tissues were gradually thawed (from 80 °C to 20 °C), sliced using a chilled McIlwain tissue chopper (200 μ m \times 200 μ m \times 3 mm) and suspended in ice cold oxygenated Krebs's Ringer solution (K R), containing 25 mM HEPES, pH 7.4, 118 mM NaCl, 4.8 mM KCl, 1.3 mM CaCl₂, 1.2 mM KH₂PO₄, 1.2 mM MgSO₄, 25 mM NaHCO₃, 10 mM glucose, 100 μ M

ascorbic acid, and protease inhibitors (approximately 20 mg/1 mL K R). Following centrifugation and 2 additional washes with 1 mL ice cold K R, brain slices were suspended in 1 mL K R.

To test the ex vivo effects of PTI 125 on A β ₄₂ incubated control and native AD tissues, PTI 125 (1 pM–1 nM) was added simultaneously with 0.1 μ M A β ₄₂. Incubation continued for 1 hour in the dark. The incubation mixture in a total incubation volume of 0.5 mL was aerated for 1 minute every 15 minutes with 95% O₂/5% CO₂. Reactions were terminated by addition of 1.5 mL ice cold Ca²⁺ free K R containing protease and protein phosphatase inhibitors, and slices were collected by a brief centrifugation.

2.4. Assessment of PTI 125 affinity for FLNA

PTI 125's affinity for FLNA was measured in synaptic membranes prepared from postmortem hippocampus of control and AD subjects. Brain tissue was homogenized and processed immediately to prepare synaptosomes (P2 fraction) as described previously (Wang et al., 2003). Synaptosomes (200 μ g) prepared from postmortem hippocampus from control and AD subjects were lysed by brief sonication in hypertonic solution (50 mM Tris HCl, pH 7.4, 11.8 mM NaCl, 0.48 mM KCl, 0.13 mM CaCl₂, 0.12 mM KH₂PO₄, 0.13 mM MgSO₄, 2.5 mM NaHCO₃, cocktail of protease, and protein phosphatase inhibitors) and used as the tissue source to determine PTI 125 affinity for FLNA by displacement radioligand binding assay in the presence of 16 concentrations of PTI 125. In this assay, nonspecific binding was defined with 1 μ M naltrexone. Briefly, a displacement curve was generated for the inhibition of [³H]naloxone (0.5 nM) binding by PTI 125 to the enriched synaptic membranes from hippocampus from control and AD subjects. A nonlinear curve fit analysis was performed using competition equation that assumed 2 saturable sites for the PTI 125 curve comprised of 16 concentrations ranging from 100 fM–1 μ M using GraphPad Prism software. Six best matched control AD pairs were included in the analysis.

In a separate experiment series, PTI 125's affinity for FLNA was determined in immunopurified FLNA using [¹⁴C]PTI 125 (57.7 Ci/mmol). Briefly, synaptosomes were prepared from postmortem hippocampus of control and AD subjects as described above. The resultant synaptosomes were sonicated in 150 μ L immunoprecipitation buffer on ice and solubilized with 0.5% NP40/0.2% Na cholate/0.5% digitonin at 4 °C for 1 hour with end over end rotation. Following centrifugation to remove insoluble debris, the protein concentrations of the resultant brain lysates were determined by the Bradford method. One milligram of brain lysates were immunoprecipitated with 5 μ g immobilized anti FLNA on protein A/G conjugated agarose beads in a total of 5 mL overnight at 4 °C. The immunocomplexes were collected by centrifugation and washed 3 times with phosphate buffered saline (PBS) containing 0.05% NP 40 and 0.02% Na cholate. The FLNA protein levels were estimated by the Bradford method by subtracting protein A/G agarose determined by the Bradford method. In this assay, nonspecific binding was defined with 100 μ M PTI 125. Briefly, a binding curve was generated by incubation of 0.1 μ g immunopurified FLNA from control or AD hippocampus with 50 fM–500 nM at 30 °C for 30 minutes. A nonlinear curve fit analysis was performed using an equation that assumed 2 saturable sites for the PTI 125 curve comprised of 16 concentrations ranging from 50 fM–500 nM using GraphPad Prism software. Six best matched control AD pairs were included in the analysis.

2.5. Isoelectric point assessment

To purify FLNA, synaptosomes were prepared from postmortem hippocampi of well matched control and AD pairs that were incubated with 1 nM PTI 125 ex vivo as described above. To ascertain whether PTI 125 exerts its effects on conformation by binding a

specific site on FLNA as previously identified (Wang et al., 2008), control and AD hippocampal synaptosomes were incubated with either 1 nM PTI 125 alone or 1 nM PTI 125 + 10 μ M VAKGL ex vivo for 1 hour as described above. Synaptosomes (200 μ g) were then sonicated for 10 seconds on ice in 200 μ L of modified hypotonic solution (50 mM Tris HCl, pH 8.0, 11.8 mM NaCl, 0.48 mM KCl, 0.13 mM CaCl₂, 0.13 mM MgSO₄, 2.5 mM NaHCO₃, cocktail of protease inhibitors) and treated with 100 μ g/mL of alkaline phosphatase at 30 °C for 30 minutes. The reaction was terminated by addition of 100 μ M sodium vanadate and 5 mM NaF with cocktail of protein phosphatase inhibitors and solubilized using 0.5% digitonin/0.2% sodium cholate/0.5% NP 40 at 4 °C with end over end rotation for 1 hour. Following centrifugation to remove insoluble debris, the obtained lysate was treated with 1% sodium dodecyl sulfate (SDS) for 1 minute to dissociate the FLNA associated proteins, diluted 10 fold with immunoprecipitation buffer, and immunopurified with immobilized anti FLNA. The resultant FLNA was eluted using 200 μ L antigen elution buffer (Thermo), neutralized immediately with 100 mM Tris HCl (pH 9.0), diluted to 500 μ L with 50 mM Tris HCl, pH 7.5, and passed through a 100 kD cut off filter to remove low molecular weight FLNA fragments. Once purified, the FLNA was suspended in 100 μ L isoelectric focusing sample buffer. Samples (50 μ L) were loaded onto pH 3–10 isoelectric focusing gels and the proteins were fractionated (100 V for 1 hour, 200 V for 1 hour, and 500 V for 30 minutes). The separated proteins were then electrophoretically transferred to nitrocellulose membranes. FLNA was identified by Western blotting with anti FLNA.

2.6. The assessment of residual PTI 125 using [¹⁴C]PTI 125 binding

The levels of residual PTI 125 in brains of treated mice were estimated using [¹⁴C]PTI 125 binding. Synaptosomes were prepared from ~10 mg prefrontal cortices from ICV A β ₄₂ infused mice treated twice daily with vehicle or PTI 125 (10 mg/kg) as well as 4 and 8 month old mice treated for 2 months orally (30 mg/kg/d of PTI 125 HCl). Tissues were lysed by brief sonication in hypertonic solutions to obtain synaptosomes. The resultant synaptic membranes were washed 3 times in 2 mL ice cold binding buffer (50 mM Tris HCl, pH 7.4, 100 mM NaCl, protease, and protein phosphatase inhibitors). To assess [¹⁴C]PTI 125 binding, 50 μ g of synaptic membranes were incubated with 1 nM [¹⁴C]PTI 125 (57.7 Ci/mmol) in 250 μ L at 30 °C for 30 minutes. The synaptic membranes were collected by filtration on GF/C filter under vacuum. Following 3 washes with ice cold binding buffer, the resultant filters were air dried and counted by scintillation spectrometry. The data are expressed as pg of PTI 125 per mg of synaptic membranes.

2.7. In vivo oral administration of PTI 125

Four and 8 month old male and female E129 mice (30–35 g) from Taconic (Germantown, NY, USA) and 3xTg AD mice (containing 3 mutations: APP Swedish, MAPT P301L, and PSEN1 M146V) of stock supplied by Dr. Frank LaFerla (Oddo et al., 2003) were maintained on a 12 hour light/dark cycle with free access to food and water. All animal procedures comply with the National Institutes of Health Guide for Care Use of Laboratory Animals and were approved by the City College of New York Animal Care and Use Committee.

Mice were housed individually for a week to assess the daily intake of water that had been sweetened with 0.25 g sucralose/100 mL purified water. The average daily water intake was found to be approximately 5 mL.

To assess the effect of in vivo PTI 125, mice received 30 mg/kg/d of PTI 125 HCl (22 mg/kg/d free base equivalent) orally via drinking water (18 mg PTI 125 HCl/100 mL purified water sweetened with

0.25 g sucralose) for 2 months. Mice were sacrificed by decapitation. Brain regions such as FCX and hippocampus from one half of the brain were homogenized and processed immediately after harvesting to obtain synaptosomes (P2 fraction) as described previously (Wang et al., 2003) for neuropharmacological assessments. Synaptosomes were washed twice and suspended in 2 mL ice cold oxygenated K R: 25 mM HEPES, pH 7.4; 118 mM NaCl, 4.8 mM KCl, 25 mM NaHCO₃, 1.3 mM CaCl₂, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 10 mM glucose, 100 μ M ascorbic acid, mixture of protease, and protein phosphatase inhibitors (Roche Diagnostics) that had been aerated for 10 minutes with 95% O₂/5% CO₂. The protein concentration was determined using the Bradford method (Bio Rad). The other brain halves were immersion fixed in cold 0.15 M phosphate buffered 10% formalin, pH 7.4, and processed for immunohistochemical determinations of intraneuronal A β ₄₂ aggregates/plaques and NFTs as well as morphological integrity.

2.8. Assessment of FLNA- α 7nAChR, FLNA-TLR4 and A β ₄₂- α 7nAChR associations by coimmunoprecipitation

These assessments used previously (Wang et al., 2012) described coimmunoprecipitation methods. Two hundred mg of synaptosomes from either postmortem brain slices or prefrontal cortex or hippocampus of treated mice were pelleted by centrifugation, solubilized by brief sonication in 250 mL of immunoprecipitation buffer (25 mM HEPES, pH 7.5; 200 mM NaCl, 1 mM EDTA, cocktail of protease, and protein phosphatase inhibitors) and incubated at 4 °C with end to end shaking for 1 hour. Following dilution with 750 mL of ice cold immunoprecipitation buffer and centrifugation (4 °C) to remove insoluble debris, the FLNA- α 7nAChR/TLR4 and A β ₄₂- α 7nAChR complexes in the lysate were isolated by immunoprecipitation with 16 hour incubation at 4 °C with respective rabbit anti FLNA (1 mg) and anti A β ₄₂ antibodies (1 mg) immobilized on protein A conjugated agarose beads. The resultant immunocomplexes were pelleted by centrifugation at 4 °C. After 3 washes with 1 mL of ice cold PBS (pH 7.2) and centrifugation, the isolated FLNA- α 7nAChR/TLR4 and A β ₄₂- α 7nAChR complexes were solubilized by boiling for 5 minutes in 100 mL of SDS polyacrylamide gel electrophoresis (PAGE) sample preparation buffer (62.5 mM Tris HCl, pH 6.8; 10% glycerol, 2% SDS; 5% 2 mercaptoethanol, 0.1% bromophenol blue). The content of α 7nAChRs/TLR4s in 50% of the anti FLNA and α 7nAChRs in 50% of the anti A β ₄₂ immunoprecipitate was determined by Western blotting with monoclonal anti α 7nAChR or TLR4 antibodies. The FLNA- α 7nAChR/TLR4 complex blots were stripped and reprobed with monoclonal anti FLNA to validate equal immunoprecipitation efficiency and loading. To determine A β ₄₂- α 7nAChR complex levels, immobilized rabbit anti actin (1 μ g) protein A conjugated agarose was added together with anti A β ₄₂ in the coimmunoprecipitation process. Immunoblotting with monoclonal anti β actin was used to determine the content of β actin in resultant immunoprecipitates to illustrate even immunoprecipitation efficiency and loading.

2.9. Tau phosphorylation and nitration

Using an established method (Wang et al., 2003, 2010), tau proteins in synaptosomes from A β ₄₂ incubated hippocampal slices from control subjects with and without 1 pM 1 nM PTI 125 were immunoprecipitated with immobilized anti tau (SC 65865), which does not discriminate between phosphorylation states. The levels of phosphorylated tau (pSer²⁰²tau, pThr²³¹tau and pThr¹⁸¹tau), nitrated tau (nYtau) as well as total tau precipitated (loading controls) were assessed by Western blotting using antibodies specific to each individual phosphopeptide, anti nitrotyrosine, and anti tau, respectively.

2.10. NMDAR and IR signaling assessments

NMDAR and IR signaling were assessed in low Mg²⁺ Krebs Ringer (LMKR): 25 mM HEPES, pH 7.4, 118 mM NaCl, 4.8 mM KCl, 1.3 mM CaCl₂, 1.2 mM KH₂PO₄, 0.3 mM MgSO₄, 25 mM NaHCO₃, 10 mM glucose, 100 μ M ascorbic acid and protease inhibitors, and K R, respectively. Slices were aerated with 95% CO₂/5% O₂ every 15 minutes for 1 minute. To assess the PTI 125 effect, postmortem hippocampal slices were exposed to PTI 125 (1 pM–1 nM) at 37 °C for 30 minutes prior to addition of NMDA/glycine or insulin. NMDAR activation and signaling were initiated by incubation of ~10 mg of ex vivo treated brain slices with either LMKR (basal) or LMKR containing 10 μ M NMDA and 1 μ M glycine at 37 °C for 30 minutes. For initiation of IR activation and signaling, ~10 mg of ex vivo treated postmortem human hippocampal slices or in vivo treated mouse prefrontal cortical slices were incubated with either K R (basal) or K R containing 1 nM insulin at 37 °C for 30 minutes. The incubation mixtures were aerated with 95% O₂/5% CO₂ every 10 minutes for 1 minute. Ligand stimulation was terminated by the addition of 1 mL ice cold Ca²⁺ free K R containing 0.5 mM aminopolycarboxylic acid (EGTA) and 0.1 mM EDTA with protease and protein phosphatase inhibitors. Slices were harvested by a brief centrifugation and homogenized in 250 μ L ice cold immunoprecipitation buffer. The homogenates were centrifuged at 1000 \times g for 5 minutes (4 °C) and the supernatant (postmitochondrial fraction) sonicated for 10 seconds (5 \times 2 seconds) on ice. The proteins were solubilized in 0.5% digitonin, 0.2% sodium cholate, and 0.5% NP 40 for 60 minutes at 4 °C with end over end rotation. The resultant lysates were cleared by centrifugation at 50,000 \times g for 5 minutes and diluted with 0.75 mL immunoprecipitation buffer. Protein concentrations were measured by the Bradford method (Bio Rad).

To determine NMDAR signaling and the NMDAR association with PSD 95, the levels of NMDAR subunits, PSD 95 and NMDAR associated signaling molecules were measured in anti NR1 immunoprecipitates. Brain slice lysates (200 μ g) were immunoprecipitated overnight at 4 °C with 2 μ g of immobilized anti NR1 onto covalently conjugated protein A/G agarose beads (Pierce ENDODEN). Anti NR1 immunoprecipitates were incubated with 75 μ L antigen elution buffer (Pierce ENDODEN) and 2% SDS for 2 minutes on ice, centrifuged to remove antibody protein A agarose complexes and neutralized immediately with 10 μ L 1.5 M Tris buffer, pH 8.8 followed by addition of 15 μ L 6 \times PAGE sample buffer and boiling for 5 minutes. Half of the obtained eluates (50 μ L) were then size fractionated on 7.5% SDS PAGE. Proteins were transferred to nitrocellulose membrane and the levels of PSD 95, and signaling proteins were measured using Western blotting with specific antibodies for PSD 95, nNOS, phospholipase C γ 1, γ protein kinase C, pY⁴⁰²PyK2, and pY⁴¹⁶Src. Blots were stripped and reprobed with anti NR1 to assess loading.

To determine IR activation and signaling, the levels of pY^{1150/1151} and pY⁹⁶⁰ IRs as well as IRS 1 recruited to IR were measured in anti IR β immunoprecipitates following incubation of brain slices with 1 nM insulin in K R for 30 minutes. These experiments followed the above procedures for assessing NMDAR signaling, but immunoprecipitated with immobilized anti IR β -protein A/G agarose beads and detected levels of activated IR (pY^{1150/1151} and pY⁹⁶⁰) and recruited IRS 1 using Western blotting with antibodies for pY^{1150/1151} IR β , pY⁹⁷² IR β or IRS 1. Blots were stripped and reprobed with anti IR β to assess loading.

2.11. Assessment of NMDAR activation induced Arc expression

To determine the effect of PTI 125 on NMDAR activation induced Arc expression, ~10 mg of ex vivo treated postmortem human hippocampal slices or in vivo treated mouse prefrontal

cortical slices were incubated at 37 °C with LMKR for 30 minutes, 10 μ M NMDA/1 μ M glycine for 10 minutes followed by LMKR for 20 minutes, in a total incubation volume of 200 μ L. Following a 30 minute incubation, protein phosphatase inhibitors were added, and the reaction mixture diluted 5 fold with ice cold Ca^{2+} LMKR and placed on ice for 5 minutes. Brain slices were collected after brief centrifugation and sonicated for 10 seconds (5×2 seconds) on ice in 200 μ L of ice cold immunoprecipitation buffer containing protease and protein phosphatase inhibitors. The homogenates were centrifuged at 1000g for 5 minutes to yield crude post mitochondrial fractions. The resultant supernatants were solubilized by addition of 0.5% digitonin/0.2% Na cholate/0.5% NP 40 at 4 °C with end over end rotation for 1 hour. Following centrifugation to remove insoluble debris, the protein concentrations of the resultant brain lysates were determined by the Bradford method. Brain lysates (200 μ g) were immunoprecipitated with 1 μ g immobilized anti Arc and actin on protein A/G conjugated agarose beads (serving as immunoprecipitation/loading control) overnight at 4 °C. The immunocomplexes were collected by centrifugation and washed 3 times with PBS containing 0.05% NP 40 and 0.02% sodium cholate and then solubilized by boiling for 5 minutes in 1 \times SDS PAGE sample preparation buffer. Following centrifugation to remove protein A/G conjugated agarose beads in the solubilized immunoprecipitates, 50% of the resulting supernatant containing Arc, actin, and their associated proteins were size fractionated by SDS PAGE.

2.12. Assessment of cytokine levels in mice

Parietal cortices (~10 mg) from vehicle and PTI 125 treated mice were thawed slowly (80 °C to 20 °C to 4 °C), homogenized in 100 μ L ice cold homogenization medium (25 mM HEPES, pH 7.5; 50 mM NaCl, mixture of protease and protein phosphatase inhibitors) by sonication and then solubilized with 0.5% NP 40, 0.2% sodium cholate, and 0.5% digitonin at 4 °C for 1 hour with end over end shaking. Following centrifugation, lysates were diluted with 500 μ L to a total volume 600 μ L.

To determine cytokine levels in the lysates, 0.5 μ g/well biotinylated mouse monoclonal anti TNF α , IL 6, and IL 1 β were coated onto streptavidin coated plates (Reacti Bind NeutrAvidin high binding capacity coated 96 well plate). Plates were washed 3 times with ice cold 50 mM Tris HCl (pH 7.4) and incubated at 30 °C with 100 μ L of lysate for 1 hour. Plates were washed 3 times with ice cold 50 mM Tris HCl (pH 7.4) and incubated at 30 °C with 0.5 mg/well unconjugated rabbit anti TNF α , IL 6, and IL 1 β for 1 hour. After 2 washes with 50 mM Tris HCl (pH 7.4), each well was incubated in 0.5 mg/well fluorescein isothiocyanate conjugated anti rabbit immunoglobulin G (human and mouse absorbed) for 1 hour at 30 °C. Plates were washed 3 times with 200 μ L ice cold Tris HCl, and the residual fluorescein isothiocyanate signals were determined by a multimode plate reader (DTX880, Beckman). Each lysate was surveyed twice.

2.13. Immunohistochemical studies of mice

Quantitative immunohistochemistry on consecutive 8 μ m sections containing prefrontal cortex and entorhinal cortex/hippocampus was used to determine the levels of A β ₄₂ aggregates/plaques and neurofibrillary pathology (NFT and paired helical filament [PHF] immunoreactivity) using single labeling immunohistochemistry as described previously (D'Andrea et al., 2001; Nagele et al., 2002; Wang et al., 2010). One section was immunostained with anti NFT or PHF. The next (consecutive) section (often containing the same neuron) was immunostained with anti A β ₄₂ antibodies to measure relative levels of accumulated A β ₄₂ peptide in neurons. The relative

A β ₄₂ accumulation was compared among different cell types using a computer assisted image analysis as described previously (Wang et al., 2000a,b). Brain tissues were fixed at 4 °C in 0.15 M phosphate buffered 10% formalin, pH 7.4 for 2 weeks, paraffin embedded, serially sectioned at 5 μ m, and processed for brightfield. The A β ₄₂ immunoreactivity was absent when preabsorbing anti A β ₄₂ with A β ₄₂ but not with A β ₄₂₋₁. Specimens were examined using a Nikon FXA microscope with a Princeton Instruments charge coupled device camera and recorded digitally. Relative intensities of the NFT/PHF and A β ₄₂ immunoreactivity were measured and compared among similar and different cell types using Image Pro Plus and Metamorph software. The correlations between the amounts of NFT/PHF immunoreactivity and A β ₄₂ positive accumulation within mature neurons were also determined.

2.14. Assessing spatial memory with Y maze

The effects of PTI 125 on hippocampus dependent spatial memory performance were assessed using Y maze with extra maze visual cues around maze as previously described (Wesierska et al., 2005). All mice were transported to the behavioral testing room in their home cages at least 1 hour before testing. Visual cues were placed above each arm of the maze and kept constant during all testing sessions. The test consisted of 2 trials, an acquisition trial and a recognition trial, separated by an inter trial interval. The first test was performed a week before the end of treatment with a 1 minute inter trial interval and served to habituate mice to the apparatus. In the acquisition trial of this initial test, the mouse was placed in a pseudo randomly chosen start arm and allowed to explore the maze freely for 5 minutes with one arm closed (the novel arm). For the inter trial interval and to control for spontaneous novelty exploration, the mouse was returned to the home cage for 1 minute. In the second (recognition) trial, the mouse was returned to the maze to explore freely with all 3 arms opened for 2 minutes. The actual test was performed a week later using a 2 hour inter trial interval between the acquisition and recognition trials. The Y maze was cleaned between trials to eliminate any olfactory cues. The time spent in the novel (previously closed) arm was calculated as the percentage of the total time spent in all arms. The experimenters were blind to the genetic background and treatment and mice were tested in random sequence. The data were analyzed without knowledge of mouse identity.

2.15. Assessing working memory using Y maze spontaneous alternation paradigm

The working memory test with Y maze was conducted as described previously (Yau et al., 2007). In this test, all 3 arms of the maze were left open. Mice were placed at the center of the maze with the facing direction randomized for each test. The number and sequence of arm entrances were recorded for 5 minutes. The percent alternation was calculated as the number of alternation (defined as entries into the 3 different arms consecutively) divided by the total possible alternations (the number of arms entered minus 2) multiplied by 100.

2.16. Nesting behavior assessment

Nesting behavior, a type of affiliative behavior, is displayed by both males and females in both parental and nonparental contexts. Mice were individually housed for at least 24 hours in clean plastic cages with approximately 1 cm of corn cob bedding lining the floor and identification cards coded to render the experimenter blind to the sex, age, and genotype of each mouse. Two hours prior to the onset of the dark phase of the lighting cycle, individual cages were

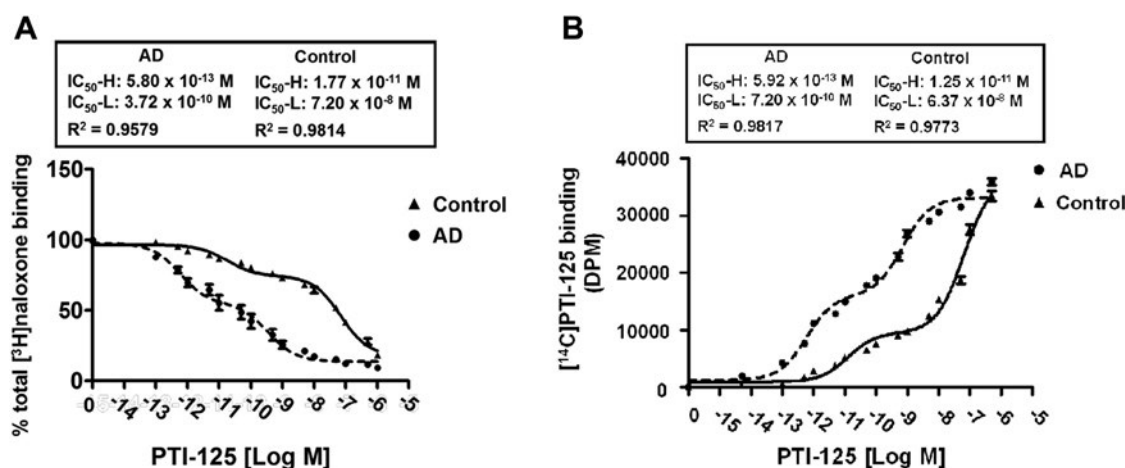


Fig. 1. PTI-125 bound AD postmortem tissue with 580 femtomolar affinity and age-matched control with 18 picomolar affinity, illustrating an altered FLNA conformation and higher binding affinity in diseased brain. A displacement binding assay used a competition curve for the inhibition of [³H]naloxone binding by 16 concentrations of PTI-125 ranging from 0.1 pM to 1 μ M in synaptic membranes from postmortem hippocampi of 6 best matched control-AD pairs (A). [¹⁴C]PTI-125 (0.05 pM–0.5 μ M) binding to FLNA immunopurified from AD and age-matched control tissue confirms that this high-affinity binding is to FLNA, and further illustrates the difference in binding affinity between AD and age-matched control (B). Abbreviations: AD, Alzheimer's disease; FLNA, filamin A.

supplied a 20 cm \times 20 cm piece of paper towel cut into approximately 5 cm squared pieces. To reduce variability in housing conditions, mice were tested in counterbalanced groups of mixed genotypes and ages. The next morning (20 hours later) cages were inspected for nest construction. Pictures were taken prior to evaluation for documentation. Paper towel nest construction was scored on a 3 point system (1 = no biting or tears on the paper, 2 = moderate biting and/or tears on the paper but no coherent nest [not grouped into a corner of the cage] and 3 = the vast majority of paper torn into approximately 1 cm pieces and grouped into a corner of the cage). This scoring system was selected after blindly assessing the pictures and noting that the paper towel material was mostly either made into a nest or not disturbed at all (not torn and scattered across the cage). Nestlet nest construction was scored using the established system of Deacon (Wesson and Wilson, 2011).

2.17. Western blot analysis

Solubilized immunoprecipitates derived from coimmunoprecipitation assays were separated by either 7.5 or 10% SDS PAGE and electrophoretically transferred to nitrocellulose membranes. Membranes were washed with PBS 3 times and blocked overnight at 4 $^{\circ}$ C with 10% milk in PBS with 0.1% Tween 20 (PBST). Following three 5 minute washes with 0.1% PBST, the membranes were incubated at room temperature for 2 hours with the appropriate antibody at 1:500–1:1000 dilutions. After three 2 minute washes in 0.1% PBST, membranes were incubated for 1 hour with anti species immunoglobulin G horseradish peroxidase (1:5000 dilution) and washed with 0.1% PBST 3 times, 2 minutes each. Immunoreactivity was visualized by reacting with chemiluminescent reagent (Pierce ENDGEN) for exactly 5 minutes and immediate exposure to X ray film. Specific bands were quantified by densitometric scanning (GS 800 calibrated densitometer, Bio Rad).

2.18. Statistical analysis

All data are presented as mean \pm standard error from the mean. Treatment/group effects were evaluated by one way analysis of variance followed by Newman–Keul's multiple comparison. Two tailed Student's *t* test was also used as the post hoc test for between group differences. The threshold for significance was *p* < 0.05.

3. Results

3.1. Mechanism of action of PTI 125

PTI 125 was derived from an iterative in silico/in vitro screening process against a known pentapeptide region of FLNA with subsequent medicinal chemistry. Because we previously showed that naloxone and naltrexone bind this site on FLNA (Wang et al., 2008), we were able to show that PTI 125 binds FLNA using a displacement assay. We showed a femtomolar binding affinity for PTI 125 in AD tissue but only picomolar affinity in control brain (Fig. 1A), suggesting an altered conformation of FLNA in AD. Confirmation that FLNA is the high affinity target of PTI 125 is provided by [¹⁴C] labeled PTI 125 binding to FLNA immunopurified from AD and age-matched control tissue (Fig. 1B). Impressively, the differential binding affinity between AD and control is maintained after immunopurification of FLNA from these 2 postmortem tissue sources.

To reveal a potential altered conformation of FLNA in AD, we compared the isoelectric focusing point (pI) of FLNA in postmortem AD tissue versus controls. An altered pI reflects a disease associated conformation (Stucky et al., 2016; Ui, 1973). A shift in pI from 5.9 to 5.3 was detected for FLNA purified from AD tissue, supporting an altered conformation in FLNA in AD brain (Fig. 2A). The pI's were not sensitive to complete dephosphorylation by alkaline phosphatase, indicating that phosphorylation state is not critical to either the native or AD conformation of FLNA. Importantly, PTI 125 in incubation at 1 nM for 1 hour largely restored FLNA to its native conformation in each (Fig. 2A). To ascertain whether the conformation reversing effect of PTI 125 is a direct result of FLNA binding, we incubated PTI 125 with a decoy pentapeptide (VAKGL) with the identical sequence of the key PTI 125 binding domain. This pentapeptide is expected to block PTI 125 from binding FLNA and thereby prevents PTI 125's effects. While neither PTI 125 nor the PTI 125/VAKGL combination affected FLNA from control tissues, the pentapeptide blocked PTI 125's ability to restore the AD related FLNA conformation to FLNA's native form (Fig. 2B). Without the decoy, PTI 125 restored 70.9% \pm 3.6% of FLNA to the native conformation; with the decoy, 98.3% \pm 0.6% remained in the altered conformation. These data clearly indicate that the reversal of FLNA's altered conformation by PTI 125 requires PTI 125 binding to FLNA.

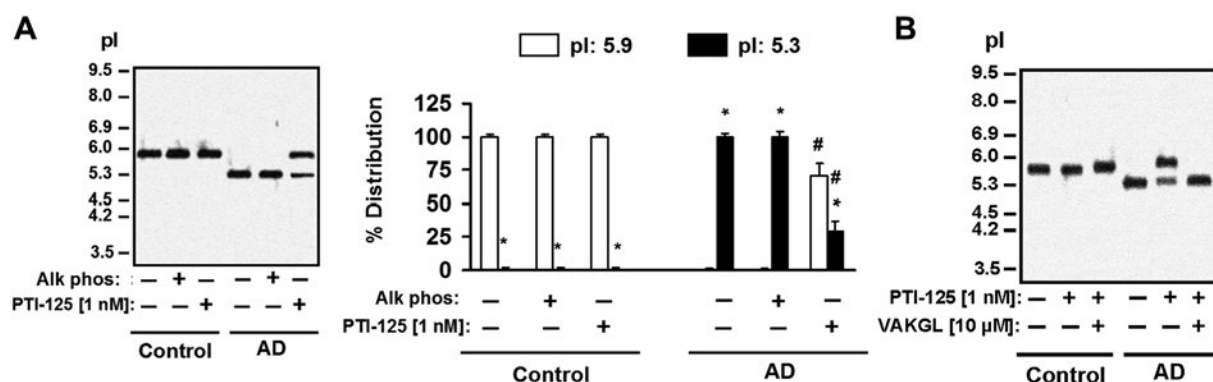


Fig. 2. FLNA conformation is altered in AD. The conformational states of the immunopurified FLNA was analyzed by separating on pH 3–10 isoelectric-focusing gels and then Western blotted with anti-FLNA. (A) FLNA in AD postmortem brain has an isoelectric focusing point (pI) that is shifted from that of FLNA in age-matched control brain. Dephosphorylation by alkaline phosphatase did not alter the conformation, illustrating that the conformations are independent of phosphorylation state. PTI-125 incubation (1 nM) largely restored the conformation of FLNA to its non-AD state. $n = 6$. * $p < 0.00001$ versus non-diseased FLNA conformation (pI 5.9) within group; # $p < 0.00001$ versus respective FLNA pI in AD without PTI-125 (with or without alk phos). (B) Addition of the decoy pentapeptide VAKGL to prevent PTI-125 binding to FLNA completely blocked PTI-125's ability to restore FLNA's native conformation by PTI-125 (representative isoelectric focusing gel of $n = 4$). Abbreviations: AD, Alzheimer's disease; FLNA, filamin A.

Abnormal FLNA was also found in the ICV A β_{42} infused mice from our earlier work (Wang et al., 2012) and in 6- and 10-month 3xTg AD mice with abundant A β_{42} and in 10-month wild type mice with age-dependent A β_{42} accumulation. PTI 125 treatment by 2-week intraperitoneal injection in ICV A β_{42} infused mice or by 2-month oral administration in 3xTg mice before and after apparent neuropathology and in older wild type mice restored FLNA to its native conformation (Fig. 3). Importantly, PTI 125 has no effect on the conformation of FLNA in younger wild type mice with no pathology.

The femtomolar PTI 125 affinity for FLNA in postmortem AD brain or in brains of ICV A β_{42} infused mice suggests an extremely low off rate. To examine this extended retention time, we measured the amount of bound PTI 125 in brains of PTI 125 treated mice in both mouse efficacy studies (Fig. 4). We incubated synaptic membranes from parietal cortices of vehicle- and PTI 125 treated mice with C^{14} labeled PTI 125 after first washing off any unbound PTI 125. As expected, the vehicle-treated mice in all groups bound the most labeled PTI 125 because there was no PTI 125 from prior treatment to occupy binding sites on FLNA. Of the PTI 125 treated mice, the most C^{14} PTI 125 binding was seen in the 6-month

wild type mice that showed no pathology, followed by the 10-month wild type mice with intermediate pathology, followed by the transgenic and ICV A β_{42} infused mice. Hence, the ICV A β_{42} infused and 3xTg AD mice—with the most FLNA in its diseased conformation—retained the most PTI 125 and the 4-month mice without pathology—and FLNA in its native conformation—retained the least. Because synaptic membranes represent 1% of total tissue, the pg/mg synaptic membranes can be converted to pg/0.1 g of total tissue or pg/0.1 mL for purposes of molarity conversion. The retained PTI 125 bound to FLNA (its only high affinity target that we know) in tissue is therefore 3 nM for ICV A β_{42} infused and 10-month transgenic mice, 2.8 nM for 6-month transgenic mice, 1.9 nM for 10-month wild type mice, and 0.45 nM for 6-month wild type mice. These data summarized in Figs. 2–4 confirm that A β_{42} induces an altered conformation of FLNA that PTI 125 binds with substantially higher affinity. This femtomolar binding of PTI 125 to the altered conformation survives washing to exert its long-lasting therapeutic benefits, in contrast to the lower affinity binding of PTI 125 to FLNA in its nondiseased state. These data also confirm that the low nanomolar brain tissue levels are in the range of expected efficacious concentrations based on adult rat

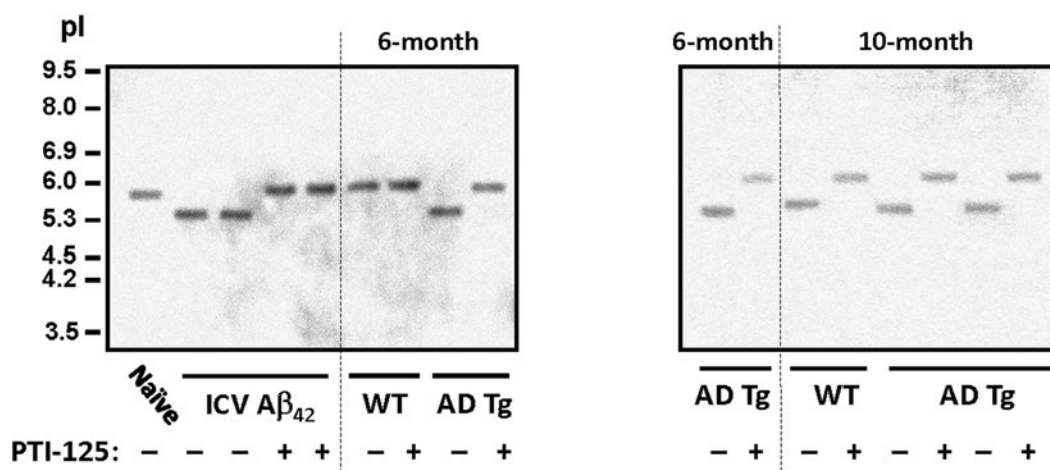


Fig. 3. As in AD postmortem tissue, the pI of FLNA in ICV A β_{42} -infused, 3xTg AD or aged mice was shifted from 5.9 to 5.3, indicating an altered FLNA conformation induced by A β_{42} infusion, by AD or simply age. PTI-125 administration in both in vivo experiments (20 mg/kg intraperitoneal in the ICV A β_{42} -infused mice and 22 mg/kg oral for transgenic and aged mice) restored this pI to that of the younger or naïve mice. Abbreviations: AD, Alzheimer's disease; FLNA, filamin A; ICV, intra-cerebroventricular; pI, focusing point; 3xTg, triple-transgenic.

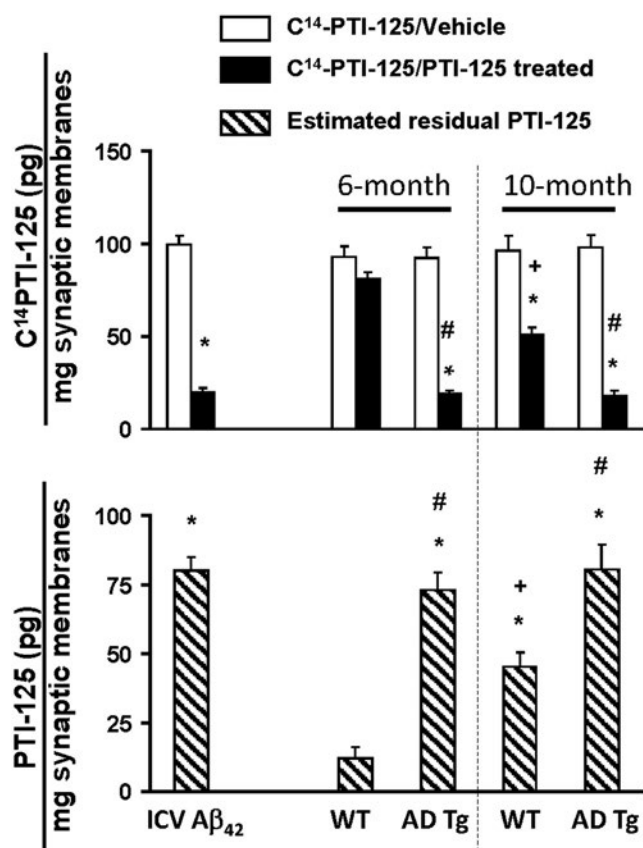


Fig. 4. C¹⁴-PTI-125 binding to brains of PTI-125-treated mice illustrated the residual, tightly-bound PTI-125 in both experiments as well as the level of abnormal FLNA with an altered conformation in each. Washed synaptic membranes were incubated with [C¹⁴]PTI-125 to assess the levels of PTI-125 binding and residual PTI-125 in the brains of treated animals. Amounts of residual PTI-125 in brains correlated with severity of Aβ₄₂ burden with the highest in Aβ₄₂-infused mice and transgenic mice, intermediate in aged mice, and least in younger control mice. **p* < 0.01 versus vehicle in each group; #*p* < 0.01 versus wildtype in respective age group; +*p* < 0.01 versus 4-month wildtype. Abbreviation: FLNA, filamin A.

brain slice cultures and the current postmortem human tissue experiments.

3.2. In vivo efficacy in 3xTg AD and aged wild type mice

To establish safety and efficacy of more chronic dosing, we performed a 2 month oral dosing study in 4 month and 8 month 3xTg AD mice, which show age dependent progressive neuropathology and associated cognitive deficits. Controls were wild type 4 and 8 month old E129 mice that by 10 months showed a notable but milder Aβ₄₂ burden and associated pathological effects. PTI 125 via drinking water (22 mg/kg/d) robustly reduced FLNA-α7nAChR/TLR4 associations (Fig. 5A). The reduced FLNA associations in turn resulted in attenuated tau phosphorylation, Aβ₄₂-α7nAChR complexes and inflammatory cytokine levels in 3xTg and aged wild type mice (Fig. 5B–D). This reduction of FLNA-α7nAChR association in hippocampus was mirrored in peripheral blood lymphocytes (data not shown), adding support to our companion biomarker PTI 125 DX. Oral administration of PTI 125 markedly reduced Aβ deposits (Fig. 6) and phosphorylated tau rich NFTs (Fig. 7) in FCX and hippocampus of 3xTg and 8 month wild type mice.

The therapeutic benefits of PTI 125 improved function of NMDA and insulin receptors (Fig. 8). NMDAR signaling was assessed by the

amounts of NMDA/glycine induced associated activated key regulatory kinases, Src (pY⁴¹⁶Src) and PyK2 (pY⁴⁰²PyK2) as well as recruited signaling molecules, phospholipase C γ1 and nNOS and scaffold protein, PSD 95 relative to the obligatory NMDAR subunit NR1 (Fig. 6A). Similarly, 2 month oral administration of PTI 125 also normalized insulin receptor function as indicated by the higher insulin induced tyrosine phosphorylated IRβ (pY^{1150/1151} and pY⁹⁶⁰) and IRS 1 recruitment (Fig. 6B). Importantly, the improved receptor function following 2 month PTI 125 treatment leads to a healthier synaptic activation. This is indicated by a more robust stimulation (by NMDA + glycine) driven expression of the master synaptic plasticity regulator Arc (activity dependent cytoskeleton associated protein) in 3xTg and 10 month old mice (Fig. 6C). These data together indicate that by improving NMDAR and IR function, PTI 125 augments synaptic plasticity.

Although group sizes in this experiment were small for behavioral assessments (*n* = 5 or 6), PTI 125 elicited improvements were noted in nesting behavior (a test of social function) and in spatial and working memory (Fig. 9). PTI 125 significantly improved nesting behavior in 6 month 3xTg AD mice (*p* < 0.01) but the improvement in 10 month 3xTg AD mice was weaker and not significant. On a test of spatial memory, 6 month 3xTg AD mice were significantly impaired compared to 6 month wildtypes (*p* < 0.05), but there was no significant difference between PTI 125-treated 6 month AD transgenics and 6 month wildtypes (treated or untreated). Spatial memory was also impaired in 10 month AD transgenics compared to 6 month wildtypes (*p* < 0.01), and PTI 125 treatment of 10 month 3xTg AD mice significantly improved spatial memory (*p* < 0.05). PTI 125 also significantly improved working memory in 6 month AD transgenic mice (*p* < 0.05).

There were no drug related findings in histopathology in 6 major organs of these treated mice, supporting PTI 125's safety. Drug exposure from this 2 month study was 1532 ± 86.7 ng/mL (5.9 μM) in plasma and 4.94 ± 1.17 ng/g (19 nM) in brain homogenate (of wildtype mice), easily in excess of the effective dose range of 1 pM to 1 nM in ex vivo postmortem human brain slices. These exposure data were obtained with an LC MS/MS bioanalytical method for plasma that has since been validated for good laboratory practice use.

3.3. Ex vivo efficacy in postmortem AD hippocampus

PTI 125's restoration of receptor function, improved synaptic plasticity and reduced tau hyperphosphorylation that were seen in vivo were also demonstrated in our ex vivo experiments with postmortem human brain tissue. We demonstrated that 1 hour incubation of 1 nM PTI 125 is effective in normalizing receptor activities in AD frontal cortices (Wang et al., 2012). To address the dose dependency of PTI 125 effects, we further investigated the efficacy of lower concentrations that are closer to PTI 125's femtomolar binding affinity in the current ex vivo experiments. Postmortem hippocampal slices from 5 pairs of AD patients and age matched controls were incubated for 1 hour with a concentration range of 1 pM–1 nM PTI 125. We also examined hippocampus to demonstrate that the effects of PTI 125 are not unique to the region earlier tested (FCX). In this study, subnanomolar concentrations of PTI 125 elicited the same beneficial effects previously shown with 1 nM PTI 125, although the magnitude of those effects were lower at 10 and 1 pM than at 100 pM or 1 nM, demonstrating a clear dose response. We also noted that the impairments in hippocampus were more severe than those noted earlier in FCX from the same (plus 6 additional) patients (Wang et al., 2012).

PTI 125 dose dependently reduced Aβ₄₂ induced FLNA coupling to α7nAChR and TLR4 in both Aβ₄₂ treated control and AD hippocampus (Fig. 10A). FLNA-TLR4 coupling was reduced starting at 10 pM in AD tissue and at 1 pM in Aβ₄₂ treated control.

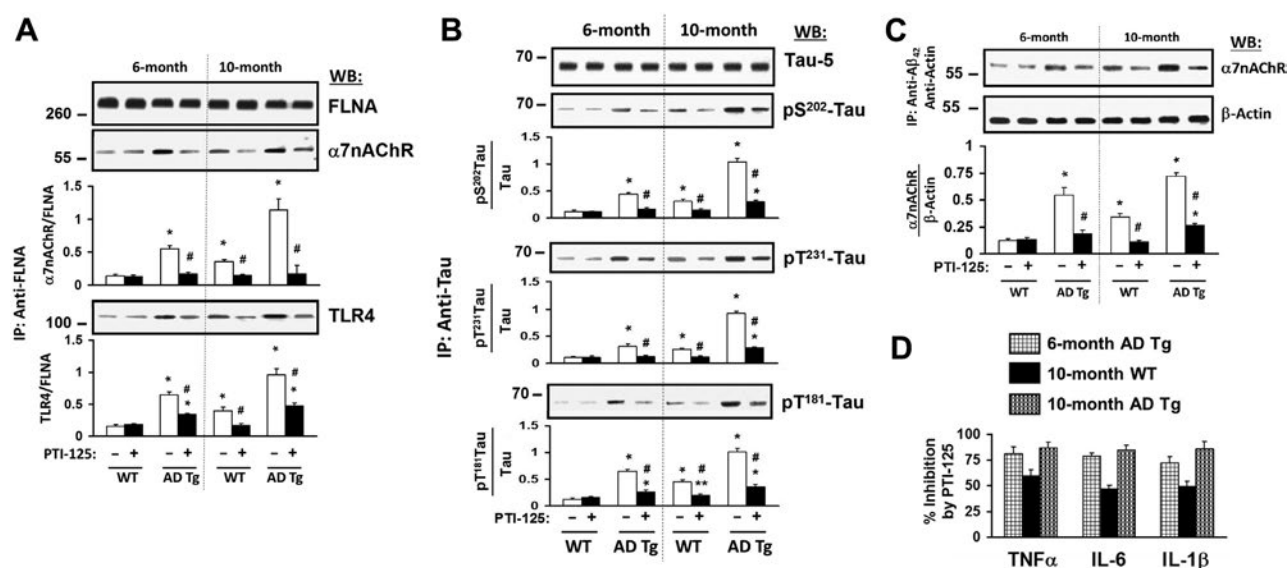


Fig. 5. Two-month administration of PTI-125 via drinking water (~22 mg/kg/d) to wild-type or 3xTg AD mice starting at 4 or 8 months of age reduced tau phosphorylation (A) and Aβ₄₂-α7nAChR complexes (B) in frontal cortex of 3xTg AD or the older wild-type mice. Demonstrating its mechanism of action, PTI-125 also reduced FLNA association with α7nAChR and TLR4 (C). Synaptosomes prepared from frontal cortex were immunoprecipitated with anti-tau or anti-Aβ₄₂ antibodies, and levels of phosphorylated tau (at 3 phosphoepitopes) or α7nAChR were respectively detected by Western blots (WB; insets) and quantified by densitometric quantitation. PTI-125 also reduced inflammatory cytokine levels in 8-month mice, measured by a fluorescence ELISA assay (D). $n = 6$. * $p < 0.01$ and ** $p < 0.05$ versus 4-month mice; # $p < 0.01$ versus vehicle-treated 8-month mice. Abbreviations: α7nAChR, α7-nicotinic acetylcholine receptor; FLNA, filamin A; TLR4, toll-like receptor 4; 3xTg, triple-transgenic.

A concentration of 1 pM was sufficient to produce a significant reduction in FLNA-α7nAChR interaction in both tissues. As a consequence, PTI 125 incubation dose dependently reduced

Aβ₄₂-α7nAChR complexes in postmortem AD or Aβ₄₂ treated age matched control hippocampus starting at 1 pM (Fig. 10B). In Aβ₄₂ treated control hippocampus, PTI 125 dose dependently

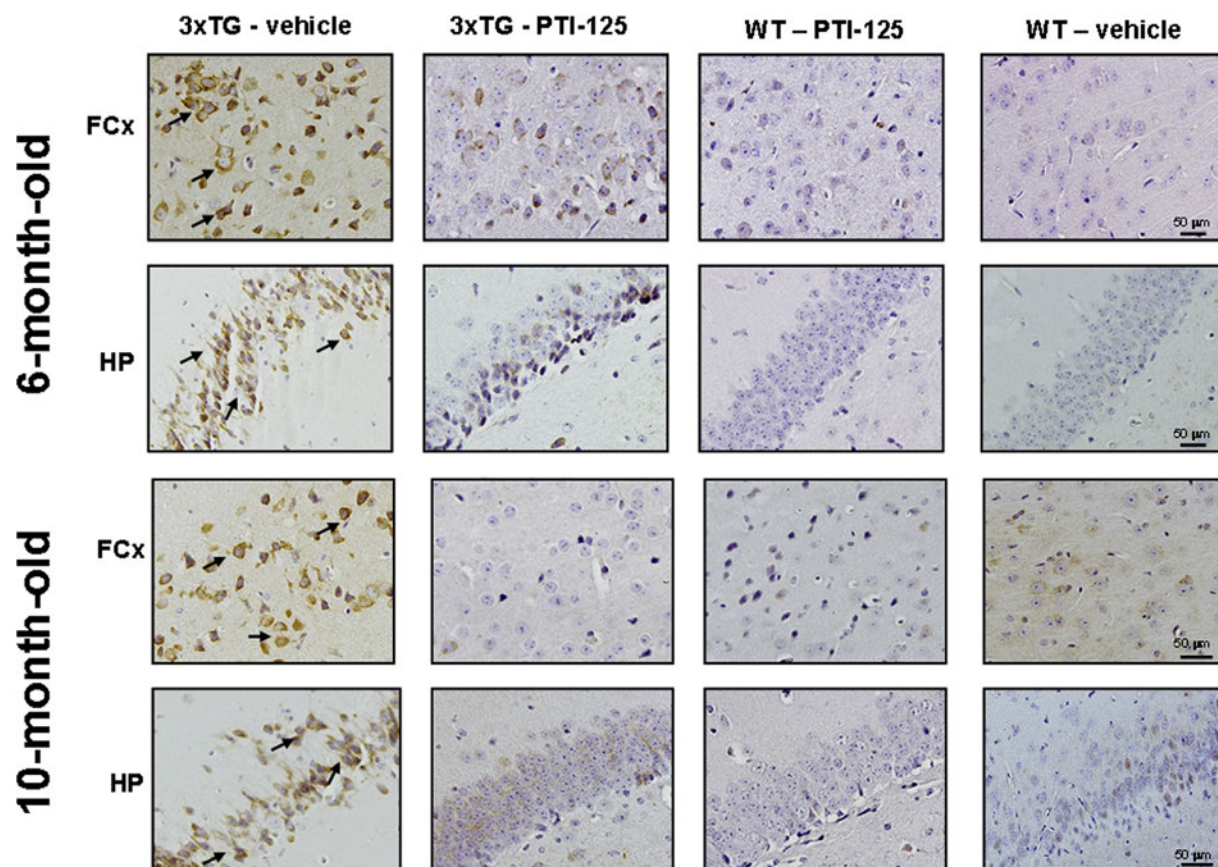


Fig. 6. Representative sections immunostained with anti-Aβ₄₂ antibodies show that PTI-125 treatment reduced Aβ₄₂ deposits in hippocampus and frontal cortex of both transgenic and older wild-type mice. Arrows indicate examples of Aβ₄₂ aggregates.

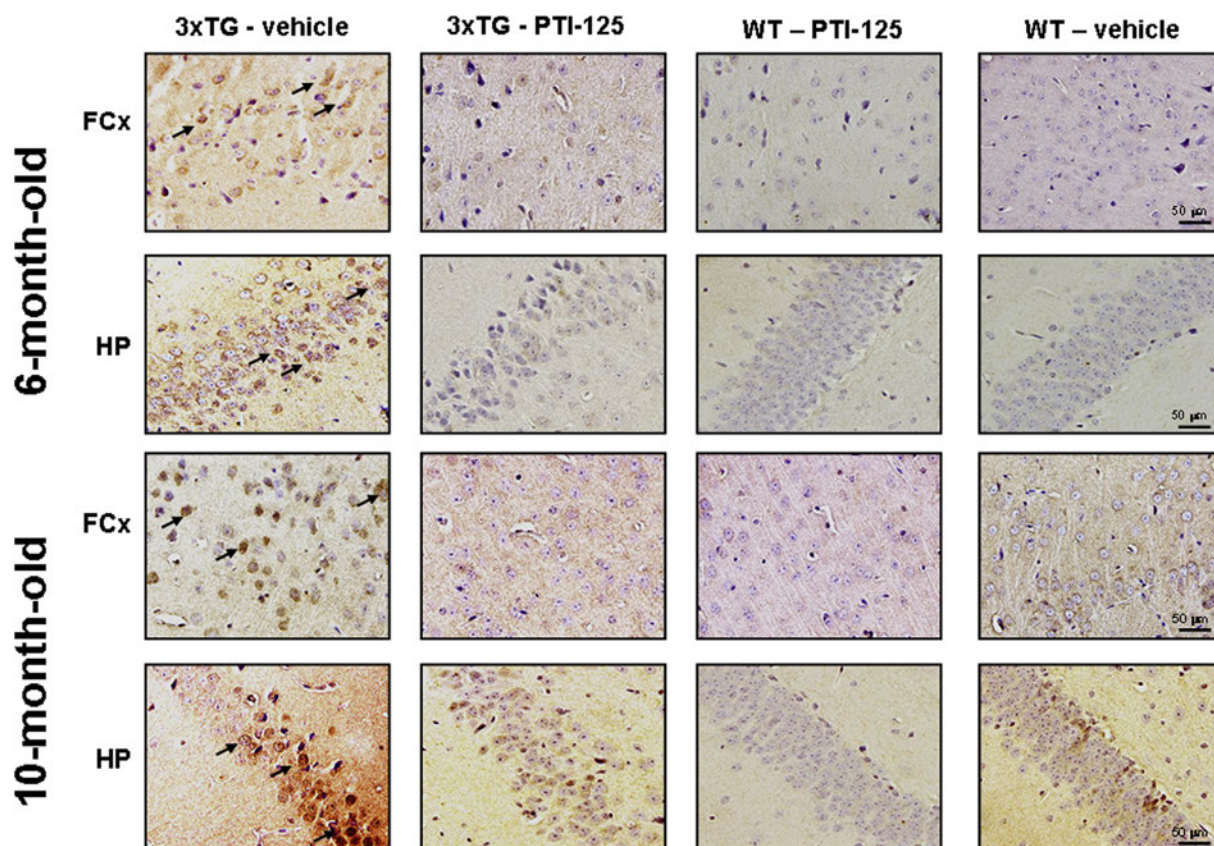


Fig. 7. Representative sections immunostained with anti-NFT (phospho-tau) antibodies show that PTI-125 treatment reduced NFT immunoreactivity in hippocampus and frontal cortex of both transgenic and older wild-type mice. Arrows indicate examples of hyperphosphorylated tau-rich NFTs. Abbreviation: NFT, neurofibrillary tangle.

reduced phosphorylated tau as well as tau nitration, an indicator of oxidative stress started at 1 pM (Fig. 11).

Similarly, PTI 125 dose dependently restored NMDA receptor signaling that is impaired in postmortem AD or A β_{42} treated

age matched control hippocampus (Fig. 12). Both A β_{42} treated control hippocampus and AD hippocampus showed approximately 70% reduction in NMDAR activity evidenced as reduced NMDA/glycine induced Src and Pyk2 activation and recruitment of

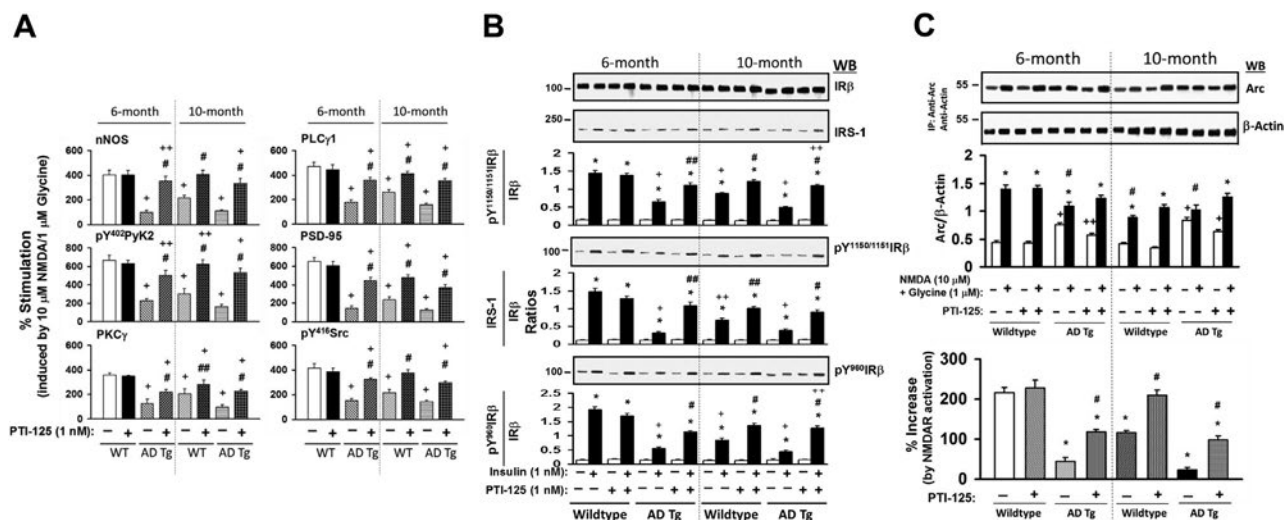


Fig. 8. PTI-125 via drinking water reduced the impairment in NMDAR (A) and IR (B) signaling. The coimmunoprecipitation assay for NMDAR signaling measured by the levels of NMDA/glycine-induced association of activated kinases and signaling molecules with NMDARs as the ratios of 6 different NMDAR-linked signaling molecules to NR1, the obligatory subunit of NMDAR. IR function was measured by the tyrosine phosphorylation of IR β and the level of the signaling adapter molecule IRS-1 recruited. NMDA/glycine-induced expression of the synaptic plasticity master regulator Arc was also impaired in 3xTg AD and aged mice (C). Total Arc was immunoprecipitated along with actin (immunoprecipitation and loading control) and analyzed by Western blotting. These impairments were ameliorated by PTI-125 oral administration (A, B, and C). Blots (inset) were analyzed by densitometric quantitation. $n = 6$. * $p < 0.01$ versus unstimulated control; # $p < 0.01$ and ## $p < 0.05$ versus vehicle; + $p < 0.01$ and ++ $p < 0.05$ versus 4-month mice. Abbreviations: AD, Alzheimer's disease; IRS-1, Insulin receptor substrate 1; NR1, NMDA receptor subunit 1; 3xTg, triple-transgenic.

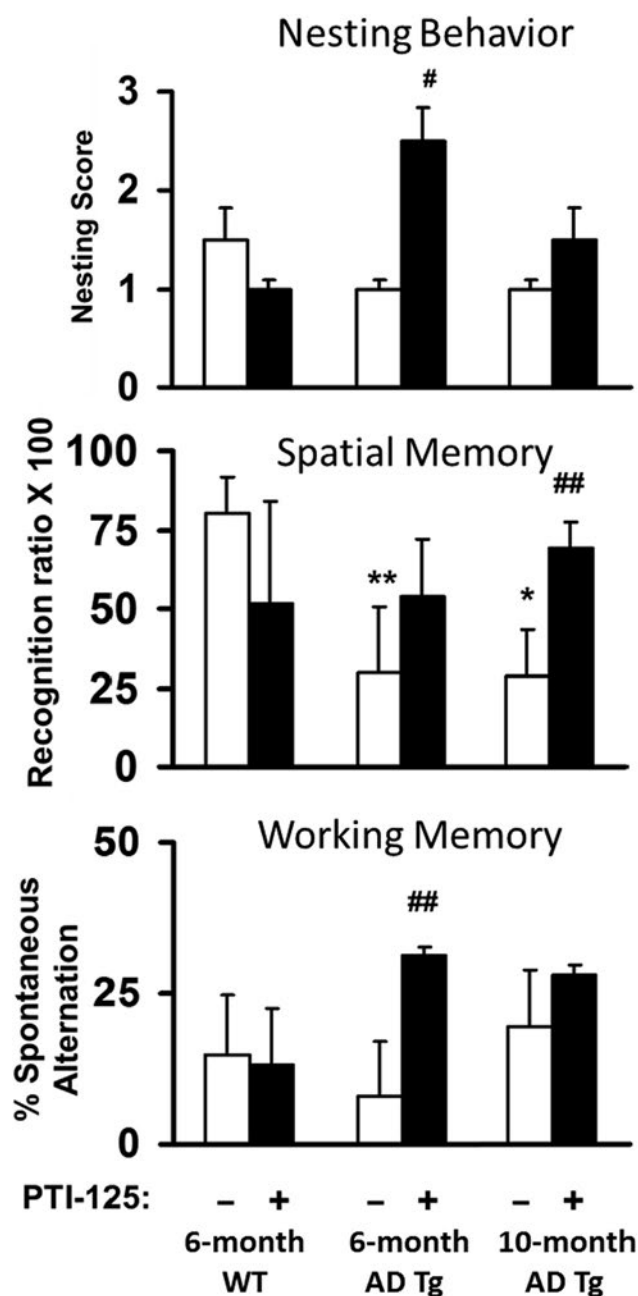


Fig. 9. PTI-125 via drinking water improved nesting behavior in 6-month 3xTg AD mice. Compared to 6-month wildtypes, spatial memory assessed using Y-maze with extra-maze visual cues was impaired in 3xTg AD mice of both ages but not in 3xTg AD mice of either age treated with PTI-125. Additionally, PTI-125 significantly improved spatial memory in 10-month 3xTg AD mice. PTI-125 significantly improved working memory assessed by Y-maze spontaneous alternation paradigm in the 10-month but not 6-month 3xTg AD mice, $n = 5$. $^*p < 0.01$, $^{**}p < 0.05$ versus 6-month-old vehicle-treated wild-type group; $^{\#}p < 0.01$, $^{##}p < 0.05$ versus respective vehicle-treated group. Abbreviations: AD, Alzheimer's disease; 3xTg, triple-transgenic.

phospholipase C $\gamma 1$, nNOS and PKC γ compared to age matched controls. In concert, these 6 indices of NMDAR dysfunction were dose dependently ameliorated by PTI 125 (Fig. 12).

The improved NMDAR function by ex vivo PTI 125 incubation correlates with the efficacy in restoring NMDAR activation induced Arc expression, indicating restored synaptic plasticity even at 1 pM (Fig. 13). In summary, PTI 125 produced significant beneficial effects starting at 1 pM in A β_{42} treated control hippocampus on all parameters and at 1 or 10 pM in AD postmortem hippocampus in

assays appropriate for AD postmortem tissue (these exclude tau phosphorylation and Arc expression). These results illustrate a PTI 125 dose response from 1 pM to 1 nM concentrations, with maximal effects at 100 pM or 1 nM, corroborating our earlier unpublished data in adult rat brain slice cultures that showed peak effects on NMDAR and $\alpha 7$ nAChR function at 1 nM with 10 nM a saturating concentration.

4. Discussion

Our early work identified the critical role of FLNA in A β_{42} signaling via $\alpha 7$ nAChR and TLR4 that leads to tau hyperphosphorylation and neuroinflammation (Wang et al., 2012). We now show that A β_{42} can induce an altered conformation of this ubiquitous scaffolding protein to intensify AD pathogenesis. By reversing FLNA to its native, nondiseased state, PTI 125 attenuates A β_{42} driven toxic events that ultimately result in tau hyperphosphorylation, receptor dysfunctions, impaired synaptic plasticity, and oxidative stress leading to neurofibrillary lesions, NFTs, and A β_{42} deposits as well as neurodegeneration. PTI 125's preferential binding to the altered FLNA conformation is indicated by a femtomolar affinity for FLNA in synaptic membranes or immunopurified from postmortem human AD hippocampus, compared to a picomolar affinity for FLNA in age matched control hippocampus. Importantly, PTI 125's lower affinity binding to native FLNA does not further change its conformation or have any apparent effects. This differential binding affinity renders the binding site markedly more accessible in the disease state and explains PTI 125's efficacy at low doses and low toxicities despite a ubiquitous target. The unique ability for PTI 125 to bind and restore pathological FLNA to its native conformation suggests that PTI 125 is a disease modifying therapeutic agent for diseases with abnormally heightened amyloid pathologies such as AD. Once FLNA is reversed to its native conformation, the affinity of PTI 125 becomes considerably lower, leading to its release.

The multiple beneficial effects of PTI 125 were initially demonstrated in an acute (2 week) ICV A β_{42} infusion mouse model and in postmortem human AD brain incubated with 1 nM PTI 125 for 1 hour. The present work extends these findings to a more chronic and oral administration in 3xTg AD mice, with treatment starting either at 4 months, when neuropathology such as A β deposits is not yet apparent or at 8 months, when the neuropathology is established in these mice. The 8 month wildtypes, a control for the 8 month 3xTg AD mice, showed age dependent A β burden and associated neuropathologies by 10 months that were milder than in transgenics of either age. In 3xTg AD and older wild type mice, PTI 125 administration for 2 months via drinking water improved receptor activities (indicated by restored receptor signaling) and synaptic plasticity (indicated by normalized NMDAR activation mediated expression of the master synaptic plasticity regulator Arc). These functional benefits were associated with improvements in nesting behavior and spatial and working memory in transgenic mice, even in small group sizes. The molecular functional results closely replicate our earlier published findings in the ICV A β_{42} infused mice treated with 2 week PTI 125 injections as well as in postmortem human AD brain (1 h ex vivo PTI 125 incubation). By decreasing the levels of FLNA– $\alpha 7$ nAChR and TLR4 associations, PTI 125 markedly reduces A β_{42} induced tau phosphorylation and inflammatory cytokine levels to a near nondisease state. These therapeutic effects are supported by the marked reduction in A β_{42} deposits and phosphorylated tau containing NFTs. Additionally, the AD pathologies noted in normal, aged mice prior to cognitive impairment supports the hypotheses that aging is a contributing factor of AD pathogenesis and that AD pathologies are initiated at least a decade ahead of apparent cognitive decline in humans. The

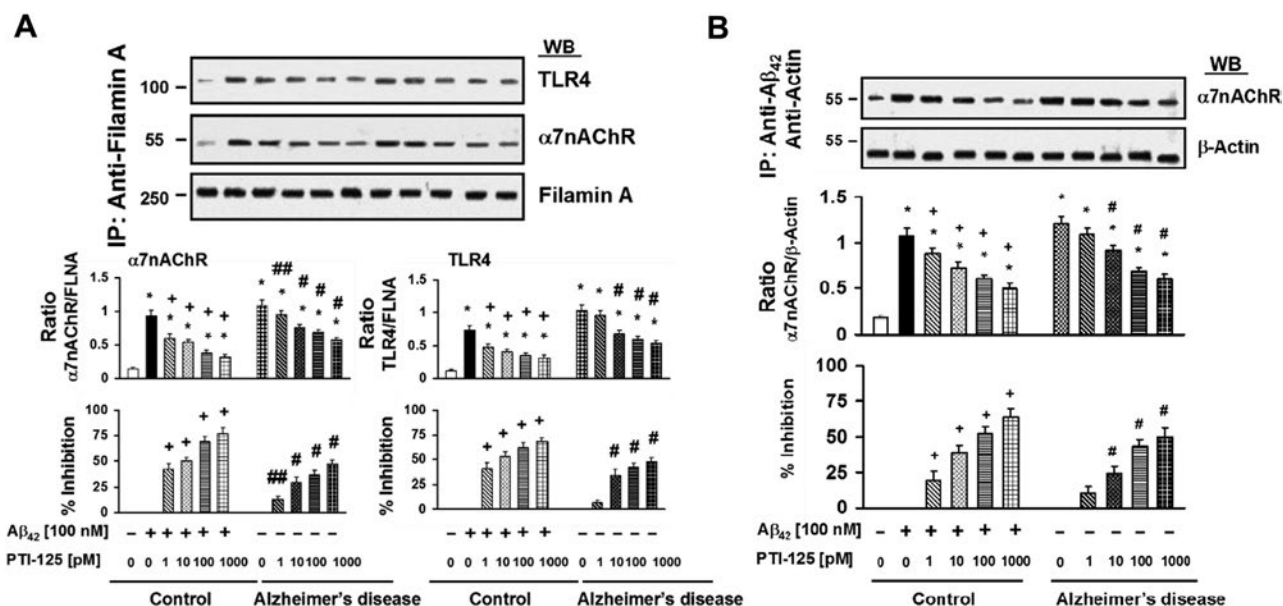


Fig. 10. PTI-125 (1 hour) dose-dependently reduced FLNA association with $\alpha 7$ nAChR and with TLR4 in postmortem AD and $A\beta_{42}$ -treated age-matched control hippocampal slices (A). PTI-125 similarly dose-dependently reduced $A\beta_{42}$ - $\alpha 7$ nAChR complexes with statistical significance starting at 1 pM in $A\beta_{42}$ -treated age-matched control and at 10 pM in AD hippocampus (B). Synaptosomes prepared from postmortem hippocampus from 5 best-matched control/AD pairs were incubated with vehicle, PTI-125 or PTI-125 + $A\beta_{42}$ (control), solubilized and immunoprecipitated with immobilized anti-FLNA, and $\alpha 7$ nAChR, and TLR4 levels in the immunoprecipitates were detected by Western blot using specific antibodies. Blots (inset) were analyzed by densitometric quantitation. $n = 5$. * $p < 0.01$ versus vehicle-treated age-matched control; + $p < 0.01$ versus $A\beta_{42}$ -treated age-matched control; # $p < 0.01$ and ## $p < 0.05$ versus vehicle-treated AD. Abbreviations: $\alpha 7$ nAChR, $\alpha 7$ -nicotinic acetylcholine receptor; AD, Alzheimer's disease; FLNA, filamin A; TLR4, toll-like receptor 4.

multiple effects of PTI 125 indicate improved neuronal health and reduced pathophysiology in both AD and normal aging.

We also investigated a concentration range for PTI 125 in postmortem hippocampus, extending our earlier findings in frontal cortical slices that used a single 1 nM concentration. Using concentrations that are closer to PTI 125's femtomolar affinity for FLNA, we now demonstrate that 1 hour incubation with concentrations as low as 1 pM dose dependently reduce neuropathologies detected in postmortem human AD hippocampus or in $A\beta_{42}$ treated age matched control hippocampus. These PTI 125 effects include improved NMDAR function, reduced tau hyperphosphorylation, reduced $A\beta_{42}$ - $\alpha 7$ nAChR complexes, and reduced FLNA association with $\alpha 7$ nAChR or TLR4. PTI 125 also reduced tau nitration, a marker of oxidative stress, and improved synaptic plasticity as indicated by the activity driven expression of the master synaptic regulator, Arc. Together with the preferential binding and reversal of the pathologic FLNA conformation, these ex vivo data show that PTI 125 is potent and highly efficacious in normalizing receptor function and reducing $A\beta$ driven pathologies.

Though other targets have been demonstrated for soluble $A\beta_{42}$, $A\beta_{42}$ generally binds these targets with high nanomolar or lower affinities, suggesting high off rates and limited target engagement. In contrast, $A\beta_{42}$'s subpicomolar affinity for $\alpha 7$ nAChR suggests it is nearly irreversible, offering one explanation for the many clinical trial failures of anti $A\beta$ antibodies. With its unique mechanism of action, PTI 125 noncompetitively reduces $A\beta_{42}$'s affinity for $\alpha 7$ nAChR by 1000 to 10,000 fold (Wang et al., 2012). $A\beta_{42}$'s greatly reduced binding affinity prevents its toxic signaling, reduces $A\beta_{42}$ accumulation on $\alpha 7$ nAChRs and even dissociates bound $A\beta_{42}$ from $\alpha 7$ nAChR in postmortem AD brain as shown here and previously (Wang et al., 2012). Interestingly, the femtomolar binding of PTI 125 to altered FLNA has a long retention time in brain to exert its beneficial effects, evidenced by [C^{14}]PTI 125 binding in brains of treated and untreated ICV $A\beta_{42}$ infused or aged mice. This tight binding was indicated by residual PTI 125 that survived washing of

brain tissue. The higher levels of residual bound PTI 125 in ICV $A\beta_{42}$ infused or 3xTg AD versus naive wild type mice and in older versus younger mice is further evidence that PTI 125's high affinity binding is to the diseased/age related conformation of FLNA.

Other targets of soluble $A\beta$ include PrP^C, a prion receptor, which $A\beta$ binds with 50–100 nanomolar affinity to suppress long term potentiation in slice cultures (Lauren et al., 2009). Acting as a coreceptor for the $A\beta$ -PrP^C complex, mGluR5 also plays a role in the impaired long term potentiation (Um et al., 2013). Importantly, PTI 125 significantly restored synaptic plasticity as illustrated by increasing activity driven expression of the master regulator Arc. Soluble $A\beta$ has also been shown to bind neuroligin 1, a membrane bound postsynaptic cell adhesion protein important to postsynaptic receptor clustering and synaptic integrity. $A\beta$'s nanomolar binding to neuroligin 1 is proposed to promote $A\beta$ oligomer formation (Dinamarca et al., 2011). It should be noted that soluble $A\beta$ in monomeric or oligomeric form can signal through $\alpha 7$ nAChR (Tong et al., 2011; Wang et al., 2000a,b, 2003). Further, amyloid induced microglial activation and neuroinflammation were shown to suppress neuroligin 1 expression through an epigenetic modification of neuroligin 1 promoter. Manipulating the inflammation modulated the promoter, glutamatergic transmission in the hippocampus and memory (Bie et al., 2014). Though untested, PTI 125 should also restore neuroligin 1 expression due to PTI 125's profound reduction of neuroinflammation.

Despite the lower affinity of $A\beta$ binding to other targets, it is difficult to assess the relative contributions of these other $A\beta$ targets or other potential disease mechanisms to overall AD neuropathology. However, the hyperphosphorylation of tau, effected by $A\beta_{42}$'s signaling via $\alpha 7$ nAChR to activate ERK1 and JNK, disrupts tau's normal function of assembling and stabilizing microtubules, critical to general neuronal processes (Stoothoff and Johnson, 2005). Dysfunctional tau and dysfunctional microtubules could impede axonal transport, leading to a wide variety of impaired neuronal function (Buee et al., 2000; Stoothoff and Johnson, 2005;

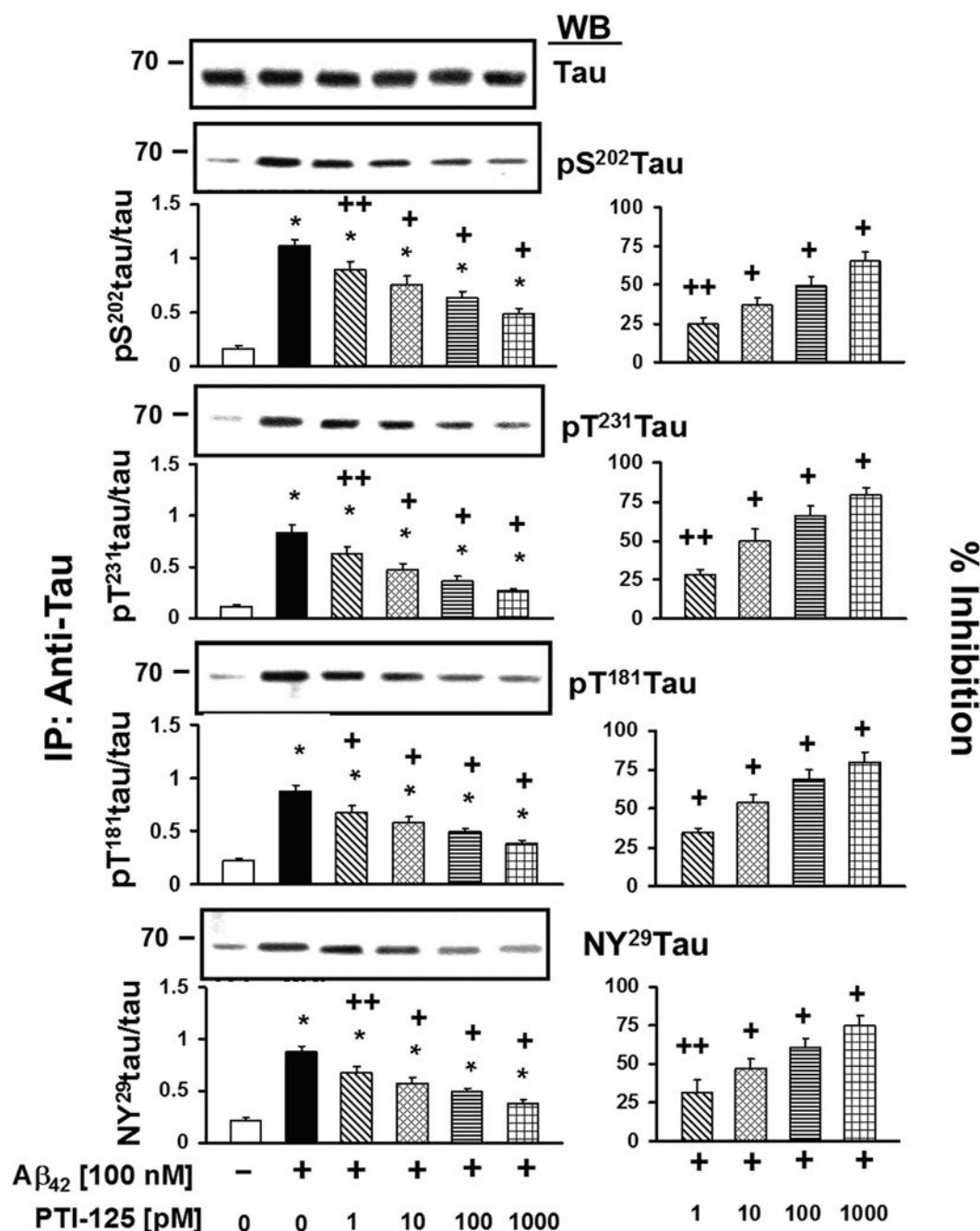


Fig. 11. PTI-125 dose-dependently decreased A β ₄₂-induced tau phosphorylation at Ser-202, Thr-231, and Thr-181 in control human hippocampus. Levels of tau protein phosphorylated at each site were measured in the immunoprecipitates of a pan anti-tau antibody that did not distinguish its phosphorylation state by Western blotting with specific antibodies separately recognizing each tau phosphopeptide. Blots (inset) were analyzed by densitometric quantitation. $n = 5$. * $p < 0.01$ versus vehicle/vehicle; + $p < 0.01$ and ++ $p < 0.05$ versus A β ₄₂/vehicle.

Wang et al., 2013). The beneficial impact of PTI 125 on a range of AD related neuropathologies, achieved by blocking A β ₄₂'s signaling to hyperphosphorylate tau, supports this theory. Neuro inflammation is an additional, prominent AD neuropathology that likely also impedes neuronal function. Suppressing both A β ₄₂ induced toxic signaling via α 7nAChRs and TLR4 signaling by binding a single target strengthens the potential broad spectrum therapeutic impact of PTI 125.

In summary, A β ₄₂'s femtomolar binding affinity to α 7nAChR, its aberrant signaling and the required FLNA- α 7nAChR association can all be markedly attenuated by restoring FLNA to its native

conformation. The result is a prevention of A β ₄₂ accumulation and the toxic signaling that hyperphosphorylates tau, drives plaque and neurofibrillary pathologies, and ultimately, neurodegeneration. Most importantly, PTI 125 alleviates deficits in synaptic plasticity, including those modulated by NMDARs. PTI 125's additional abilities to reduce insulin resistance, another prominent AD pathology, to markedly reduce neuroinflammation by attenuating TLR4 signaling, and to minimize oxidative stress as evidenced by reducing A β ₄₂ induced tau nitration should also benefit synaptic transmission and improve neuronal resilience. The myriad of beneficial effects by this promising novel therapeutic candidate

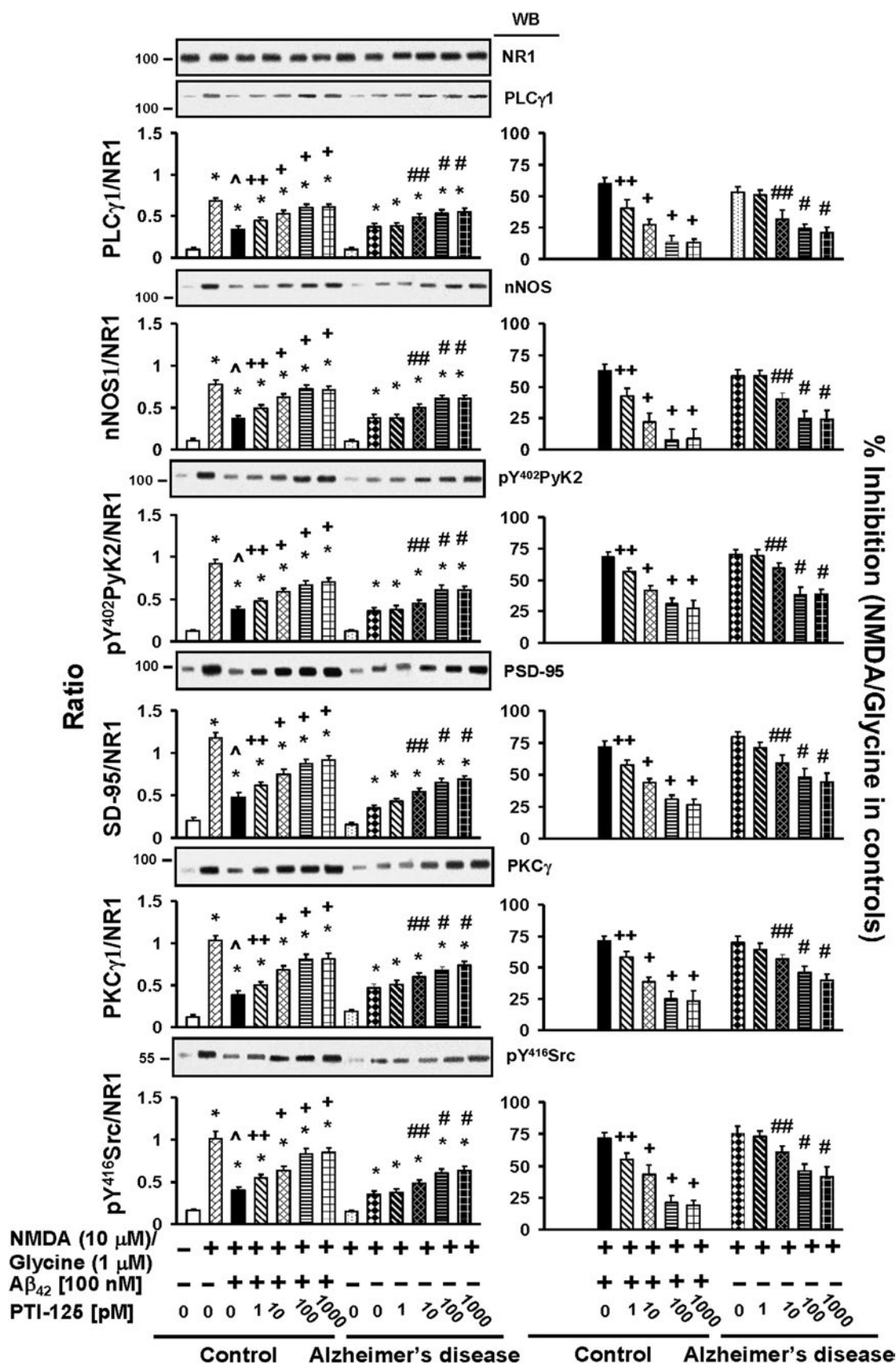


Fig. 12. In postmortem AD and Aβ₄₂-treated age-matched control hippocampus, PTI-125 (1 hour) dose-dependently improved NMDAR function, evidenced by the levels of 6 signaling molecules coimmunoprecipitated with NMDARs using antibodies against NR1, the NMDAR obligatory subunit. Blots (inset) were analyzed by densitometric quantitation. *n* = 5. **p* < 0.01 versus control basal; *p* < 0.01 Aβ₄₂ + NMDA/glycine versus NMDA/glycine; +*p* < 0.01 and ++*p* < 0.05 versus Aβ₄₂ in controls; #*p* < 0.01 and ##*p* < 0.05 versus AD NMDA/glycine. Abbreviations: AD, Alzheimer's disease; NR1, NMDA receptor subunit 1.

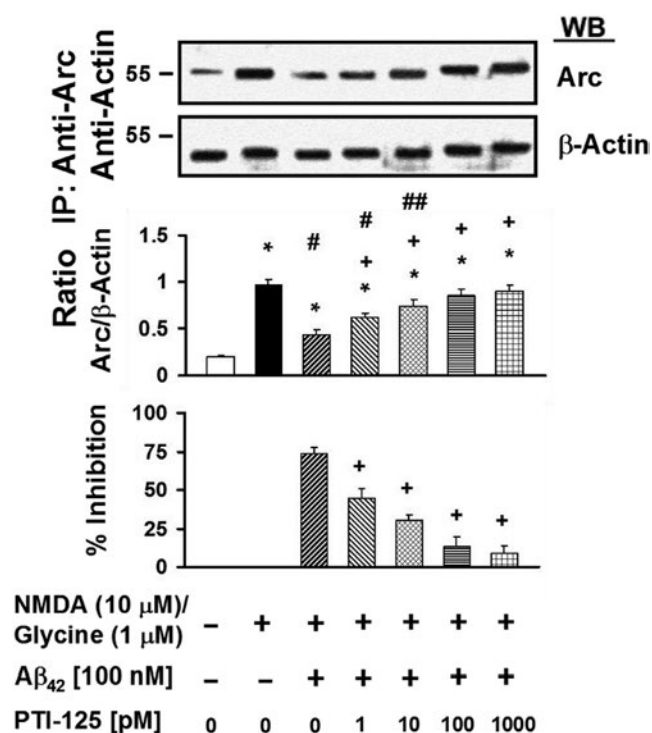


Fig. 13. In control hippocampus, A β ₄₂ impaired NMDA/glycine-induced expression of the master synaptic plasticity regulator, Arc. PTI-125 dose-dependently improved NMDA/glycine-induced Arc expression. Control hippocampal slices were incubated with A β ₄₂ alone or A β ₄₂ + PTI-125 (1 pM–1 nM). Tissues solubilized and Arc was immunoprecipitated along with actin (served as immunoprecipitation/loading control). The levels of Arc and β -actin were determined by Western blotting. Blots (inset) were analyzed by densitometric quantitation. $n = 5$. * $p < 0.01$ versus basal; # $p < 0.01$ and ## $p < 0.05$ versus NMDA/glycine control; + $p < 0.01$ versus A β ₄₂ + NMDA/glycine.

validates FLNA as an important novel target and reinforces A β ₄₂ signaling via α 7nAChR and TLR4 as prominent pathogenic mechanisms in AD. PTI 125's mechanism of action, reversing proteopathy by binding and restoring the disease altered protein conformation to its nondiseased state, underscores the importance of protein conformation in neuronal health and disease.

Disclosure statement

PTI 125 is a proprietary compound of Pain Therapeutics, Inc (PTI). Dr. Burns is an employee and Dr. Wang is a consultant for this company.

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From: Suzhen Chen <SChen@IGlobe-USA.com>
Sent time: 08/05/2021 08:02:02 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: your 2017 paper

Thank you very much!

Sent from my iPhone

> On Aug 4, 2021, at 11:00 PM, Hoau-yan Wang wrote:

>

> Dear Dr. Chen,

>

>

> Please find a PDF copy of our 2017 Neurobiol of Aging paper you have requested.

>

>

> Thank you.

>

>

> Best,

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>

> Hoau-Yan

>

>

> Hoau-Yan Wang, Ph.D.

>

> Medical Professor

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> CUNY SOM

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> _____
> From: Suzhen Chen

> Sent: Wednesday, August 4, 2021 4:13 PM

> To: Hoau-yan Wang

> Subject: [EXTERNAL] your 2017 paper

>

> Dear Dr. Wang,

>

> May I have a PDF copy of your paper "PTI-125 binds and reverses an altered conformation of
filamin A to reduce Alzheimer's disease pathogenesis"?

>

> Thank you,

>

> Suzhen

>

> https://urldefense.proofpoint.com/v2/url?u=https-3A__www.linkedin.com_in_suzhen-2Dchen_&d=DwIGaQ&c=4NmamNZG3KTnUCoC6InoLJ6KV1tbVKrkZXHRwtIMGmo&r=YAnDdTh9IEWHiy_3lavstLajOSlrKTXLS4AccHSzT3c&m=DPFkyUcEsFx2_UemSzHdlkbBvuA3uQAsMRgFQZc7-Wc&s=1Ye2I1IKcqUFRBjRPtKATzVMURMrCHGAdmqyAQT8uCg&e=

>

From: Hoau-yan Wang
Sent time: 08/06/2021 04:29:26 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

As always, I am completely booked up with research activities. Your questions kept me thinking. I answer your questions directly underneath each of your queries.

Hope all is well,

Thank you.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, July 31, 2021 2:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Thanks for your kindly reply during busy hours as always. Knocking off hard nuts is especially tough especially there was no precedent before. Your persistence and genuine contributions to global AD community is obvious. I am happy that your finding of the bad guy will eventually be a history of AD and even mankind. Your family and friends will be certainly proud of you after so many tough years spent in lab and related researches.

Your answers to my naïve questions are plain and understandable. To my personal curiosity which might be common to most people, I have additional questions as below.

1. Is there any plateau effect after months of oral treatment of PTI-125 since biomarkers of neuroinflammation and neurodegeneration will eventually reach their peaks ? Will responded patients need to take oral treatments of PTI-125 in their lifetime ? *True. neuroinflammation and neurodegeneration will reach a breaking point down the road without treatments. Our hope is that this treatment will delay the neuroinflammation and neurodegeneration so that brain can recover (those not dead yet) some so that brain can function better. My guess is that there is some sort of limitations (not plateau per se). We hope the window is big enough (beyond the nature life span).*
2. When temporal changes of individual patient during the span of treatments will be revealed ? This information might show more consistent and clearer trend of treatment effects. *I am not sure what you are referring to. It would be difficult to gauge patient's response rate since each patient is different in many aspects (other diseases, genetic make up etc). Very difficult to tell.*
3. For neurons already beyond repairs or dead, is there any viable therapeutic or complimentary solution ? *No. Raise from death is NOT any humans can do.*
4. Would mental or physical rehabilitations for patients during or after treatments add more values to their health ? *We have evidence to show exercise and good nutrients (diet) help to elevate the treatment effects.*

There must be lots of works needed to be done after this stage. For all your dedication, I believe that all time spent in search of better treatments will be meaningful and greatly appreciated. Thanks again in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, July 31, 2021 1:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your encouragements always and giving your opinions and questions as I need such reminders to keep my comments plain and understandable.

I will **answer your questions directly underneath each query you posted**. Since I am blind to all patient related info, I can only answer in general terms.

Hope all is well with you and your family.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Thursday, July 29, 2021 10:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Congratulation to your researches going with a gigantic step forward. After reading updated PTI-125 related papers in CCAI 2021, I had a feeling that your lab works have gradually verified the MOA of Filamin A with abnormal conformation. There are thoughts with results of SavaDx and 9-month data as follows :

- 1) Correlation studies of Abnormal Filamin A in phase 2b patients is a positive step. That is a great findings and direction in the framework of diagnosis tool. However, taking Abnormal Filamin A as a biomarker needs more works to establish that which level of Abnormal Filamin A should be detected as an early sign of AD. I am wondering if a totally new or compatible antibody in your earlier works of SavaDx is employed in this study.
- Indeed, this is just the initial steps. The antibodies used obviously required constant verifications using that was used earlier. It is a tedious work but there are no short cuts. We need to define the timeline when the abnormal FLNA can be detected (not an easy task because we don't even know when is early).
- 2) Cognition Improvement of 3.0 Points on ADAS-Cog at 9 Months ($p < 0.001$) is great for patients as a process of Filamin A normalization. However, most people are wondering why NPI score in 9 month improved less than in 6 month by 0.6 points. All tested biomarkers are consistent with improvements which relieved lots of overhangs.
- People forget Alzheimer's disease is a progressive neurodegenerative disease with multiple factors at play. As patients deteriorate cognitively due to brain function declines, there are added factors hence the magnitude of improvements become less comparing the the baseline. The 0.6 points less at 9 month reflects just that (obviously it also depends on the stage of disease when patients first enrolled) but the curve will be stabilize for period of time.
- 3) 22% of patients declined less than reported in the science literature at 9 months. Why these patients are so hard to respond to treatment of simufilam ? Any other upstream catalyst for these patients ?
- Well, we don't actually know but my guess is that these patients have other issues or they were selected at later stage of the disease even though their MMSE or ADAS-Cog when enrolled were not bad. While we like to have 100% responsive rate, it is an unrealistic expectation. This drive home the importance of early diagnosis. I am sure if we treat earlier, we will see a better result.
- 4) As reported earlier, Evonik will supply Cassava Sciences with large-scale, clinical-grade quantities of simufilam. I am wondering if Evonik will produce good qualities of simufilam as in phase 2b study and it should be carefully verified before entering phase 3.
- Clearly, QC will be done carefully.
- 5) Finally, is abnormal filamin A responsible for the symptom or modifying answer to AD ?
- While we all want to find the "bad" guy (abnormal FLNA is a critical but one of the bad guys I am sure there are many others). Fortunately, fixing abnormal FLNA promotes healthier and more resilient brain but unfortunately can't fix anything already beyond repairs or dead. I am a realistic person by showing people what I saw but I don't want to give a wrong impression that fixing abnormal FLNA can bring back what have already damaged.

I am honored to be with your ongoing researches and contributions to AD patients. Thanks for your hard works.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, June 30, 2021 8:29 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Sorry for my late reply. I often just get occupied by too many tasks in hand and consequently delay in my response to you and many.

Yes, lots efforts had been on the multiple fronts and there should be an update in phase 2b study. I will be interest in learning of your comments.

I watch the COVID-19 situation in Taiwan closely. It is most unfortunately some careless acts led to such a spread. Even though it is pale by comparison to US and EU, it is still very concerning especially in Taipei (the worst in transparency) and New Taipei. A solution to this monumental disaster must include understand the pathogen (virus) so that more effective medications together with vaccination can put this pandemic out for good.

Best wishes to you and your family, it is looking better recently so that normalcy is near.

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, June 22, 2021 12:18 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After reading a recent news from Cassava Sciences, I realized that there will be a presentation at AAIC during the week of July 26-30th about SavaDx clinical dataset from PTI-125's Phase 2b study of 64 patients. Look forward to seeing more updates of SavaDx developments which you must devote lots of time and energy.

Affected by recent COVID-19 impacts in Taiwan, I have been working from home more than 1 month. Hope that this history-making pandemics will be alleviated or solved by pharmaceutical solutions. The same goes to PTI-125 to help patients in need. Thanks.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 23, 2021 10:26 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

The MOA for PTI-125 is very different from that of ANVS401. PTI-125 reverses an abnormal filamin A thereby reducing the toxic signaling pathways that drive neurodegeneration and inflammation. ANVS401 functions as a translational blockers that presumably (based on cell and transgenic models) to reduce toxic substances such as amyloid beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. The major problem is that reducing those "toxic" substances do not work in humans. In fact, ANVS401 blocks APP (amyloid precursor protein) to reduce amyloid beta. APP is a known trophic factor whose expression increases when brain is injured. More of the problem, we know reduction in amyloid beta by beta or gamma secretase inhibitors do not stop Alzheimer's disease progression and in some cases actually worsen cognitive impairments. Hence, I don't predict any synergy between PTI-125 and ANVS401.

Postmortem brains are not suitable to study metabolic dysfunction because one can only show there is metabolic disturbance but can not conclusively show the source, when and how the metabolic dysfunction occur. Transgenic animal models are partial models at best and are very different from actual disease, therefore they are inheritably insufficient to any pathogenic pathway questions just about any diseases.

I hope my explanations help answering your questions.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, February 21, 2021 3:05 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

I had some thoughts again regarding to the upstream causes of Alzheimer disease and MOA of PTI-125.

As you mentioned earlier, there were complicated lab works deriving chemical compounds of PTI-125 to restore of Filamin A with abnormal conformation. I am curious to know what is the chemical MOA of PTI-125 which differentiates from other approaches such as ANVS401 of Annovis Bio Inc. to decrease multiple neurotoxic in Cerebrospinal Fluid (CSF) and improve axonal transport of nerve cell. Their therapeutic target also aims for reductions of neuroinflammation and neurodegeneration. Is there any synergetic effect to combine PTI-125 and ANVS401 ?

As in previous email, I am skeptical about causes of metabolic dysfunction related to Alzheimer disease. Is there any direct proof from human postmortem model instead of mouse model ?

Thanks again for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 16, 2021 1:08 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

First, Happy Lunar New Year. Wishing you and your family a happy, healthy and prosperous year of Ox.

Regarding your question, Donepezil's ADAS-cog score you are referring to are raw score. Once taking placebo control into consideration, the improvement achieved by 24 months of 5 mg and 10 mg daily dose of donepezil were around 0.35 and 0.39 (page 16 stat significant). By now we know donepezil's clinical effectiveness eventually diminished as disease progresses. Obviously, we hope the cognitive benefit of PTI-125 continues based on the biomarker data. The improvement in cognition is depending on the baseline state of the patients (how severe the dementia and obviously the accuracy of diagnosis). I can't say too much and frankly nobody is all that certain.

Based on the mechanism of action, we predict the therapeutic effects of PTI-125 are applicable to a broad range of Alzheimer's disease patients. Again, the magnitude of benefits depend on the severity of dementia - the earlier the better. Hence, it is important to have a reliable early diagnosis tool though we still not entirely sure how to define "early".

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, February 15, 2021 10:32 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After some thoughts and review of data during Chinese New Year, I have some questions needed for your comments as follows :

1. ADAS-Cog Improvement between ARICEPT and PTI-125 : In https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively after 24 weeks of treatment. These differences were statistically significant for 473 patients. Compared with baseline, 5 mg/day and 10 mg/day treatments of donepezil at 24 weeks showed 1.06 and 1.6 benefits in a controlled study. However, the press release of Cassava Sciences on Feb. 2, 2021 mentioned that six months of PTI-

125 treatment improved cognition scores by 1.6 points on ADAS-Cog11.

These comparative improvements did not clearly distinguish the therapeutic advantage of PTI-125 compared with ARICEPT in 24 weeks of treatment. Is it true for this simple observation as above ? Is there any indication that PTI-125 will have better effects after prolonged period of time (such as 1 year) by restoring of Filamin A with abnormal conformation ?

2. You mentioned that collective efforts try to bring some solutions for Alzheimer's disease patients. Does it mean that a subset of Alzheimer patients would be appropriate for therapeutic effects of PTI-125 and diagnosis tool of SavaDx ? While other patients are not ideal enough ?

Thanks so much for your insights again.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, February 4, 2021 4:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thank you for your well wishes and positive comments. Your continued interests in finding solutions for Alzheimer's disease research motivate us and I can truly say I am trying my very best . I thank you for keeping me informed and discussions on the findings from other investigators. We will keep moving forward and hope our collective efforts can bring some solutions for Alzheimer's disease patients.

Will keep safe the best I can as the COVID pandemic is still very bad here. Hopefully, with vaccination the situation improves in the coming months.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, February 2, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

Nice to know that the interim result of PTI-125 is positive and brings lights to the Alzheimer community. Congratulation to your continued efforts. There must be lots of persons sending emails to you regarding to this matter. To continue your clinical endeavors, I truly wish you to keep safe in this covid-19 epidemics. Your academic and real-word contributions are very much appreciated.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, January 21, 2021 11:55 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for keeping me informed of the recent development. I am all tied up by my extensive teaching load and research activities (this pandemic has caused tremendous pain with limited access).

Regarding the levels of N-terminal fragment of tau in the blood as a predictor of cognitive decline, this is really nothing new because we know the levels of tau in the CSF and blood positively correlate with the extent of neuronal damage

(tau exist exclusively in neurons). The question is the sensitivity of detection that allow us to sound the alarm. With the more sensitive mass spectrometry we obviously are better equipped than before.

Thanks again. I will find time to answer your earlier queries.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 20, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] some development of diagnosis tool for reference

Dear Hoau :

There is some development of blood test for Alzheimer's disease to predict future cognitive decline in healthy people with levels of N-terminal fragment of tau (NT1). Data link is as <https://www.sciencedaily.com/releases/2020/12/201209115147.htm>. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, January 16, 2021 3:44 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks always for your info that keeping me in the loop of current Alzheimer's disease findings.

The problem is that this type of academic research using (genetically modified) rodent models that bear little resemblance to human Alzheimer's disease lead us to nowhere and frankly confuse & dilute our efforts. Hydrogen sulfide is no doubt playing a regulatory role in many physiological activities. Just because it is decreased with aging and replacing it can improve cognition in rodents doesn't mean it is therapeutically possible. Don't forget the hydrogen sulfide is quite toxic one should worry the accumulation can severely hurt the brain function. Most importantly, there is no evidence rodent models have neurodegeneration (unlike brains in humans with Alzheimer's disease). GSK3a/b is one of the hubs in metabolism/energy regulation and as one of the tau kinases that have a sophisticate feed forward and feedback regulators. There is no evidence there is anything change in GSK3a/b in Alzheimer's disease. In general, kinases and phosphatases are terrible targets because they all have tons of regulators once activated or inhibited in a progressively changing brain like in Alzheimer's disease is predictably short-lived and ineffective especially when the disease becomes symptomatic (much too late).

Thanks. Have a good weekend.

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 13, 2021 10:36 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

It seems to me more and more researches trying to target early pathogenesis of Alzheimer's disease which might be inspired by evidences of many clinical results. There is a recent research from John Hopkins Medicine working with University of Exeter concerning with effects of hydrogen sulfide, GSK3 β and other proteins involved in the pathogenesis of Alzheimer's disease. Their data link is https://medicalxpress.com/news/2021-01-hydrogen-sulfide-alzheimer-disease.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter. Hope that this information would be interesting to you. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 13, 2021 2:13 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Sorry for my late reply, sometimes I made a mental note to reply but I got busy and kind of putting it off. The impacts of concussion obviously vary according to the severity and frequency (multiple mild concussions can be quite damaging). It sounds like your father had a severe concussion that resulted in motor/sensory imbalance and dementia. I understand how hard it is to see your father suffer but unable to help.

There is no doubt vascular dysfunction is a risk factor and often accompanies Alzheimer's disease (cerebral amyloid angiopathy). That said, the cause-effect relationship between vascular dysfunction and Alzheimer's disease is not straight forward.

Indeed, upstream is a relative term. Abnormal filamin A can be induced by sub-chronic amyloid (soluble) infusion into brains. If abnormality in filamin A is blocked (by PTI-125), there is significant reduction in amyloid plaques (dead neurons) and neurofibrillary tangles. More importantly, brain activities with higher receptor and synaptic activities and function improve at least in mouse model of Alzheimer's disease. These data indicate reversing abnormality of filamin A especially when at the stage when mild clinical dementia is detected may be a promising way to treatment Alzheimer's disease.

Hope I answer your questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, January 4, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your comments. After two decades of researches, your important findings have a step forward which is a remarkable achievement. I do admire your courage and patience with regard to this tough disease in which early detections are probably with both natures of science and art. My father was in a healthy condition before concussion and developed with signs of body imbalance and occurrence of Alzheimer disease. It was heartbreaking without ways to lessen his burden.

My assumption of root occurrence from vascular dysfunction might be wrong. It seems to me that finding a solution with very early detection before massive degeneration occurs is more than challenging. I am wondering which events trigger the formation of abnormal filamin A. If you could come up with a diagnosis tool tracing up the root cause of abnormal filamin A, it might be a better start than random guesses. I am not sure if I am right in this direction.

BTW, you mentioned that abnormal filamin A is an upstream event. Would you shed some lights on which upstream events are already verified up to now since upstream is a relative word ? Thanks so much for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, January 5, 2021 1:07 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

There is no doubt vascular dysfunction is an important part of the Alzheimer's disease (AD) pathology. Filamin A with abnormal conformation is found in plasma from AD patients doesn't necessary mean abnormal filamin A from platelets

is resulted from vascular pathology including amyloid angiopathy, infarcts. More importantly, the abnormal filamin A in peripheral may be the result of brain pathogenic changes (occurs later).

Our data indicate abnormal filamin A is an upstream event. However, AD treatment effects are better if starts earlier (hence early detection before massive degeneration occurs is the key). I always think multiple therapeutic agents may be synergistic or additive. Again, if all the treatments administered after massive degeneration there is no treatments strong enough.

Thanks.

All the best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, January 3, 2021 7:50 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks for your kindly reply. Happy New Year !

Since conformational filamin A is structurally found in palates, I therefore assume that vascular pathologies are related to this disease. Your researches in various aspects of insulin resistances were published and your comments really show how hard it is to trace pathogenic events.

I really appreciate your continued research and endeavor to find more upstream targets treating Alzheimer disease effectively. It seems to me in your comments that restoration of conformational filamin A is not strong enough to show disease modifying effects. Is it true ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Monday, January 4, 2021 3:14 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Happy New Year. Wishing you and your family a healthy and prosperous year 2021.

It is my life time goal to help bring effective treatments and early diagnosis of the Alzheimer's disease (and other diseases with cognitive impairments). For the last two decades, I worked to identify possible drug and diagnostic targets. I'm mindful of the burden of the Alzheimer's disease caregivers, especially the potential of depression.

Regarding your question, there is no concrete data to show the function of blood platelet had changed in Alzheimer's disease (plausible of course). There are diverse pathogenic mechanisms and of course diseases such as diabetes (causes vascular pathologies) and history of concussion (multiple) had been suspected to be culprits to promote Alzheimer's disease. Surely, prevent such problems is useful but whether such measurements can reverse the damages that already done is everyone's guess. We had tried to control insulin resistance for years but the results thus far showed not much of effects. This may indicate that brain insulin resistance is not an early pathogenic event. We will do more to find more upstream targets so that we can more effective to treat Alzheimer's disease.

Thanks for your continuing interests and communications.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, December 29, 2020 7:38 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your kindly reply. For my father, a better treatment of Alzheimer disease is motivated and caregivers deserve to be with less burden. Regarding to the timing of conformational changes, I am curious to know if this is related to conditional changes of palates which caused by blood clotting, vascular abnormality or concussion, etc. Your endeavor of this tough disease is really appreciated.

Please be safe since pandemic and cold weather persist in northern atmosphere. Have a wonderful and peaceful New Year to you and your family.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 30, 2020 6:56 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks for your email.

Your friend is correct regarding the difficulty of finding specific antibodies for the filamin A with altered conformation in Alzheimer's disease. Indeed, the epitope of the altered filamin A may be hidden or had been processed. Obviously, computational approaches had been used to help us find viable antibodies. We still don't know when the conformational changes occur during the Alzheimer's disease pathogenesis even though we think this event occur early. But, what is early? This timing issue also requires some attention.

Yes, one-year extension of the open-label study is well under the way. Obviously, we will be looking for cognitive improvement and reduction in pathogenic drives such as reduction in inflammatory markers and degeneration.

Thanks again for your continued interests in getting the Alzheimer's disease treatment. I am working hard to get to this goal.

Happy New Year to you and your family.

Best regards,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, December 28, 2020 4:58 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Wish you a happy holiday and healthy new year, too. Regarding to the issue of diagnosis, my friend specialized in chemistry of antibody suggested to me recently that an exhaustive search of appropriate antibody to be connected with conformational filamin A in human palates might be required to have a solution of universal antibody for different races. A modern equipment with computerized tools would be helpful in this exhaustive search process. Since the epitope of conformational filamin A might be structurally hidden, an appropriate antibody might be sensitively or selectively enough to be effective. Hope that this information is useful.

A one-year, open label study of PTI-125 was initiated in March 2020 and enrolled over 60% of patients as mentioned in public. Supposedly, safety issues are not a big concern since expanded clinical trials still proceed. How about attributes of reduced inflammatory cytokine levels and improved cognition/behavior in this perspective since earlier enrolled

patients had been treated with more than 6 months ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 23, 2020 4:03 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Season Greetings

Dear 宜明,

Sorry for my late reply as I am deep in the semester end exam and grading.

Wow, time flies by so quickly. It has been more than a year already since we started our communication. It is my pleasure to discuss the field of neuroscience even though we actually are learning on the way. I am thankful for the opportunities you have given me to think about the questions you have posted in different angles. Truly, we all hope we have grown some in knowledge and get effective Alzheimer's disease treatments forward to contain this terrible disease. I am for one will do everything I can and work tireless toward this goal. It takes collective efforts to get this under control so that I am collaborating with academic and industrial partners to look into as many ways we can investigate and test the effectiveness. Thanks to you for keeping me informed of many new strategies other have come up with in Alzheimer's disease diagnosis and treatments.

We all hope we can better handle this COVID pandemic. With the approval of 2 vaccines, I am hopeful we are better equipped to start limiting the death tolls and eventually control this horrific virus. I sincerely hope people learn from this as we all have to play a part (wearing mask, wash hands frequently etc). This experience certainly humbles us as we humans appear more vulnerable (at least not as invincible) than we think. The fact Taiwan has done so well in controlling COVID makes me proud to be a Taiwanese.

Wishing you and your family happy holidays and a healthy, peaceful and prosperous year 2021.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, December 20, 2020 8:43 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Season Greetings

Dear Hoau-Yan :

It's been more than 1 year since I have this particular opportunity to know you. Your in-depth and insightful knowledge has given me more understandings in this tough field of neuroscience. Your assistances and comments are really appreciated. Hopefully, we will be better off with more solutions of pandemics and preventive measures next year. At this time of season, I truly wish you a Merry Christmas and happy New Year !

Best Regards,
宜明



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鄭宜明 Eddy Jeng - [CDIB的電子郵件地址已變更為yiming_j@cdibcapital.com](mailto:yiming_j@cdibcapital.com), 請您更新該人員之電子郵件地址資訊。

鄭宜明 Eddy Jeng - CDIB's email address has been changed from @cdibh.com to yiming_j@cdibcapital.com, please update your contact information.

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From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent time: 08/07/2021 02:16:21 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Nice to have your replies especially when you are fully occupied. Your answers to my naïve questions help me to understand more properties of PTI-125 which surely would provide viable solutions to needed patients never before. Especially for meaningful researches, PTI-125 would have more indications and implications as time goes on. If you could find additional bad guys behind AD, a Nobel prize for you is not too far away.

Stay safe when delta virus poses new threats in US. In Taiwan, we are cautious about recent pandemic developments with protective measures. Looking ahead, I would expect an oral solution with protease inhibitor or some combination therapy would truly alleviate this human dilemma. Thanks again for your insights and sharing with me.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, August 7, 2021 4:29 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

As always, I am completely booked up with research activities. Your questions kept me thinking. I answer your questions directly underneath each of your queries.

Hope all is well,

Thank you.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, July 31, 2021 2:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Thanks for your kindly reply during busy hours as always. Knocking off hard nuts is especially tough especially there was no precedent before. Your persistence and genuine contributions to global AD community is obvious. I am happy that your finding of the bad guy will eventually be a history of AD and even mankind. Your family and friends will be certainly proud of you after so many tough years spent in lab and related researches.

Your answers to my naïve questions are plain and understandable. To my personal curiosity which might be common to most people, I have additional questions as below.

1. Is there any plateau effect after months of oral treatment of PTI-125 since biomarkers of neuroinflammation and neurodegeneration will eventually reach their peaks ? Will responded patients need to take oral treatments of PTI-125 in their lifetime ? *True. neuroinflammation and neurodegeneration will reach a breaking point down the road without treatments. Our hope is that this treatment will delay the neuroinflammation and neurodegeneration so that brain can recover (those not dead yet) some so that brain can function better. My guess is that there is some sort of limitations (not plateau per se). We hope the window is big enough (beyond the nature life span).*
2. When temporal changes of individual patient during the span of treatments will be revealed ? This information might show more consistent and clearer trend of treatment effects. *I am not sure what you are referring to. It would be difficult to gauge patient's response rate since each patient is different in many aspects (other diseases, genetic make up etc). Very difficult to tell.*
3. For neurons already beyond repairs or dead, is there any viable therapeutic or complimentary solution ? *No. Raise from death is NOT any humans can do.*
4. Would mental or physical rehabilitations for patients during or after treatments add more values to their health ? *We have evidence to show exercise and good nutrients (diet) help to elevate the treatment effects.*

There must be lots of works needed to be done after this stage. For all your dedication, I believe that all time spent in search of better treatments will be meaningful and greatly appreciated. Thanks again in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, July 31, 2021 1:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your encouragements always and giving your opinions and questions as I need such reminders to keep my comments plain and understandable.

I will **answer your questions directly underneath each query you posted**. Since I am blind to all patient related info, I can only answer in general terms.

Hope all is well with you and your family.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Thursday, July 29, 2021 10:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Congratulation to your researches going with a gigantic step forward. After reading updated PTI-125 related papers in CCAI 2021, I had a feeling that your lab works have gradually verified the MOA of Filamin A with abnormal

conformation. There are thoughts with results of SavaDx and 9-month data as follows :

- 1) Correlation studies of Abnormal Filamin A in phase 2b patients is a positive step. That is a great findings and direction in the framework of diagnosis tool. However, taking Abnormal Filamin A as a biomarker needs more works to establish that which level of Abnormal Filamin A should be detected as an early sign of AD. I am wondering if a totally new or compatible antibody in your earlier works of SavaDx is employed in this study.
- Indeed, this is just the initial steps. The antibodies used obviously required constant verifications using that was used earlier. It is a tedious work but there are no short cuts. We need to define the timeline when the abnormal FLNA can be detected (not an easy task because we don't even know when is early).
- 2) Cognition Improvement of 3.0 Points on ADAS-Cog at 9 Months ($p < 0.001$) is great for patients as a process of Filamin A normalization. However, most people are wondering why NPI score in 9 month improved less than in 6 month by 0.6 points. All tested biomarkers are consistent with improvements which relieved lots of overhangs.
- People forget Alzheimer's disease is a progressive neurodegenerative disease with multiple factors at play. As patients deteriorate cognitively due to brain function declines, there are added factors hence the magnitude of improvements become less comparing the the baseline. The 0.6 points less at 9 month reflects just that (obviously it also depends on the stage of disease when patients first enrolled) but the curve will be stabilize for period of time.
- 3) 22% of patients declined less than reported in the science literature at 9 months. Why these patients are so hard to respond to treatment of simufilam ? Any other upstream catalyst for these patients ?
- Well, we don't actually know but my guess is that these patients have other issues or they were selected at later stage of the disease even though their MMSE or ADAS-Cog when enrolled were not bad. While we like to have 100% responsive rate, it is an unrealistic expectation. This drive home the importance of early diagnosis. I am sure if we treat earlier, we will see a better result.
- 4) As reported earlier, Evonik will supply Cassava Sciences with large-scale, clinical-grade quantities of simufilam. I am wondering if Evonik will produce good qualities of simufilam as in phase 2b study and it should be carefully verified before entering phase 3.
- Clearly, QC will be done carefully.
- 5) Finally, is abnormal filamin A responsible for the symptom or modifying answer to AD ?
- While we all want to find the "bad" guy (abnormal FLNA is a critical but one of the bad guys I am sure there are many others). Fortunately, fixing abnormal FLNA promotes healthier and more resilient brain but unfortunately can't fix anything already beyond repairs or dead. I am a realistic person by showing people what I saw but I don't want to give a wrong impression that fixing abnormal FLNA can bring back what have already damaged.

I am honored to be with your ongoing researches and contributions to AD patients. Thanks for your hard works.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, June 30, 2021 8:29 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Sorry for my late reply. I often just get occupied by too many tasks in hand and consequently delay in my response to you and many.

Yes, lots efforts had been on the multiple fronts and there should be an update in phase 2b study. I will be interest in learning of your comments.

I watch the COVID-19 situation in Taiwan closely. It is most unfortunately some careless acts led to such a spread. Even though it is pale by comparison to US and EU, it is still very concerning especially in Taipei (the worst in transparency) and New Taipei. A solution to this monumental disaster must include understand the pathogen (virus) so that more effective medications together with vaccination can put this pandemic out for good.

Best wishes to you and your family, it is looking better recently so that normalcy is near.

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, June 22, 2021 12:18 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After reading a recent news from Cassava Sciences, I realized that there will be a presentation at AAIC during the week of July 26-30th about SavaDx clinical dataset from PTI-125's Phase 2b study of 64 patients. Look forward to seeing more updates of SavaDx developments which you must devote lots of time and energy.

Affected by recent COVID-19 impacts in Taiwan, I have been working from home more than 1 month. Hope that this history-making pandemics will be alleviated or solved by pharmaceutical solutions. The same goes to PTI-125 to help patients in need. Thanks.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 23, 2021 10:26 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

The MOA for PTI-125 is very different from that of ANVS401. PTI-125 reverses an abnormal filamin A thereby reducing the toxic signaling pathways that drive neurodegeneration and inflammation. ANVS401 functions as a translational blockers that presumably (based on cell and transgenic models) to reduce toxic substances such as amyloid beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. The major problem is that reducing those "toxic" substances do not work in humans. In fact, ANVS401 blocks APP (amyloid precursor protein) to reduce amyloid beta. APP is a known trophic factor whose expression increases when brain is injured. More of the problem, we know reduction in amyloid beta by beta or gamma secretase inhibitors do not stop Alzheimer's disease progression and in some cases actually worsen cognitive impairments. Hence, I don't predict any synergy between PTI-125 and ANVS401.

Postmortem brains are not suitable to study metabolic dysfunction because one can only show there is metabolic disturbance but can not conclusively show the source, when and how the metabolic dysfunction occur. Transgenic animal models are partial models at best and are very different from actual disease, therefore they are inheritably insufficient to any pathogenic pathway questions just about any diseases.

I hope my explanations help answering your questions.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, February 21, 2021 3:05 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

I had some thoughts again regarding to the upstream causes of Alzheimer disease and MOA of PTI-125.

As you mentioned earlier, there were complicated lab works deriving chemical compounds of PTI-125 to restore of Filamin A with abnormal conformation. I am curious to know what is the chemical MOA of PTI-125 which differentiates from other approaches such as ANVS401 of Annovis Bio Inc. to decrease multiple neurotoxic in Cerebrospinal Fluid (CSF) and improve axonal transport of nerve cell. Their therapeutic target also aims for reductions of neuroinflammation and neurodegeneration. Is there any synergetic effect to combine PTI-125 and ANVS401 ?

As in previous email, I am skeptical about causes of metabolic dysfunction related to Alzheimer disease. Is there any direct proof from human postmortem model instead of mouse model ?

Thanks again for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 16, 2021 1:08 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

First, Happy Lunar New Year. Wishing you and your family a happy, healthy and prosperous year of Ox.

Regarding your question, Donepezil's ADAS-cog score you are referring to are raw score. Once taking placebo control into consideration, the improvement achieved by 24 months of 5 mg and 10 mg daily dose of donepezil were around 0.35 and 0.39 (page 16 stat significant). By now we know donepezil's clinical effectiveness eventually diminished as disease progresses. Obviously, we hope the cognitive benefit of PTI-125 continues based on the biomarker data. The improvement in cognition is depending on the baseline state of the patients (how severe the dementia and obviously the accuracy of diagnosis). I can't say too much and frankly nobody is all that certain.

Based on the mechanism of action, we predict the therapeutic effects of PTI-125 are applicable to a broad range of Alzheimer's disease patients. Again, the magnitude of benefits depend on the severity of dementia - the earlier the better. Hence, it is important to have a reliable early diagnosis tool though we still not entirely sure how to define "early".

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, February 15, 2021 10:32 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After some thoughts and review of data during Chinese New Year, I have some questions needed for your comments as follows :

1. ADAS-Cog Improvement between ARICEPT and PTI-125 : In https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively after 24 weeks of treatment. These differences were statistically significant for 473 patients. Compared with baseline, 5 mg/day and 10 mg/day treatments of donepezil at 24 weeks showed 1.06 and 1.6 benefits in a controlled study. However, the press release of Cassava Sciences on Feb. 2, 2021 mentioned that six months of PTI-125 treatment improved cognition scores by 1.6 points on ADAS-Cog11.

These comparative improvements did not clearly distinguish the therapeutic advantage of PTI-125 compared with ARICEPT in 24 weeks of treatment. Is it true for this simple observation as above ? Is there any indication that PTI-125 will have better effects after prolonged period of time (such as 1 year) by restoring of Filamin A with abnormal conformation ?

2. You mentioned that collective efforts try to bring some solutions for Alzheimer's disease patients. Does it mean that a subset of Alzheimer patients would be appropriate for therapeutic effects of PTI-125 and diagnosis tool of SavaDx ? While other patients are not ideal enough ?

Thanks so much for your insights again.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, February 4, 2021 4:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thank you for your well wishes and positive comments. Your continued interests in finding solutions for Alzheimer's disease research motivate us and I can truly say I am trying my very best . I thank you for keeping me informed and discussions on the findings from other investigators. We will keep moving forward and hope our collective efforts can bring some solutions for Alzheimer's disease patients.

Will keep safe the best I can as the COVID pandemic is still very bad here. Hopefully, with vaccination the situation improves in the coming months.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, February 2, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

Nice to know that the interim result of PTI-125 is positive and brings lights to the Alzheimer community. Congratulation to your continued efforts. There must be lots of persons sending emails to you regarding to this matter. To continue your clinical endeavors, I truly wish you to keep safe in this covid-19 epidemics. Your academic and real-word contributions are very much appreciated.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, January 21, 2021 11:55 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for keeping me informed of the recent development. I am all tied up by my extensive teaching load and research activities (this pandemic has caused tremendous pain with limited access).

Regarding the levels of N-terminal fragment of tau in the blood as a predictor of cognitive decline, this is really nothing new because we know the levels of tau in the CSF and blood positively correlate with the extent of neuronal damage (tau exist exclusively in neurons). The question is the sensitivity of detection that allow us to sound the alarm. With the more sensitive mass spectrometry we obviously are better equipped than before.

Thanks again. I will find time to answer your earlier queries.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 20, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] some development of diagnosis tool for reference

Dear Hoau :

There is some development of blood test for Alzheimer's disease to predicte future cognitive decline in healthy people with levels of N-terminal fragment of tau (NT1). Data link is as
<https://www.sciencedaily.com/releases/2020/12/201209115147.htm>. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, January 16, 2021 3:44 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks always for your info that keeping me in the loop of current Alzheimer's disease findings.

The problem is that this type of academic research using (genetically modified) rodent models that bear little resemblance to human Alzheimer's disease lead us to nowhere and frankly confuse & dilute our efforts. Hydrogen

sulfide is no doubt playing a regulatory role in many physiological activities. Just because it is decreased with aging and replacing it can improve cognition in rodents doesn't mean it is therapeutically possible. Don't forget the hydrogen sulfide is quite toxic one should worry the accumulation can severely hurt the brain function. Most importantly, there is no evidence rodent models have neurodegeneration (unlike brains in humans with Alzheimer's disease). GSK3a/b is one of the hubs in metabolism/energy regulation and as one of the tau kinases that have a sophisticated feed forward and feedback regulators. There is no evidence there is anything change in GSK3a/b in Alzheimer's disease. In general, kinases and phosphatases are terrible targets because they all have tons of regulators once activated or inhibited in a progressively changing brain like in Alzheimer's disease is predictably short-lived and ineffective especially when the disease becomes symptomatic (much too late).

Thanks. Have a good weekend.

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Wednesday, January 13, 2021 10:36 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

It seems to me more and more researches trying to target early pathogenesis of Alzheimer's disease which might be inspired by evidences of many clinical results. There is a recent research from John Hopkins Medicine working with University of Exeter concerning with effects of hydrogen sulfide, GSK3 β and other proteins involved in the pathogenesis of Alzheimer's disease. Their data link is https://medicalxpress.com/news/2021-01-hydrogen-sulfide-alzheimer-disease.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter. Hope that this information would be interesting to you. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, January 13, 2021 2:13 PM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Sorry for my late reply, sometimes I made a mental note to reply but I got busy and kind of putting it off. The impacts of concussion obviously vary according to the severity and frequency (multiple mild concussions can be quite damaging). It sounds like your father had a severe concussion that resulted in motor/sensory imbalance and dementia. I understand how hard it is to see your father suffer but unable to help.

There is no doubt vascular dysfunction is a risk factor and often accompanies Alzheimer's disease (cerebral amyloid angiopathy). That said, the cause-effect relationship between vascular dysfunction and Alzheimer's disease is not straight forward.

Indeed, upstream is a relative term. Abnormal filamin A can be induced by sub-chronic amyloid (soluble) infusion into brains. If abnormality in filamin A is blocked (by PTI-125), there is significant reduction in amyloid plaques (dead neurons) and neurofibrillary tangles. More importantly, brain activities with higher receptor and synaptic activities and function improve at least in mouse model of Alzheimer's disease. These data indicate reversing abnormality of filamin

A especially when at the stage when mild clinical dementia is detected may be a promising way to treatment Alzheimer's disease.

Hope I answer your questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, January 4, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your comments. After two decades of researches, your important findings have a step forward which is a remarkable achievement. I do admire your courage and patience with regard to this tough disease in which early detections are probably with both natures of science and art. My father was in a healthy condition before concussion and developed with signs of body imbalance and occurrence of Alzheimer disease. It was heartbreaking without ways to lessen his burden.

My assumption of root occurrence from vascular dysfunction might be wrong. It seems to me that finding a solution with very early detection before massive degeneration occurs is more than challenging. I am wondering which events trigger the formation of abnormal filamin A. If you could come up with a diagnosis tool tracing up the root cause of abnormal filamin A, it might be a better start than random guesses. I am not sure if I am right in this direction.

BTW, you mentioned that abnormal filamin A is an upstream event. Would you shed some lights on which upstream events are already verified up to now since upstream is a relative word ? Thanks so much for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, January 5, 2021 1:07 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

There is no doubt vascular dysfunction is an important part of the Alzheimer's disease (AD) pathology. Filamin A with abnormal conformation is found in plasma from AD patients doesn't necessary mean abnormal filamin A from platelets is resulted from vascular pathology including amyloid angiopathy, infarcts. More importantly, the abnormal filamin A in peripheral may be the result of brain pathogenic changes (occurs later).

Our data indicate abnormal filamin A is an upstream event. However, AD treatment effects are better if starts earlier (hence early detection before massive degeneration occurs is the key). I always think multiple therapeutic agents may be synergistic or additive. Again, if all the treatments administered after massive degeneration there is no treatments strong enough.

Thanks.

All the best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, January 3, 2021 7:50 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks for your kindly reply. Happy New Year !

Since conformational filamin A is structurally found in palates, I therefore assume that vascular pathologies are related to this disease. Your researches in various aspects of insulin resistances were published and your comments really show how hard it is to trace pathogenic events.

I really appreciate your continued research and endeavor to find more upstream targets treating Alzheimer disease effectively. It seems to me in your comments that restoration of conformational filamin A is not strong enough to show disease modifying effects. Is it true ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Monday, January 4, 2021 3:14 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Happy New Year. Wishing you and your family a healthy and prosperous year 2021.

It is my life time goal to help bring effective treatments and early diagnosis of the Alzheimer's disease (and other diseases with cognitive impairments). For the last two decades, I worked to identify possible drug and diagnostic targets. I'm mindful of the burden of the Alzheimer's disease caregivers, especially the potential of depression.

Regarding your question, there is no concrete data to show the function of blood platelet had changed in Alzheimer's disease (plausible of course). There are diverse pathogenic mechanisms and of course diseases such as diabetes (causes vascular pathologies) and history of concussion (multiple) had been suspected to be culprits to promote Alzheimer's disease. Surely, prevent such problems is useful but whether such measurements can reverse the damages that already done is everyone's guess. We had tried to control insulin resistance for years but the results thus far showed not much of effects. This may indicate that brain insulin resistance is not an early pathogenic event. We will do more to find more upstream targets so that we can more effective to treat Alzheimer's disease.

Thanks for your continuing interests and communications.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, December 29, 2020 7:38 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your kindly reply. For my father, a better treatment of Alzheimer disease is motivated and caregivers deserve to be with less burden. Regarding to the timing of conformational changes, I am curious to know if this is related to conditional changes of palates which caused by blood clotting, vascular abnormality or concussion, etc. Your endeavor of this tough disease is really appreciated.

Please be safe since pandemic and cold weather persist in northern atmosphere. Have a wonderful and peaceful New Year to you and your family.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, December 30, 2020 6:56 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks for your email.

Your friend is correct regarding the difficulty of finding specific antibodies for the filamin A with altered conformation in Alzheimer's disease. Indeed, the epitope of the altered filamin A may be hidden or had been processed. Obviously, computational approaches had been used to help us find viable antibodies. We still don't know when the conformational changes occur during the Alzheimer's disease pathogenesis even though we think this event occur early. But, what is early? This timing issue also requires some attention.

Yes, one-year extension of the open-label study is well under the way. Obviously, we will be looking for cognitive improvement and reduction in pathogenic drives such as reduction in inflammatory markers and degeneration.

Thanks again for your continued interests in getting the Alzheimer's disease treatment. I am working hard to get to this goal.

Happy New Year to you and your family.

Best regards,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, December 28, 2020 4:58 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Wish you a happy holiday and healthy new year, too. Regarding to the issue of diagnosis, my friend specialized in chemistry of antibody suggested to me recently that an exhaustive search of appropriate antibody to be connected with conformational filamin A in human palates might be required to have a solution of universal antibody for different races. A modern equipment with computerized tools would be helpful in this exhaustive search process. Since the epitope of conformational filamin A might be structurally hidden, an appropriate antibody might be sensitively or selectively enough to be effective. Hope that this information is useful.

A one-year, open label study of PTI-125 was initiated in March 2020 and enrolled over 60% of patients as mentioned in public. Supposedly, safety issues are not a big concern since expanded clinical trials still proceed. How about attributes of reduced inflammatory cytokine levels and improved cognition/behavior in this perspective since earlier enrolled patients had been treated with more than 6 months ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 23, 2020 4:03 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Season Greetings

Dear 宜明,

Sorry for my late reply as I am deep in the semester end exam and grading.

Wow, time flies by so quickly. It has been more than a year already since we started our communication. It is my pleasure to discuss the field of neuroscience even though we actually are learning on the way. I am thankful for the opportunities you have given me to think about the questions you have posted in different angles. Truly, we all hope we have grown some in knowledge and get effective Alzheimer's disease treatments forward to contain this terrible disease. I am for one will do everything I can and work tireless toward this goal. It takes collective efforts to get this under control so that I am collaborating with academic and industrial partners to look into as many ways we can investigate and test the effectiveness. Thanks to you for keeping me informed of many new strategies other have come up with in Alzheimer's disease diagnosis and treatments.

We all hope we can better handle this COVID pandemic. With the approval of 2 vaccines, I am hopeful we are better equipped to start limiting the death tolls and eventually control this horrific virus. I sincerely hope people learn from this as we all have to play a part (wearing mask, wash hands frequently etc). This experience certainly humbles us as we humans appear more vulnerable (at least not as invincible) than we think. The fact Taiwan has done so well in controlling COVID makes me proud to be a Taiwanese.

Wishing you and your family happy holidays and a healthy, peaceful and prosperous year 2021.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, December 20, 2020 8:43 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] Season Greetings

Dear Hoau-Yan :

It's been more than 1 year since I have this particular opportunity to know you. Your in-depth and insightful knowledge has given me more understandings in this tough field of neuroscience. Your assistances and comments are really appreciated. Hopefully, we will be better off with more solutions of pandemics and preventive measures next year. At this time of season, I truly wish you a Merry Christmas and happy New Year !

Best Regards,
宜明



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From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent time: 08/07/2021 09:28:04 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference (corrected)

Dear Hoau-Yan,

Normalization of altered filamin A alone should deserve a Noble prize, in my personal opinion. Correct my mistake in previous email. Keep up good works !

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, August 7, 2021 4:29 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

As always, I am completely booked up with research activities. Your questions kept me thinking. I answer your questions directly underneath each of your queries.

Hope all is well,

Thank you.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, July 31, 2021 2:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Thanks for your kindly reply during busy hours as always. Knocking off hard nuts is especially tough especially there was no precedent before. Your persistence and genuine contributions to global AD community is obvious. I am happy that your finding of the bad guy will eventually be a history of AD and even mankind. Your family and friends will be certainly proud of you after so many tough years spent in lab and related researches.

Your answers to my naïve questions are plain and understandable. To my personal curiosity which might be common to most people, I have additional questions as below.

1. Is there any plateau effect after months of oral treatment of PTI-125 since biomarkers of neuroinflammation and neurodegeneration will eventually reach their peaks ? Will responded patients need to take oral treatments of PTI-125 in their lifetime ? *True. neuroinflammation and neurodegeneration will reach a breaking point down the road without treatments. Our hope is that this treatment will delay the neuroinflammation and neurodegeneration so that brain can recover (those not dead yet) some so that*

brain can function better. My guess is that there is some sort of limitations (not plateau per se). We hope the window is big enough (beyond the nature life span).

2. When temporal changes of individual patient during the span of treatments will be revealed ? This information might show more consistent and clearer trend of treatment effects. *I am not sure what you are referring to. It would be difficult to gauge patient's response rate since each patient is different in many aspects (other diseases, genetic make up etc). Very difficult to tell.*
3. For neurons already beyond repairs or dead, is there any viable therapeutic or complimentary solution ? *No. Raise from death is NOT any humans can do.*
4. Would mental or physical rehabilitations for patients during or after treatments add more values to their health ? *We have evidence to show exercise and good nutrients (diet) help to elevate the treatment effects.*

There must be lots of works needed to be done after this stage. For all your dedication, I believe that all time spent in search of better treatments will be meaningful and greatly appreciated. Thanks again in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, July 31, 2021 1:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your encouragements always and giving your opinions and questions as I need such reminders to keep my comments plain and understandable.

I will **answer your questions directly underneath each query you posted**. Since I am blind to all patient related info, I can only answer in general terms.

Hope all is well with you and your family.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Thursday, July 29, 2021 10:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Congratulation to your researches going with a gigantic step forward. After reading updated PTI-125 related papers in CCAI 2021, I had a feeling that your lab works have gradually verified the MOA of Filamin A with abnormal conformation. There are thoughts with results of SavaDx and 9-month data as follows :

- 1) Correlation studies of Abnormal Filamin A in phase 2b patients is a positive step. That is a great findings and direction in the framework of diagnosis tool. However, taking Abnormal Filamin A as a biomarker needs more works to establish that which level of Abnormal Filamin A should be detected as an early sign of AD. I am wondering if a totally new or compatible antibody in your earlier works of SavaDx is employed in this study.

- Indeed, this is just the initial steps. The antibodies used obviously required constant verifications using that was used earlier. It is a tedious work but there are no short cuts. We need to define the timeline when the abnormal FLNA can be detected (not an easy task because we don't even know when is early).
 - 2) Cognition Improvement of 3.0 Points on ADAS-Cog at 9 Months ($p < 0.001$) is great for patients as a process of Filamin A normalization. However, most people are wondering why NPI score in 9 month improved less than in 6 month by 0.6 points. All tested biomarkers are consistent with improvements which relieved lots of overhangs.
 - People forget Alzheimer's disease is a progressive neurodegenerative disease with multiple factors at play. As patients deteriorate cognitively due to brain function declines, there are added factors hence the magnitude of improvements become less comparing the the baseline. The 0.6 points less at 9 month reflects just that (obviously it also depends on the stage of disease when patients first enrolled) but the curve will be stabilize for period of time.
 - 3) 22% of patients declined less than reported in the science literature at 9 months. Why these patients are so hard to respond to treatment of simufilam ? Any other upstream catalyst for these patients ?
 - Well, we don't actually know but my guess is that these patients have other issues or they were selected at later stage of the disease even though their MMSE or ADAS-Cog when enrolled were not bad. While we like to have 100% responsive rate, it is an unrealistic expectation. This drive home the importance of early diagnosis. I am sure if we treat earlier, we will see a better result.
 - 4) As reported earlier, Evonik will supply Cassava Sciences with large-scale, clinical-grade quantities of simufilam. I am wondering if Evonik will produce good qualities of simufilam as in phase 2b study and it should be carefully verified before entering phase 3.
 - Clearly, QC will be done carefully.
 - 5) Finally, is abnormal filamin A responsible for the symptom or modifying answer to AD ?
 - While we all want to find the "bad" guy (abnormal FLNA is a critical but one of the bad guys I am sure there are many others). Fortunately, fixing abnormal FLNA promotes healthier and more resilient brain but unfortunately can't fix anything already beyond repairs or dead. I am a realistic person by showing people what I saw but I don't want to give a wrong impression that fixing abnormal FLNA can bring back what have already damaged.
- I am honored to be with your ongoing researches and contributions to AD patients. Thanks for your hard works.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, June 30, 2021 8:29 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Sorry for my late reply. I often just get occupied by too many tasks in hand and consequently delay in my response to you and many.

Yes, lots efforts had been on the multiple fronts and there should be an update in phase 2b study. I will be interest in learning of your comments.

I watch the COVID-19 situation in Taiwan closely. It is most unfortunately some careless acts led to such a spread. Even though it is pale by comparison to US and EU, it is still very concerning especially in Taipei (the worst in transparency) and New Taipei. A solution to this monumental disaster must include understand the pathogen (virus) so that more effective medications together with vaccination can put this pandemic out for good.

Best wishes to you and your family, it is looking better recently so that normalcy is near.

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, June 22, 2021 12:18 AM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After reading a recent news from Cassava Sciences, I realized that there will be a presentation at AAIC during the week of July 26-30th about SavaDx clinical dataset from PTI-125's Phase 2b study of 64 patients. Look forward to seeing more updates of SavaDx developments which you must devote lots of time and energy.

Affected by recent COVID-19 impacts in Taiwan, I have been working from home more than 1 month. Hope that this history-making pandemics will be alleviated or solved by pharmaceutical solutions. The same goes to PTI-125 to help patients in need. Thanks.

Best Regards,

宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Tuesday, February 23, 2021 10:26 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

The MOA for PTI-125 is very different from that of ANVS401. PTI-125 reverses an abnormal filamin A thereby reducing the toxic signaling pathways that drive neurodegeneration and inflammation. ANVS401 functions as a translational blockers that presumably (based on cell and transgenic models) to reduce toxic substances such as amyloid beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. The major problem is that reducing those "toxic" substances do not work in humans. In fact, ANVS401 blocks APP (amyloid precursor protein) to reduce amyloid beta. APP is a known trophic factor whose expression increases when brain is injured. More of the problem, we know reduction in amyloid beta by beta or gamma secretase inhibitors do not stop Alzheimer's disease progression and in some cases actually worsen cognitive impairments. Hence, I don't predict any synergy between PTI-125 and ANVS401.

Postmortem brains are not suitable to study metabolic dysfunction because one can only show there is metabolic disturbance but can not conclusively show the source, when and how the metabolic dysfunction occur. Transgenic animal models are partial models at best and are very different from actual disease, therefore they are inheritably insufficient to any pathogenic pathway questions just about any diseases.

I hope my explanations help answering your questions.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, February 21, 2021 3:05 AM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

I had some thoughts again regarding to the upstream causes of Alzheimer disease and MOA of PTI-125.

As you mentioned earlier, there were complicated lab works deriving chemical compounds of PTI-125 to restore of Filamin A with abnormal conformation. I am curious to know what is the chemical MOA of PTI-125 which differentiates from other approaches such as ANVS401 of Annovis Bio Inc. to decrease multiple neurotoxic in Cerebrospinal Fluid (CSF) and improve axonal transport of nerve cell. Their therapeutic target also aims for reductions of neuroinflammation and neurodegeneration. Is there any synergetic effect to combine PTI-125 and ANVS401 ?

As in previous email, I am skeptical about causes of metabolic dysfunction related to Alzheimer disease. Is there any direct proof from human postmortem model instead of mouse model ?
Thanks again for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 16, 2021 1:08 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

First, Happy Lunar New Year. Wishing you and your family a happy, healthy and prosperous year of Ox.

Regarding your question, Donepezil's ADAS-cog score you are referring to are raw score. Once taking placebo control into consideration, the improvement achieved by 24 months of 5 mg and 10 mg daily dose of donepezil were around 0.35 and 0.39 (page 16 stat significant). By now we know donepezil's clinical effectiveness eventually diminished as disease progresses. Obviously, we hope the cognitive benefit of PTI-125 continues based on the biomarker data. The improvement in cognition is depending on the baseline state of the patients (how severe the dementia and obviously the accuracy of diagnosis). I can't say too much and frankly nobody is all that certain.

Based on the mechanism of action, we predict the therapeutic effects of PTI-125 are applicable to a broad range of Alzheimer's disease patients. Again, the magnitude of benefits depend on the severity of dementia - the earlier the better. Hence, it is important to have a reliable early diagnosis tool though we still not entirely sure how to define "early".

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, February 15, 2021 10:32 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After some thoughts and review of data during Chinese New Year, I have some questions needed for your comments as follows :

1. ADAS-Cog Improvement between ARICEPT and PTI-125 : In https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively after 24 weeks

of treatment. These differences were statistically significant for 473 patients. Compared with baseline, 5 mg/day and 10 mg/day treatments of donepezil at 24 weeks showed 1.06 and 1.6 benefits in a controlled study. However, the press release of Cassava Sciences on Feb. 2, 2021 mentioned that six months of PTI-125 treatment improved cognition scores by 1.6 points on ADAS-Cog11.

These comparative improvements did not clearly distinguish the therapeutic advantage of PTI-125 compared with ARICEPT in 24 weeks of treatment. Is it true for this simple observation as above ? Is there any indication that PTI-125 will have better effects after prolonged period of time (such as 1 year) by restoring of Filamin A with abnormal conformation ?

2. You mentioned that collective efforts try to bring some solutions for Alzheimer's disease patients. Does it mean that a subset of Alzheimer patients would be appropriate for therapeutic effects of PTI-125 and diagnosis tool of SavaDx ? While other patients are not ideal enough ?

Thanks so much for your insights again.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, February 4, 2021 4:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thank you for your well wishes and positive comments. Your continued interests in finding solutions for Alzheimer's disease research motivate us and I can truly say I am trying my very best . I thank you for keeping me informed and discussions on the findings from other investigators. We will keep moving forward and hope our collective efforts can bring some solutions for Alzheimer's disease patients.

Will keep safe the best I can as the COVID pandemic is still very bad here. Hopefully, with vaccination the situation improves in the coming months.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, February 2, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

Nice to know that the interim result of PTI-125 is positive and brings lights to the Alzheimer community. Congratulation to your continued efforts. There must be lots of persons sending emails to you regarding to this matter. To continue your clinical endeavors, I truly wish you to keep safe in this covid-19 epidemics. Your academic and real-word contributions are very much appreciated.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Thursday, January 21, 2021 11:55 PM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for keeping me informed of the recent development. I am all tied up by my extensive teaching load and research activities (this pandemic has caused tremendous pain with limited access).

Regarding the levels of N-terminal fragment of tau in the blood as a predictor of cognitive decline, this is really nothing new because we know the levels of tau in the CSF and blood positively correlate with the extent of neuronal damage (tau exist exclusively in neurons). The question is the sensitivity of detection that allow us to sound the alarm. With the more sensitive mass spectrometry we obviously are better equipped than before.

Thanks again. I will find time to answer your earlier queries.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Wednesday, January 20, 2021 7:54 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] some development of diagnosis tool for reference

Dear Hoau :

There is some development of blood test for Alzheimer's disease to predict future cognitive decline in healthy people with levels of N-terminal fragment of tau (NT1). Data link is as <https://www.sciencedaily.com/releases/2020/12/201209115147.htm>. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Saturday, January 16, 2021 3:44 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks always for your info that keeping me in the loop of current Alzheimer's disease findings.

The problem is that this type of academic research using (genetically modified) rodent models that bear little resemblance to human Alzheimer's disease lead us to nowhere and frankly confuse & dilute our efforts. Hydrogen sulfide is no doubt playing a regulatory role in many physiological activities. Just because it is decreased with aging and replacing it can improve cognition in rodents doesn't mean it is therapeutically possible. Don't forget the hydrogen sulfide is quite toxic one should worry the accumulation can severely hurt the brain function. Most importantly, there is no evidence rodent models have neurodegeneration (unlike brains in humans with Alzheimer's disease). GSK3a/b is one of the hubs in metabolism/energy regulation and as one of the tau kinases that have a sophisticate feed forward and

feedback regulators. There is no evidence there is anything change in GSK3a/b in Alzheimer's disease. In general, kinases and phosphatases are terrible targets because they all have tons of regulators once activated or inhibited in a progressively changing brain like in Alzheimer's disease is predictably short-lived and ineffective especially when the disease becomes symptomatic (much too late).

Thanks. Have a good weekend.

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Wednesday, January 13, 2021 10:36 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

It seems to me more and more researches trying to target early pathogenesis of Alzheimer's disease which might be inspired by evidences of many clinical results. There is a recent research from John Hopkins Medicine working with University of Exeter concerning with effects of hydrogen sulfide, GSK3 β and other proteins involved in the pathogenesis of Alzheimer's disease. Their data link is https://medicalxpress.com/news/2021-01-hydrogen-sulfide-alzheimer-disease.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter. Hope that this information would be interesting to you. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, January 13, 2021 2:13 PM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Sorry for my late reply, sometimes I made a mental note to reply but I got busy and kind of putting it off. The impacts of concussion obviously vary according to the severity and frequency (multiple mild concussions can be quite damaging). It sounds like your father had a severe concussion that resulted in motor/sensory imbalance and dementia. I understand how hard it is to see your father suffer but unable to help.

There is no doubt vascular dysfunction is a risk factor and often accompanies Alzheimer's disease (cerebral amyloid angiopathy). That said, the cause-effect relationship between vascular dysfunction and Alzheimer's disease is not straight forward.

Indeed, upstream is a relative term. Abnormal filamin A can be induced by sub-chronic amyloid (soluble) infusion into brains. If abnormality in filamin A is blocked (by PTI-125), there is significant reduction in amyloid plaques (dead neurons) and neurofibrillary tangles. More importantly, brain activities with higher receptor and synaptic activities and function improve at least in mouse model of Alzheimer's disease. These data indicate reversing abnormality of filamin A especially when at the stage when mild clinical dementia is detected may be a promising way to treatment Alzheimer's disease.

Hope I answer your questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Monday, January 4, 2021 7:54 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your comments. After two decades of researches, your important findings have a step forward which is a remarkable achievement. I do admire your courage and patience with regard to this tough disease in which early detections are probably with both natures of science and art. My father was in a healthy condition before concussion and developed with signs of body imbalance and occurrence of Alzheimer disease. It was heartbreaking without ways to lessen his burden.

My assumption of root occurrence from vascular dysfunction might be wrong. It seems to me that finding a solution with very early detection before massive degeneration occurs is more than challenging. I am wondering which events trigger the formation of abnormal filamin A. If you could come up with a diagnosis tool tracing up the root cause of abnormal filamin A, it might be a better start than random guesses. I am not sure if I am right in this direction.

BTW, you mentioned that abnormal filamin A is an upstream event. Would you shed some lights on which upstream events are already verified up to now since upstream is a relative word ? Thanks so much for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Tuesday, January 5, 2021 1:07 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

There is no doubt vascular dysfunction is an important part of the Alzheimer's disease (AD) pathology. Filamin A with abnormal conformation is found in plasma from AD patients doesn't necessary mean abnormal filamin A from platelets is resulted from vascular pathology including amyloid angiopathy, infarcts. More importantly, the abnormal filamin A in peripheral may be the result of brain pathogenic changes (occurs later).

Our data indicate abnormal filamin A is an upstream event. However, AD treatment effects are better if starts earlier (hence early detection before massive degeneration occurs is the key). I always think multiple therapeutic agents may be synergistic or additive. Again, if all the treatments administered after massive degeneration there is no treatments strong enough.

Thanks.

All the best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, January 3, 2021 7:50 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks for your kindly reply. Happy New Year !

Since conformational filamin A is structurally found in palates, I therefore assume that vascular pathologies are related to this disease. Your researches in various aspects of insulin resistances were published and your comments really show how hard it is to trace pathogenic events.

I really appreciate your continued research and endeavor to find more upstream targets treating Alzheimer disease effectively. It seems to me in your comments that restoration of conformational filamin A is not strong enough to show disease modifying effects. Is it true ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Monday, January 4, 2021 3:14 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Happy New Year. Wishing you and your family a healthy and prosperous year 2021.

It is my life time goal to help bring effective treatments and early diagnosis of the Alzheimer's disease (and other diseases with cognitive impairments). For the last two decades, I worked to identify possible drug and diagnostic targets. I'm mindful of the burden of the Alzheimer's disease caregivers, especially the potential of depression.

Regarding your question, there is no concrete data to show the function of blood platelet had changed in Alzheimer's disease (plausible of course). There are diverse pathogenic mechanisms and of course diseases such as diabetes (causes vascular pathologies) and history of concussion (multiple) had been suspected to be culprits to promote Alzheimer's disease. Surely, prevent such problems is useful but whether such measurements can reverse the damages that already done is everyone's guess. We had tried to control insulin resistance for years but the results thus far showed not much of effects. This may indicate that brain insulin resistance is not an early pathogenic event. We will do more to find more upstream targets so that we can more effective to treat Alzheimer's disease.

Thanks for your continuing interests and communications.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, December 29, 2020 7:38 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your kindly reply. For my father, a better treatment of Alzheimer disease is motivated and caregivers deserve to be with less burden. Regarding to the timing of conformational changes, I am curious to know if this is related to conditional changes of palates which caused by blood clotting, vascular abnormality or concussion, etc. Your endeavor of this tough disease is really appreciated.

Please be safe since pandemic and cold weather persist in northern atmosphere. Have a wonderful and peaceful New Year to you and your family.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, December 30, 2020 6:56 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks for your email.

Your friend is correct regarding the difficulty of finding specific antibodies for the filamin A with altered conformation in Alzheimer's disease. Indeed, the epitope of the altered filamin A may be hidden or had been processed. Obviously, computational approaches had been used to help us find viable antibodies. We still don't know when the conformational changes occur during the Alzheimer's disease pathogenesis even though we think this event occur early. But, what is early? This timing issue also requires some attention.

Yes, one-year extension of the open-label study is well under the way. Obviously, we will be looking for cognitive improvement and reduction in pathogenic drives such as reduction in inflammatory markers and degeneration.

Thanks again for your continued interests in getting the Alzheimer's disease treatment. I am working hard to get to this goal.

Happy New Year to you and your family.

Best regards,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Monday, December 28, 2020 4:58 AM

To: Hoau-yan Wang

Subject: [EXTERNAL] Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Wish you a happy holiday and healthy new year, too. Regarding to the issue of diagnosis, my friend specialized in chemistry of antibody suggested to me recently that an exhaustive search of appropriate antibody to be connected with conformational filamin A in human palates might be required to have a solution of universal antibody for different races. A modern equipment with computerized tools would be helpful in this exhaustive search process. Since the epitope of conformational filamin A might be structurally hidden, an appropriate antibody might be sensitively or selectively enough to be effective. Hope that this information is useful.

A one-year, open label study of PTI-125 was initiated in March 2020 and enrolled over 60% of patients as mentioned in public. Supposedly, safety issues are not a big concern since expanded clinical trials still proceed. How about attributes of reduced inflammatory cytokine levels and improved cognition/behavior in this perspective since earlier enrolled patients had been treated with more than 6 months ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 23, 2020 4:03 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Season Greetings

Dear 宜明,

Sorry for my late reply as I am deep in the semester end exam and grading.

Wow, time flies by so quickly. It has been more than a year already since we started our communication. It is my pleasure to discuss the field of neuroscience even though we actually are learning on the way. I am thankful for the opportunities you have given me to think about the questions you have posted in different angles. Truly, we all hope we have grown some in knowledge and get effective Alzheimer's disease treatments forward to contain this terrible disease. I am for one will do everything I can and work tireless toward this goal. It takes collective efforts to get this under control so that I am collaborating with academic and industrial partners to look into as many ways we can investigate and test the effectiveness. Thanks to you for keeping me informed of many new strategies other have come up with in Alzheimer's disease diagnosis and treatments.

We all hope we can better handle this COVID pandemic. With the approval of 2 vaccines, I am hopeful we are better equipped to start limiting the death tolls and eventually control this horrific virus. I sincerely hope people learn from this as we all have to play a part (wearing mask, wash hands frequently etc). This experience certainly humbles us as we humans appear more vulnerable (at least not as invincible) than we think. The fact Taiwan has done so well in controlling COVID makes me proud to be a Taiwanese.

Wishing you and your family happy holidays and a healthy, peaceful and prosperous year 2021.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, December 20, 2020 8:43 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] Season Greetings

Dear Hoau-Yan :

It's been more than 1 year since I have this particular opportunity to know you. Your in-depth and insightful knowledge has given me more understandings in this tough field of neuroscience. Your assistances and comments are really appreciated. Hopefully, we will be better off with more solutions of pandemics and preventive measures next year. At this time of season, I truly wish you a Merry Christmas and happy New Year !

Best Regards,
宜明



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From: Hoau-yan Wang
Sent time: 08/09/2021 12:07:53 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your kind words. Your questions keep me thinking of my answers so that I can be as clear as possible in my answers to most. I am truly impressed with and appreciate your viewpoints. Obviously, we have a lot of unknown factors in Alzheimer's disease that harboring many pathogenic pathways. I am working as hard as I can to find other possible pathogenic triggers - bad guys (aging process is one of them, and I think mental stress may also push the brain into neurodegenerative path). Regardless, we got to find these damaging pathways as soon as we can - early diagnosis that is.

Thanks for the reminder of the COVID delta variants. I am glad that Taiwan is very cautious on this pandemic development. In US, there are people still hesitate to be vaccinated. Unlike Taiwan, the availability of vaccine is less a problem because 4 mainstream vaccines are produced in US. I think Taiwan's domestic vaccines look great and more importantly can solve the supply issues although I do not get there are politicians that constantly trying to discredit these vaccines. In any case, please be very careful still especially in Taipei and New Taipei cities.

Thanks again for your support and keeping me informed of other developments. Please also keep asking questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, August 7, 2021 2:16 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Nice to have your replies especially when you are fully occupied. Your answers to my naïve questions help me to understand more properties of PTI-125 which surely would provide viable solutions to needed patients never before. Especially for meaningful researches, PTI-125 would have more indications and implications as time goes on. If you could find additional bad guys behind AD, a Nobel prize for you is not too far away.

Stay safe when delta virus poses new threats in US. In Taiwan, we are cautious about recent pandemic developments with protective measures. Looking ahead, I would expect an oral solution with protease inhibitor or some combination therapy would truly alleviate this human dilemma. Thanks again for your insights and sharing with me.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, August 7, 2021 4:29 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

As always, I am completely booked up with research activities. Your questions kept me thinking. I answer your questions directly underneath each of your queries.

Hope all is well,

Thank you.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, July 31, 2021 2:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Thanks for your kindly reply during busy hours as always. Knocking off hard nuts is especially tough especially there was no precedent before. Your persistence and genuine contributions to global AD community is obvious. I am happy that your finding of the bad guy will eventually be a history of AD and even mankind. Your family and friends will be certainly proud of you after so many tough years spent in lab and related researches.

Your answers to my naïve questions are plain and understandable. To my personal curiosity which might be common to most people, I have additional questions as below.

1. Is there any plateau effect after months of oral treatment of PTI-125 since biomarkers of neuroinflammation and neurodegeneration will eventually reach their peaks ? Will responded patients need to take oral treatments of PTI-125 in their lifetime ? *True. neuroinflammation and neurodegeneration will reach a breaking point down the road without treatments. Our hope is that this treatment will delay the neuroinflammation and neurodegeneration so that brain can recover (those not dead yet) some so that brain can function better. My guess is that there is some sort of limitations (not plateau per se). We hope the window is big enough (beyond the nature life span).*
2. When temporal changes of individual patient during the span of treatments will be revealed ? This information might show more consistent and clearer trend of treatment effects. *I am not sure what you are referring to. It would be difficult to gauge patient's response rate since each patient is different in many aspects (other diseases, genetic make up etc). Very difficult to tell.*
3. For neurons already beyond repairs or dead, is there any viable therapeutic or complimentary solution ? *No. Raise from death is NOT any humans can do.*
4. Would mental or physical rehabilitations for patients during or after treatments add more values to their health ? *We have evidence to show exercise and good nutrients (diet) help to elevate the treatment effects.*

There must be lots of works needed to be done after this stage. For all your dedication, I believe that all time spent in search of better treatments will be meaningful and greatly appreciated. Thanks again in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, July 31, 2021 1:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your encouragements always and giving your opinions and questions as I need such reminders to keep my comments plain and understandable.

I will **answer your questions directly underneath each query you posted**. Since I am blind to all patient related info, I can only answer in general terms.

Hope all is well with you and your family.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Thursday, July 29, 2021 10:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Congratulation to your researches going with a gigantic step forward. After reading updated PTI-125 related papers in CCAI 2021, I had a feeling that your lab works have gradually verified the MOA of Filamin A with abnormal conformation. There are thoughts with results of SavaDx and 9-month data as follows :

- 1) Correlation studies of Abnormal Filamin A in phase 2b patients is a positive step. That is a great findings and direction in the framework of diagnosis tool. However, taking Abnormal Filamin A as a biomarker needs more works to establish that which level of Abnormal Filamin A should be detected as an early sign of AD. I am wondering if a totally new or compatible antibody in your earlier works of SavaDx is employed in this study.
- Indeed, this is just the initial steps. The antibodies used obviously required constant verifications using that was used earlier. It is a tedious work but there are no short cuts. We need to define the timeline when the abnormal FLNA can be detected (not an easy task because we don't even know when is early).
- 2) Cognition Improvement of 3.0 Points on ADAS-Cog at 9 Months ($p < 0.001$) is great for patients as a process of Filamin A normalization. However, most people are wondering why NPI score in 9 month improved less than in 6 month by 0.6 points. All tested biomarkers are consistent with improvements which relieved lots of overhangs.
- People forget Alzheimer's disease is a progressive neurodegenerative disease with multiple factors at play. As patients deteriorate cognitively due to brain function declines, there are added factors hence the magnitude of improvements become less comparing the the baseline. The 0.6 points less at 9 month reflects just that (obviously it also depends on the stage of disease when patients first enrolled) but the curve will be stabilize for period of time.
- 3) 22% of patients declined less than reported in the science literature at 9 months. Why these patients are so hard to respond to treatment of simufilam ? Any other upstream catalyst for these patients ?
- Well, we don't actually know but my guess is that these patients have other issues or they were selected at later stage of the disease even though their MMSE or ADAS-Cog when enrolled were not bad. While we like to have 100% responsive rate, it is an unrealistic expectation. This drive home the importance of early diagnosis. I am sure if we treat earlier, we will see a better result.
- 4) As reported earlier, Evonik will supply Cassava Sciences with large-scale, clinical-grade quantities of simufilam. I am wondering if Evonik will produce good qualities of simufilam as in phase 2b study and it should be carefully verified before entering phase 3.
- Clearly, QC will be done carefully.
- 5) Finally, is abnormal filamin A responsible for the symptom or modifying answer to AD ?
- While we all want to find the "bad" guy (abnormal FLNA is a critical but one of the bad guys I am sure there are many others). Fortunately, fixing abnormal FLNA promotes healthier and more resilient brain but unfortunately can't fix anything already beyond repairs or dead. I am a realistic person by showing people what I saw but I don't want to give a wrong impression that fixing abnormal FLNA can bring back what have already damaged.

I am honored to be with your ongoing researches and contributions to AD patients. Thanks for your hard works.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, June 30, 2021 8:29 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Sorry for my late reply. I often just get occupied by too many tasks in hand and consequently delay in my response to you and many.

Yes, lots efforts had been on the multiple fronts and there should be an update in phase 2b study. I will be interest in learning of your comments.

I watch the COVID-19 situation in Taiwan closely. It is most unfortunately some careless acts led to such a spread. Even though it is pale by comparison to US and EU, it is still very concerning especially in Taipei (the worst in transparency) and New Taipei. A solution to this monumental disaster must include understand the pathogen (virus) so that more effective medications together with vaccination can put this pandemic out for good.

Best wishes to you and your family, it is looking better recently so that normalcy is near.

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, June 22, 2021 12:18 AM

To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After reading a recent news from Cassava Sciences, I realized that there will be a presentation at AAIC during the week of July 26-30th about SavaDx clinical dataset from PTI-125's Phase 2b study of 64 patients. Look forward to seeing more updates of SavaDx developments which you must devote lots of time and energy.

Affected by recent COVID-19 impacts in Taiwan, I have been working from home more than 1 month. Hope that this history-making pandemics will be alleviated or solved by pharmaceutical solutions. The same goes to PTI-125 to help patients in need. Thanks.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 23, 2021 10:26 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

The MOA for PTI-125 is very different from that of ANVS401. PTI-125 reverses an abnormal filamin A thereby reducing the toxic signaling pathways that drive neurodegeneration and inflammation. ANVS401 functions as a translational blockers that presumably (based on cell and transgenic models) to reduce toxic substances such as amyloid beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. The major problem is that reducing those "toxic" substances do not work in humans. In fact, ANVS401 blocks APP (amyloid precursor protein) to reduce amyloid beta. APP is a known trophic factor whose expression increases when brain is injured. More of the problem, we know reduction in amyloid beta by beta or gamma secretase inhibitors do not stop Alzheimer's disease progression and in some cases actually worsen cognitive impairments. Hence, I don't predict any synergy between PTI-125 and ANVS401.

Postmortem brains are not suitable to study metabolic dysfunction because one can only show there is metabolic disturbance but can not conclusively show the source, when and how the metabolic dysfunction occur. Transgenic animal models are partial models at best and are very different from actual disease, therefore they are inheritably insufficient to any pathogenic pathway questions just about any diseases.

I hope my explanations help answering your questions.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, February 21, 2021 3:05 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

I had some thoughts again regarding to the upstream causes of Alzheimer disease and MOA of PTI-125.

As you mentioned earlier, there were complicated lab works deriving chemical compounds of PTI-125 to restore of Filamin A with abnormal conformation. I am curious to know what is the chemical MOA of PTI-125 which differentiates from other approaches such as ANVS401 of Annovis Bio Inc. to decrease multiple neurotoxic in Cerebrospinal Fluid (CSF) and improve axonal transport of nerve cell. Their therapeutic target also aims for reductions of neuroinflammation and neurodegeneration. Is there any synergetic effect to combine PTI-125 and ANVS401 ?

As in previous email, I am skeptical about causes of metabolic dysfunction related to Alzheimer disease. Is there any direct proof from human postmortem model instead of mouse model ?

Thanks again for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 16, 2021 1:08 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

First, Happy Lunar New Year. Wishing you and your family a happy, healthy and prosperous year of Ox.

Regarding your question, Donepezil's ADAS-cog score you are referring to are raw score. Once taking placebo control into consideration, the improvement achieved by 24 months of 5 mg and 10 mg daily dose of donepezil were around 0.35 and 0.39 (page 16 stat significant). By now we know donepezil's clinical effectiveness eventually diminished as disease progresses. Obviously, we hope the cognitive benefit of PTI-125 continues based on the biomarker data. The improvement in cognition is depending on the baseline state of the patients (how severe the dementia and obviously the accuracy of diagnosis). I can't say too much and frankly nobody is all that certain.

Based on the mechanism of action, we predict the therapeutic effects of PTI-125 are applicable to a broad range of Alzheimer's disease patients. Again, the magnitude of benefits depend on the severity of dementia - the earlier the better. Hence, it is important to have a reliable early diagnosis tool though we still not entirely sure how to define "early".

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, February 15, 2021 10:32 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After some thoughts and review of data during Chinese New Year, I have some questions needed for your comments as follows :

1. ADAS-Cog Improvement between ARICEPT and PTI-125 : In https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively after 24 weeks of treatment. These differences were statistically significant for 473 patients. Compared with baseline, 5 mg/day and 10 mg/day treatments of donepezil at 24 weeks showed 1.06 and 1.6 benefits in a controlled study. However, the press release of Cassava Sciences on Feb. 2, 2021 mentioned that six months of PTI-125 treatment improved cognition scores by 1.6 points on ADAS-Cog11.

These comparative improvements did not clearly distinguish the therapeutic advantage of PTI-125 compared with ARICEPT in 24 weeks of treatment. Is it true for this simple observation as above ? Is there any indication that PTI-125 will have better effects after prolonged period of time (such as 1 year) by restoring of Filamin A with abnormal conformation ?

2. You mentioned that collective efforts try to bring some solutions for Alzheimer's disease patients. Does it mean that a subset of Alzheimer patients would be appropriate for therapeutic effects of PTI-125 and diagnosis tool of SavaDx ? While other patients are not ideal enough ?

Thanks so much for your insights again.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, February 4, 2021 4:39 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thank you for your well wishes and positive comments. Your continued interests in finding solutions for Alzheimer's disease research motivate us and I can truly say I am trying my very best. I thank you for keeping me informed and discussions on the findings from other investigators. We will keep moving forward and hope our collective efforts can bring some solutions for Alzheimer's disease patients.

Will keep safe the best I can as the COVID pandemic is still very bad here. Hopefully, with vaccination the situation improves in the coming months.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, February 2, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

Nice to know that the interim result of PTI-125 is positive and brings lights to the Alzheimer community. Congratulation to your continued efforts. There must be lots of persons sending emails to you regarding to this matter. To continue your clinical endeavors, I truly wish you to keep safe in this covid-19 epidemics. Your academic and real-word contributions are very much appreciated.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, January 21, 2021 11:55 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for keeping me informed of the recent development. I am all tied up by my extensive teaching load and research activities (this pandemic has caused tremendous pain with limited access).

Regarding the levels of N-terminal fragment of tau in the blood as a predictor of cognitive decline, this is really nothing new because we know the levels of tau in the CSF and blood positively correlate with the extent of neuronal damage (tau exist exclusively in neurons). The question is the sensitivity of detection that allow us to sound the alarm. With the more sensitive mass spectrometry we obviously are better equipped than before.

Thanks again. I will find time to answer your earlier queries.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 20, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] some development of diagnosis tool for reference

Dear Hoau :

There is some development of blood test for Alzheimer's disease to predict future cognitive decline in healthy people with levels of N-terminal fragment of tau (NT1). Data link is as
<https://www.sciencedaily.com/releases/2020/12/201209115147.htm>. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, January 16, 2021 3:44 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks always for your info that keeping me in the loop of current Alzheimer's disease findings.

The problem is that this type of academic research using (genetically modified) rodent models that bear little resemblance to human Alzheimer's disease lead us to nowhere and frankly confuse & dilute our efforts. Hydrogen sulfide is no doubt playing a regulatory role in many physiological activities. Just because it is decreased with aging and replacing it can improve cognition in rodents doesn't mean it is therapeutically possible. Don't forget the hydrogen sulfide is quite toxic one should worry the accumulation can severely hurt the brain function. Most importantly, there is no evidence rodent models have neurodegeneration (unlike brains in humans with Alzheimer's disease). GSK3a/b is one of the hubs in metabolism/energy regulation and as one of the tau kinases that have a sophisticate feed forward and feedback regulators. There is no evidence there is anything change in GSK3a/b in Alzheimer's disease. In general, kinases and phosphatases are terrible targets because they all have tons of regulators once activated or inhibited in a progressively changing brain like in Alzheimer's disease is predictably short-lived and ineffective especially when the disease becomes symptomatic (much too late).

Thanks. Have a good weekend.

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 13, 2021 10:36 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

It seems to me more and more researches trying to target early pathogenesis of Alzheimer's disease which might be inspired by evidences of many clinical results. There is a recent research from John Hopkins Medicine working with University of Exeter concerning with effects of hydrogen sulfide, GSK3 β and other proteins involved in the pathogenesis of Alzheimer's disease. Their data link is https://medicalxpress.com/news/2021-01-hydrogen-sulfide-alzheimer-disease.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter. Hope that this information would be interesting to you. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 13, 2021 2:13 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Sorry for my late reply, sometimes I made a mental note to reply but I got busy and kind of putting it off. The impacts of concussion obviously vary according to the severity and frequency (multiple mild concussions can be quite damaging). It sounds like your father had a severe concussion that resulted in motor/sensory imbalance and dementia. I understand how hard it is to see your father suffer but unable to help.

There is no doubt vascular dysfunction is a risk factor and often accompanies Alzheimer's disease (cerebral amyloid angiopathy). That said, the cause-effect relationship between vascular dysfunction and Alzheimer's disease is not straight forward.

Indeed, upstream is a relative term. Abnormal filamin A can be induced by sub-chronic amyloid (soluble) infusion into

brains. If abnormality in filamin A is blocked (by PTI-125), there is significant reduction in amyloid plaques (dead neurons) and neurofibrillary tangles. More importantly, brain activities with higher receptor and synaptic activities and function improve at least in mouse model of Alzheimer's disease. These data indicate reversing abnormality of filamin A especially when at the stage when mild clinical dementia is detected may be a promising way to treatment Alzheimer's disease.

Hope I answer your questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, January 4, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your comments. After two decades of researches, your important findings have a step forward which is a remarkable achievement. I do admire your courage and patience with regard to this tough disease in which early detections are probably with both natures of science and art. My father was in a healthy condition before concussion and developed with signs of body imbalance and occurrence of Alzheimer disease. It was heartbreaking without ways to lessen his burden.

My assumption of root occurrence from vascular dysfunction might be wrong. It seems to me that finding a solution with very early detection before massive degeneration occurs is more than challenging. I am wondering which events trigger the formation of abnormal filamin A. If you could come up with a diagnosis tool tracing up the root cause of abnormal filamin A, it might be a better start than random guesses. I am not sure if I am right in this direction.

BTW, you mentioned that abnormal filamin A is an upstream event. Would you shed some lights on which upstream events are already verified up to now since upstream is a relative word ? Thanks so much for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, January 5, 2021 1:07 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

There is no doubt vascular dysfunction is an important part of the Alzheimer's disease (AD) pathology. Filamin A with abnormal conformation is found in plasma from AD patients doesn't necessary mean abnormal filamin A from platelets is resulted from vascular pathology including amyloid angiopathy, infarcts. More importantly, the abnormal filamin A in peripheral may be the result of brain pathogenic changes (occurs later).

Our data indicate abnormal filamin A is an upstream event. However, AD treatment effects are better if starts earlier (hence early detection before massive degeneration occurs is the key). I always think multiple therapeutic agents may be synergistic or additive. Again, if all the treatments administered after massive degeneration there is no treatments strong enough.

Thanks.

All the best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, January 3, 2021 7:50 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks for your kindly reply. Happy New Year !

Since conformational filamin A is structurally found in palates, I therefore assume that vascular pathologies are related to this disease. Your researches in various aspects of insulin resistances were published and your comments really show how hard it is to trace pathogenic events.

I really appreciate your continued research and endeavor to find more upstream targets treating Alzheimer disease effectively. It seems to me in your comments that restoration of conformational filamin A is not strong enough to show disease modifying effects. Is it true ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, January 4, 2021 3:14 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Happy New Year. Wishing you and your family a healthy and prosperous year 2021.

It is my life time goal to help bring effective treatments and early diagnosis of the Alzheimer's disease (and other diseases with cognitive impairments). For the last two decades, I worked to identify possible drug and diagnostic targets. I'm mindful of the burden of the Alzheimer's disease caregivers, especially the potential of depression.

Regarding your question, there is no concrete data to show the function of blood platelet had changed in Alzheimer's disease (plausible of course). There are diverse pathogenic mechanisms and of course diseases such as diabetes (causes vascular pathologies) and history of concussion (multiple) had been suspected to be culprits to promote Alzheimer's disease. Surely, prevent such problems is useful but whether such measurements can reverse the damages that already done is everyone's guess. We had tried to control insulin resistance for years but the results thus far showed not much of effects. This may indicate that brain insulin resistance is not an early pathogenic event. We will do more to find more upstream targets so that we can more effective to treat Alzheimer's disease.

Thanks for your continuing interests and communications.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, December 29, 2020 7:38 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your kindly reply. For my father, a better treatment of Alzheimer disease is motivated and caregivers deserve to be with less burden. Regarding to the timing of conformational changes, I am curious to know if this is related to conditional changes of palates which caused by blood clotting, vascular abnormality or concussion, etc. Your endeavor of this tough disease is really appreciated.

Please be safe since pandemic and cold weather persist in northern atmosphere. Have a wonderful and peaceful New Year to you and your family.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 30, 2020 6:56 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks for your email.

Your friend is correct regarding the difficulty of finding specific antibodies for the filamin A with altered conformation in Alzheimer's disease. Indeed, the epitope of the altered filamin A may be hidden or had been processed. Obviously, computational approaches had been used to help us find viable antibodies. We still don't know when the conformational changes occur during the Alzheimer's disease pathogenesis even though we think this event occur early. But, what is early? This timing issue also requires some attention.

Yes, one-year extension of the open-label study is well under the way. Obviously, we will be looking for cognitive improvement and reduction in pathogenic drives such as reduction in inflammatory markers and degeneration.

Thanks again for your continued interests in getting the Alzheimer's disease treatment. I am working hard to get to this goal.

Happy New Year to you and your family.

Best regards,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, December 28, 2020 4:58 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Wish you a happy holiday and healthy new year, too. Regarding to the issue of diagnosis, my friend specialized in chemistry of antibody suggested to me recently that an exhaustive search of appropriate antibody to be connected with conformational filamin A in human palates might be required to have a solution of universal antibody for different races. A modern equipment with computerized tools would be helpful in this exhaustive search process. Since the epitope of conformational filamin A might be structurally hidden, an appropriate antibody might be sensitively or selectively enough to be effective. Hope that this information is useful.

A one-year, open label study of PTI-125 was initiated in March 2020 and enrolled over 60% of patients as mentioned in public. Supposedly, safety issues are not a big concern since expanded clinical trials still proceed. How about attributes of reduced inflammatory cytokine levels and improved cognition/behavior in this perspective since earlier enrolled patients had been treated with more than 6 months ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 23, 2020 4:03 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Season Greetings

Dear 宜明,

Sorry for my late reply as I am deep in the semester end exam and grading.

Wow, time flies by so quickly. It has been more than a year already since we started our communication. It is my pleasure to discuss the field of neuroscience even though we actually are learning on the way. I am thankful for the opportunities you have given me to think about the questions you have posted in different angles. Truly, we all hope we have grown some in knowledge and get effective Alzheimer's disease treatments forward to contain this terrible

disease. I am for one will do everything I can and work tireless toward this goal. It takes collective efforts to get this under control so that I am collaborating with academic and industrial partners to look into as many ways we can investigate and test the effectiveness. Thanks to you for keeping me informed of many new strategies other have come up with in Alzheimer's disease diagnosis and treatments.

We all hope we can better handle this COVID pandemic. With the approval of 2 vaccines, I am hopeful we are better equipped to start limiting the death tolls and eventually control this horrific virus. I sincerely hope people learn from this as we all have to play a part (wearing mask, wash hands frequently etc). This experience certainly humbles us as we humans appear more vulnerable (at least not as invincible) than we think. The fact Taiwan has done so well in controlling COVID makes me proud to be a Taiwanese.

Wishing you and your family happy holidays and a healthy, peaceful and prosperous year 2021.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, December 20, 2020 8:43 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Season Greetings

Dear Hoau-Yan :

It's been more than 1 year since I have this particular opportunity to know you. Your in-depth and insightful knowledge has given me more understandings in this tough field of neuroscience. Your assistances and comments are really appreciated. Hopefully, we will be better off with more solutions of pandemics and preventive measures next year. At this time of season, I truly wish you a Merry Christmas and happy New Year !

Best Regards,
宜明



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From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent time: 08/09/2021 08:37:55 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Thanks for your kind words and taking time to reply my email. Working with/for you should be inspirational and delighted. Look forward to sharing more positive developments which are beneficial for persons in need. Hope that things are getting better everyday.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, August 10, 2021 12:08 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your kind words. Your questions keep me thinking of my answers so that I can be as clear as possible in my answers to most. I am truly impressed with and appreciate your viewpoints. Obviously, we have a lot of unknown factors in Alzheimer's disease that harboring many pathogenic pathways. I am working as hard as I can to find other possible pathogenic triggers - bad guys (aging process is one of them, and I think mental stress may also push the brain into neurodegenerative path). Regardless, we got to find these damaging pathways as soon as we can - early diagnosis that is.

Thanks for the reminder of the COVID delta variants. I am glad that Taiwan is very cautious on this pandemic development. In US, there are people still hesitate to be vaccinated. Unlike Taiwan, the availability of vaccine is less a problem because 4 mainstream vaccines are produced in US. I think Taiwan's domestic vaccines look great and more importantly can solve the supply issues although I do not get there are politicians that constantly trying to discredit these vaccines. In any case, please be very careful still especially in Taipei and New Taipei cities.

Thanks again for your support and keeping me informed of other developments. Please also keep asking questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, August 7, 2021 2:16 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Nice to have your replies especially when you are fully occupied. Your answers to my naïve questions help me to understand more properties of PTI-125 which surely would provide viable solutions to needed patients never before. Especially for meaningful researches, PTI-125 would have more indications and implications as time goes on. If you could find additional bad guys behind AD, a Nobel prize for you is not too far away.

Stay safe when delta virus poses new threats in US. In Taiwan, we are cautious about recent pandemic developments with protective measures. Looking ahead, I would expect an oral solution with protease inhibitor or some combination therapy would truly alleviate this human dilemma. Thanks again for your insights and sharing with me.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, August 7, 2021 4:29 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

As always, I am completely booked up with research activities. Your questions kept me thinking. I answer your questions directly underneath each of your queries.

Hope all is well,

Thank you.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, July 31, 2021 2:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Thanks for your kindly reply during busy hours as always. Knocking off hard nuts is especially tough especially there was no precedent before. Your persistence and genuine contributions to global AD community is obvious. I am happy that your finding of the bad guy will eventually be a history of AD and even mankind. Your family and friends will be certainly proud of you after so many tough years spent in lab and related researches.

Your answers to my naïve questions are plain and understandable. To my personal curiosity which might be common to most people, I have additional questions as below.

1. Is there any plateau effect after months of oral treatment of PTI-125 since biomarkers of neuroinflammation and neurodegeneration will eventually reach their peaks ? Will responded patients need to take oral treatments of PTI-125 in their lifetime ? *True. neuroinflammation and neurodegeneration will reach a breaking point down the road without treatments. Our hope is that this treatment will delay the neuroinflammation and neurodegeneration so that brain can recover (those not dead yet) some so that brain can function better. My guess is that there is some sort of limitations (not plateau per se). We hope the window is big enough (beyond the nature life span).*
2. When temporal changes of individual patient during the span of treatments will be revealed ? This information might show more consistent and clearer trend of treatment effects. *I am not sure what you are referring to. It would be difficult to gauge patient's response rate since each patient is different in many aspects (other diseases, genetic make up etc). Very difficult to tell.*
3. For neurons already beyond repairs or dead, is there any viable therapeutic or complimentary solution ? *No. Raise from death is NOT any humans can do.*
4. Would mental or physical rehabilitations for patients during or after treatments add more values to their health ? *We have evidence to show exercise and good nutrients (diet) help to elevate the treatment effects.*

There must be lots of works needed to be done after this stage. For all your dedication, I believe that all time spent in search of better treatments will be meaningful and greatly appreciated. Thanks again in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, July 31, 2021 1:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your encouragements always and giving your opinions and questions as I need such reminders to keep my comments plain and understandable.

I will **answer your questions directly underneath each query you posted**. Since I am blind to all patient related info, I can only answer in general terms.

Hope all is well with you and your family.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Thursday, July 29, 2021 10:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Congratulation to your researches going with a gigantic step forward. After reading updated PTI-125 related papers in CCAI 2021, I had a feeling that your lab works have gradually verified the MOA of Filamin A with abnormal conformation. There are thoughts with results of SavaDx and 9-month data as follows :

- 1) Correlation studies of Abnormal Filamin A in phase 2b patients is a positive step. That is a great findings and direction in the framework of diagnosis tool. However, taking Abnormal Filamin A as a biomarker needs more works to establish that which level of Abnormal Filamin A should be detected as an early sign of AD. I am wondering if a totally new or compatible antibody in your earlier works of SavaDx is employed in this study.
- Indeed, this is just the initial steps. The antibodies used obviously required constant verifications using that was used earlier. It is a tedious work but there are no short cuts. We need to define the timeline when the abnormal FLNA can be detected (not an easy task because we don't even know when is early).
- 2) Cognition Improvement of 3.0 Points on ADAS-Cog at 9 Months ($p < 0.001$) is great for patients as a process of Filamin A normalization. However, most people are wondering why NPI score in 9 month improved less than in 6 month by 0.6 points. All tested biomarkers are consistent with improvements which relieved lots of overhangs.
- People forget Alzheimer's disease is a progressive neurodegenerative disease with multiple factors at play. As patients deteriorate cognitively due to brain function declines, there are added factors hence the magnitude of improvements become less comparing the the baseline. The 0.6 points less at 9 month reflects just that (obviously it also depends on the stage of disease when patients first enrolled) but the curve will be stabilize for period of time.
- 3) 22% of patients declined less than reported in the science literature at 9 months. Why these patients are so hard to respond to treatment of simufilam ? Any other upstream catalyst for these patients ?
- Well, we don't actually know but my guess is that these patients have other issues or they were selected at later stage of the disease even though their MMSE or ADAS-Cog when enrolled were not bad. While we like to have 100% responsive rate, it is an unrealistic expectation. This drive home the importance of early diagnosis. I am sure if we treat earlier, we will see a better result.
- 4) As reported earlier, Evonik will supply Cassava Sciences with large-scale, clinical-grade quantities of simufilam. I am wondering if Evonik will produce good qualities of simufilam as in phase 2b study and it should be carefully verified before entering phase 3.
- Clearly, QC will be done carefully.
- 5) Finally, is abnormal filamin A responsible for the symptom or modifying answer to AD ?
- While we all want to find the "bad" guy (abnormal FLNA is a critical but one of the bad guys I am sure there are many others). Fortunately, fixing abnormal FLNA promotes healthier and more resilient brain but unfortunately can't fix anything already beyond repairs or dead. I am a realistic person by showing people what I saw but I don't want to give a wrong impression that fixing abnormal FLNA can bring back what have already damaged.

I am honored to be with your ongoing researches and contributions to AD patients. Thanks for your hard works.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, June 30, 2021 8:29 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Sorry for my late reply. I often just get occupied by too many tasks in hand and consequently delay in my response to you and many.

Yes, lots efforts had been on the multiple fronts and there should be an update in phase 2b study. I will be interest in learning of your comments.

I watch the COVID-19 situation in Taiwan closely. It is most unfortunately some careless acts led to such a spread. Even though it is pale by comparison to US and EU, it is still very concerning especially in Taipei (the worst in transparency) and New Taipei. A solution to this monumental disaster must include understand the pathogen (virus) so that more effective medications together with vaccination can put this pandemic out for good.

Best wishes to you and your family, it is looking better recently so that normalcy is near.

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, June 22, 2021 12:18 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After reading a recent news from Cassava Sciences, I realized that there will be a presentation at AAIC during the week of July 26-30th about SavaDx clinical dataset from PTI-125's Phase 2b study of 64 patients. Look forward to seeing more updates of SavaDx developments which you must devote lots of time and energy.

Affected by recent COVID-19 impacts in Taiwan, I have been working from home more than 1 month. Hope that this history-making pandemics will be alleviated or solved by pharmaceutical solutions. The same goes to PTI-125 to help patients in need. Thanks.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 23, 2021 10:26 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

The MOA for PTI-125 is very different from that of ANVS401. PTI-125 reverses an abnormal filamin A thereby reducing the toxic signaling pathways that drive neurodegeneration and inflammation. ANVS401 functions as a translational blockers that presumably (based on cell and transgenic models) to reduce toxic substances such as amyloid beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. The major problem is that reducing those "toxic" substances do not work in humans. In fact, ANVS401 blocks APP (amyloid precursor protein) to reduce amyloid beta. APP is a known trophic factor whose expression increases when brain is injured. More of the problem, we know reduction in amyloid beta by beta or gamma secretase inhibitors do not stop Alzheimer's disease progression and in some cases actually worsen cognitive impairments. Hence, I don't predict any synergy between PTI-125 and ANVS401.

Postmortem brains are not suitable to study metabolic dysfunction because one can only show there is metabolic disturbance but can not conclusively show the source, when and how the metabolic dysfunction occur. Transgenic animal models are partial models at best and are very different from actual disease, therefore they are inheritably insufficient to any pathogenic pathway questions just about any diseases.

I hope my explanations help answering your questions.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, February 21, 2021 3:05 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

I had some thoughts again regarding to the upstream causes of Alzheimer disease and MOA of PTI-125.

As you mentioned earlier, there were complicated lab works deriving chemical compounds of PTI-125 to restore of Filamin A with abnormal conformation. I am curious to know what is the chemical MOA of PTI-125 which differentiates from other approaches such as ANVS401 of Annovis Bio Inc. to decrease multiple neurotoxic in Cerebrospinal Fluid (CSF) and improve axonal transport of nerve cell. Their therapeutic target also aims for reductions of neuroinflammation and neurodegeneration. Is there any synergetic effect to combine PTI-125 and ANVS401 ?

As in previous email, I am skeptical about causes of metabolic dysfunction related to Alzheimer disease. Is there any direct proof from human postmortem model instead of mouse model ?

Thanks again for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 16, 2021 1:08 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

First, Happy Lunar New Year. Wishing you and your family a happy, healthy and prosperous year of Ox.

Regarding your question, Donepezil's ADAS-cog score you are referring to are raw score. Once taking placebo control into consideration, the improvement achieved by 24 months of 5 mg and 10 mg daily dose of donepezil were around 0.35 and 0.39 (page 16 stat significant). By now we know donepezil's clinical effectiveness eventually diminished as disease progresses. Obviously, we hope the cognitive benefit of PTI-125 continues based on the biomarker data. The improvement in cognition is depending on the baseline state of the patients (how severe the dementia and obviously the accuracy of diagnosis). I can't say too much and frankly nobody is all that certain.

Based on the mechanism of action, we predict the therapeutic effects of PTI-125 are applicable to a broad range of Alzheimer's disease patients. Again, the magnitude of benefits depend on the severity of dementia - the earlier the better. Hence, it is important to have a reliable early diagnosis tool though we still not entirely sure how to define "early".

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, February 15, 2021 10:32 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After some thoughts and review of data during Chinese New Year, I have some questions needed for your comments as follows :

1. ADAS-Cog Improvement between ARICEPT and PTI-125 : In https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively after 24 weeks of treatment. These differences were statistically significant for 473 patients. Compared with baseline, 5 mg/day and 10 mg/day treatments of donepezil at 24 weeks showed 1.06 and 1.6 benefits in a controlled study. However, the press release of Cassava Sciences on Feb. 2, 2021 mentioned that six months of PTI-125 treatment improved cognition scores by 1.6 points on ADAS-Cog11.

These comparative improvements did not clearly distinguish the therapeutic advantage of PTI-125 compared with ARICEPT in 24 weeks of treatment. Is it true for this simple observation as above ? Is there any indication that PTI-125 will have better effects after prolonged period of time (such as 1 year) by restoring of Filamin A with abnormal

conformation ?

2. You mentioned that collective efforts try to bring some solutions for Alzheimer's disease patients. Does it mean that a subset of Alzheimer patients would be appropriate for therapeutic effects of PTI-125 and diagnosis tool of SavaDx ? While other patients are not ideal enough ?

Thanks so much for your insights again.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, February 4, 2021 4:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thank you for your well wishes and positive comments. Your continued interests in finding solutions for Alzheimer's disease research motivate us and I can truly say I am trying my very best . I thank you for keeping me informed and discussions on the findings from other investigators. We will keep moving forward and hope our collective efforts can bring some solutions for Alzheimer's disease patients.

Will keep safe the best I can as the COVID pandemic is still very bad here. Hopefully, with vaccination the situation improves in the coming months.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, February 2, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

Nice to know that the interim result of PTI-125 is positive and brings lights to the Alzheimer community. Congratulation to your continued efforts. There must be lots of persons sending emails to you regarding to this matter. To continue your clinical endeavors, I truly wish you to keep safe in this covid-19 epidemics. Your academic and real-word contributions are very much appreciated.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, January 21, 2021 11:55 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for keeping me informed of the recent development. I am all tied up by my extensive teaching load and research activities (this pandemic has caused tremendous pain with limited access).

Regarding the levels of N-terminal fragment of tau in the blood as a predictor of cognitive decline, this is really nothing new because we know the levels of tau in the CSF and blood positively correlate with the extent of neuronal damage (tau exist exclusively in neurons). The question is the sensitivity of detection that allow us to sound the alarm. With the more sensitive mass spectrometry we obviously are better equipped than before.

Thanks again. I will find time to answer your earlier queries.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 20, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] some development of diagnosis tool for reference

Dear Hoau :

There is some development of blood test for Alzheimer's disease to predict future cognitive decline in healthy people with levels of N-terminal fragment of tau (NT1). Data link is as <https://www.sciencedaily.com/releases/2020/12/201209115147.htm>. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, January 16, 2021 3:44 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks always for your info that keeping me in the loop of current Alzheimer's disease findings.

The problem is that this type of academic research using (genetically modified) rodent models that bear little resemblance to human Alzheimer's disease lead us to nowhere and frankly confuse & dilute our efforts. Hydrogen sulfide is no doubt playing a regulatory role in many physiological activities. Just because it is decreased with aging and replacing it can improve cognition in rodents doesn't mean it is therapeutically possible. Don't forget the hydrogen sulfide is quite toxic one should worry the accumulation can severely hurt the brain function. Most importantly, there is no evidence rodent models have neurodegeneration (unlike brains in humans with Alzheimer's disease). GSK3a/b is one of the hubs in metabolism/energy regulation and as one of the tau kinases that have a sophisticate feed forward and feedback regulators. There is no evidence there is anything change in GSK3a/b in Alzheimer's disease. In general, kinases and phosphatases are terrible targets because they all have tons of regulators once activated or inhibited in a progressively changing brain like in Alzheimer's disease is predictably short-lived and ineffective especially when the disease becomes symptomatic (much too late).

Thanks. Have a good weekend.

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 13, 2021 10:36 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

It seems to me more and more researches trying to target early pathogenesis of Alzheimer's disease which might be inspired by evidences of many clinical results. There is a recent research from John Hopkins Medicine working with University of Exeter concerning with effects of hydrogen sulfide, GSK3 β and other proteins involved in the pathogenesis of Alzheimer's disease. Their data link is https://medicalxpress.com/news/2021-01-hydrogen-sulfide-alzheimer-disease.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter. Hope that this information would be interesting to you. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 13, 2021 2:13 PM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Sorry for my late reply, sometimes I made a mental note to reply but I got busy and kind of putting it off. The impacts of concussion obviously vary according to the severity and frequency (multiple mild concussions can be quite damaging). It sounds like your father had a severe concussion that resulted in motor/sensory imbalance and dementia. I understand how hard it is to see your father suffer but unable to help.

There is no doubt vascular dysfunction is a risk factor and often accompanies Alzheimer's disease (cerebral amyloid angiopathy). That said, the cause-effect relationship between vascular dysfunction and Alzheimer's disease is not straight forward.

Indeed, upstream is a relative term. Abnormal filamin A can be induced by sub-chronic amyloid (soluble) infusion into brains. If abnormality in filamin A is blocked (by PTI-125), there is significant reduction in amyloid plaques (dead neurons) and neurofibrillary tangles. More importantly, brain activities with higher receptor and synaptic activities and function improve at least in mouse model of Alzheimer's disease. These data indicate reversing abnormality of filamin A especially when at the stage when mild clinical dementia is detected may be a promising way to treatment Alzheimer's disease.

Hope I answer your questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Monday, January 4, 2021 7:54 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your comments. After two decades of researches, your important findings have a step forward which is a remarkable achievement. I do admire your courage and patience with regard to this tough disease in which early detections are probably with both natures of science and art. My father was in a healthy condition before concussion and developed with signs of body imbalance and occurrence of Alzheimer disease. It was heartbreaking without ways to lessen his burden.

My assumption of root occurrence from vascular dysfunction might be wrong. It seems to me that finding a solution with very early detection before massive degeneration occurs is more than challenging. I am wondering which events trigger the formation of abnormal filamin A. If you could come up with a diagnosis tool tracing up the root cause of abnormal filamin A, it might be a better start than random guesses. I am not sure if I am right in this direction.

BTW, you mentioned that abnormal filamin A is an upstream event. Would you shed some lights on which upstream events are already verified up to now since upstream is a relative word ? Thanks so much for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Tuesday, January 5, 2021 1:07 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

There is no doubt vascular dysfunction is an important part of the Alzheimer's disease (AD) pathology. Filamin A with abnormal conformation is found in plasma from AD patients doesn't necessary mean abnormal filamin A from platelets is resulted from vascular pathology including amyloid angiopathy, infarcts. More importantly, the abnormal filamin A in peripheral may be the result of brain pathogenic changes (occurs later).

Our data indicate abnormal filamin A is an upstream event. However, AD treatment effects are better if starts earlier (hence early detection before massive degeneration occurs is the key). I always think multiple therapeutic agents may

be synergistic or additive. Again, if all the treatments administered after massive degeneration there is no treatments strong enough.

Thanks.

All the best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, January 3, 2021 7:50 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks for your kindly reply. Happy New Year !

Since conformational filamin A is structurally found in palates, I therefore assume that vascular pathologies are related to this disease. Your researches in various aspects of insulin resistances were published and your comments really show how hard it is to trace pathogenic events.

I really appreciate your continued research and endeavor to find more upstream targets treating Alzheimer disease effectively. It seems to me in your comments that restoration of conformational filamin A is not strong enough to show disease modifying effects. Is it true ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Monday, January 4, 2021 3:14 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Happy New Year. Wishing you and your family a healthy and prosperous year 2021.

It is my life time goal to help bring effective treatments and early diagnosis of the Alzheimer's disease (and other diseases with cognitive impairments). For the last two decades, I worked to identify possible drug and diagnostic targets. I'm mindful of the burden of the Alzheimer's disease caregivers, especially the potential of depression.

Regarding your question, there is no concrete data to show the function of blood platelet had changed in Alzheimer's disease (plausible of course). There are diverse pathogenic mechanisms and of course diseases such as diabetes (causes vascular pathologies) and history of concussion (multiple) had been suspected to be culprits to promote Alzheimer's disease. Surely, prevent such problems is useful but whether such measurements can reverse the damages that already done is everyone's guess. We had tried to control insulin resistance for years but the results thus far showed not much of effects. This may indicate that brain insulin resistance is not an early pathogenic event. We will do more to find more upstream targets so that we can more effective to treat Alzheimer's disease.

Thanks for your continuing interests and communications.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, December 29, 2020 7:38 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your kindly reply. For my father, a better treatment of Alzheimer disease is motivated and caregivers deserve to be with less burden. Regarding to the timing of conformational changes, I am curious to know if this is related to conditional changes of palates which caused by blood clotting, vascular abnormality or concussion, etc. Your endeavor of this tough disease is really appreciated.

Please be safe since pandemic and cold weather persist in northern atmosphere. Have a wonderful and peaceful New Year to you and your family.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 30, 2020 6:56 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks for your email.

Your friend is correct regarding the difficulty of finding specific antibodies for the filamin A with altered conformation in Alzheimer's disease. Indeed, the epitope of the altered filamin A may be hidden or had been processed. Obviously, computational approaches had been used to help us find viable antibodies. We still don't know when the conformational changes occur during the Alzheimer's disease pathogenesis even though we think this event occur early. But, what is early? This timing issue also requires some attention.

Yes, one-year extension of the open-label study is well under the way. Obviously, we will be looking for cognitive improvement and reduction in pathogenic drives such as reduction in inflammatory markers and degeneration.

Thanks again for your continued interests in getting the Alzheimer's disease treatment. I am working hard to get to this goal.

Happy New Year to you and your family.

Best regards,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, December 28, 2020 4:58 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Wish you a happy holiday and healthy new year, too. Regarding to the issue of diagnosis, my friend specialized in chemistry of antibody suggested to me recently that an exhaustive search of appropriate antibody to be connected with conformational filamin A in human palates might be required to have a solution of universal antibody for different races. A modern equipment with computerized tools would be helpful in this exhaustive search process. Since the epitope of conformational filamin A might be structurally hidden, an appropriate antibody might be sensitively or selectively enough to be effective. Hope that this information is useful.

A one-year, open label study of PTI-125 was initiated in March 2020 and enrolled over 60% of patients as mentioned in public. Supposedly, safety issues are not a big concern since expanded clinical trials still proceed. How about attributes of reduced inflammatory cytokine levels and improved cognition/behavior in this perspective since earlier enrolled patients had been treated with more than 6 months ?

Thanks again for your comments in advance.

Best Regards,

宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 23, 2020 4:03 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Season Greetings

Dear 宜明,

Sorry for my late reply as I am deep in the semester end exam and grading.

Wow, time flies by so quickly. It has been more than a year already since we started our communication. It is my pleasure to discuss the field of neuroscience even though we actually are learning on the way. I am thankful for the opportunities you have given me to think about the questions you have posted in different angles. Truly, we all hope we have grown some in knowledge and get effective Alzheimer's disease treatments forward to contain this terrible disease. I am for one will do everything I can and work tireless toward this goal. It takes collective efforts to get this under control so that I am collaborating with academic and industrial partners to look into as many ways we can investigate and test the effectiveness. Thanks to you for keeping me informed of many new strategies other have come up with in Alzheimer's disease diagnosis and treatments.

We all hope we can better handle this COVID pandemic. With the approval of 2 vaccines, I am hopeful we are better equipped to start limiting the death tolls and eventually control this horrific virus. I sincerely hope people learn from this as we all have to play a part (wearing mask, wash hands frequently etc). This experience certainly humbles us as we humans appear more vulnerable (at least not as invincible) than we think. The fact Taiwan has done so well in controlling COVID makes me proud to be a Taiwanese.

Wishing you and your family happy holidays and a healthy, peaceful and prosperous year 2021.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, December 20, 2020 8:43 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Season Greetings

Dear Hoau-Yan :

It's been more than 1 year since I have this particular opportunity to know you. Your in-depth and insightful knowledge has given me more understandings in this tough field of neuroscience. Your assistances and comments are really appreciated. Hopefully, we will be better off with more solutions of pandemics and preventive measures next year. At this time of season, I truly wish you a Merry Christmas and happy New Year !

Best Regards,
宜明



鄭宜明 Eddy Jeng - [CDIB的電子郵件地址已變更為yiming_j@cdibcapital.com](mailto:yiming_j@cdibcapital.com), 請您更新該人員之電子郵件地址資訊。

鄭宜明 Eddy Jeng - CDIB's email address has been changed from @cdibh.com to yiming_j@cdibcapital.com, please update your contact information.

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鄭宜明 Eddy Jeng - [CDIB的電子郵件地址已變更為yiming_j@cdibcapital.com](mailto:yiming_j@cdibcapital.com), 請您更新該人員之電子郵件地址資訊。

鄭宜明 Eddy Jeng - CDIB's email address has been changed from @cdibh.com to yiming_j@cdibcapital.com, please update your contact information.

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From: Suzhen Chen <SChen@1Globe-USA.com>
Sent time: 08/11/2021 04:16:09 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: your 2017 paper

Dear Dr. Wang,

We got a few questions regarding the assays described in your papers to determine the binding affinity of PTI-125 to FLNA.

You have used age matched tissues from control and AD patients to determine the differential binding affinities of PTI-125 to normal and conformation altered FLNA. Where do you obtain the tissues? How hard to get these tissues?

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I thank you for your time and kind consideration.

Suzhen

From: Hoau-yan Wang [mailto:hywang@med.cuny.edu]
Sent: Wednesday, August 04, 2021 11:00 PM
To: Suzhen Chen <SChen@1Globe-USA.com>
Subject: Re: your 2017 paper

Dear Dr. Chen,

Please find a PDF copy of our 2017 Neurobiol of Aging paper you have requested.

Thank you.

Best,

Hoau-Yan

*Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY SOM*

From: Suzhen Chen <SChen@1Globe-USA.com>
Sent: Wednesday, August 4, 2021 4:13 PM
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Thank you,

Suzhen

<https://www.linkedin.com/in/suzhen-chen/>

From: Hoau-yan Wang
Sent time: 08/11/2021 07:40:49 PM
To: Suzhen Chen <SChen@1Globe-USA.com>
Subject: Re: your 2017 paper

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From: Hoau-yan Wang
Sent time: 08/11/2021 07:51:11 PM
To: Lindsay Burns <lburns@cassavasciences.com>
Subject: Fw: your 2017 paper

FYI

She had requested our 2017 Neurobiol of Aging. I answered her questions generically. From her questions, you can see she had no clues. Her Linkin info is at the her first email. This organization is apparently composed of oversea Chinese entrepreneurs. Apparently, there were a lot of searches done for the past few weeks.

Hoau

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<https://www.linkedin.com/in/suzhen-chen/>

From: Suzhen Chen <SChen@1Globe-USA.com>
Sent time: 08/11/2021 08:27:32 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: your 2017 paper

Dear Hoau-tan,

I sincerely appreciate your thoughtful and helpful response to our questions.

I agree that we shall start with normal FLNA.

Best regards,

Suzhen

On Aug 11, 2021, at 7:41 PM, Hoau-yan Wang <hywang@med.cuny.edu> wrote:

Dear Dr. Chen,

The postmortem tissues were obtained from brain banks. Best matched samples (age, gender and postmortem interval matched samples are limited and more difficult to obtain).

Recombinant FLNA can be obtained via commercial sources. But, conformation altered FLNA only exist in pathological conditions. I would start by using commercially available recombinant FLNA. If you see any affinity, then you can think of acquiring pathological tissues.

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Suzhen

<https://www.linkedin.com/in/suzhen-chen/>

From: Lindsay Burns <lburns@cassavasciences.com>
Sent time: 08/11/2021 08:42:53 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: your 2017 paper

Thanks.

Lindsay

On Aug 11, 2021, at 6:51 PM, Hoau-yan Wang <hywang@med.cuny.edu> wrote:

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

FYI

She had requested our 2017 Neurobiol of Aging. I answered her questions generically. From her questions, you can see she had no clues. Her Linkin info is at the her first email. This organization is apparently composed of oversea Chinese entrepreneurs. Apparently, there were a lot of searches done for the past few weeks.

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Suzhen

<https://www.linkedin.com/in/suzhen-chen/>

From: Suzhen Chen <SChen@1Globe-USA.com>
Sent time: 08/23/2021 12:12:32 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: your 2017 paper

Dear Hoau-Yan,

We are searching for high purity of commercially available recombinant human FLNA for binding assay. Would you please provide a source if you have used any?

Thank you,

Suzhen

From: Hoau-yan Wang [mailto:hywang@med.cuny.edu]
Sent: Wednesday, August 11, 2021 7:41 PM
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Suzhen

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From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent time: 08/24/2021 09:02:08 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] A Law firm mentioned CUNY lab and requests that the FDA halt the current clinical studies of Simuflam PTI-125
Attachments: FDA-2021-P-0930-0004_content.pdf

Dear Hoau-Yan,

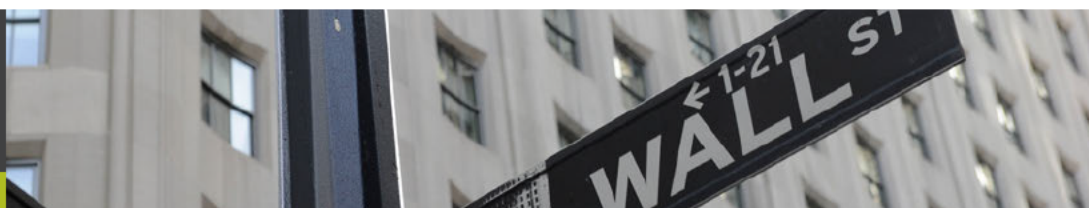
I was surprised to learn that a law firm in NY has issued to FDA with attachments which focused to attack you and CUNY labs. Normally, these accusations from law firm were ignored by me with specific manipulated motivations. However, their provided information has targeted on your reputation and hard works. This would probably involve your time and energy with this extra matter. That's why I attached this information for your reference. Hope that this issue will be clarified soon. Take care.

Best Regard,
宜明

鄭宜明 Eddy Jeng - CDIB的電子郵件地址已變更為yiming_j@cdibcapital.com, 請您更新該人員之電子郵件地址資訊。

鄭宜明 Eddy Jeng - CDIB's email address has been changed from @cdibh.com to yiming_j@cdibcapital.com, please update your contact information.

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Statement of Concern Regarding the Accuracy and Integrity of Clinical and Preclinical Data Supporting the Ongoing Clinical Evaluation of Compound PTI-125, Also Known As Simufilam

August 18, 2021

Jordan A. Thomas
Labaton Sucharow LLP
140 Broadway
New York, New York 10005
(212) 907-0700 (main)
907-0836 (direct)
jthomas@labaton.com

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A. Executive Summary

For over 15 years, Cassava Sciences (previously Pain Therapeutics, Inc, PTI) has funded the lab of Dr. Hoau-Yan Wang at City University of New York (CUNY). Together with Dr. Lindsay Burns at Cassava, Dr. Wang has published nearly a dozen papers connecting Filamin A protein with pain and Alzheimer's disease (AD).

Cassava Sciences created a drug candidate called simufilam (previously PTI-125) that they claim binds Filamin A and has beneficial effects in biochemical and animal models of AD. The studies from Drs. Wang and Burns discussed in this dossier were used by Cassava Sciences to garner NIH grants and to open an investigational new drug (IND) application to study simufilam in AD patients. They form the basic science foundation for two completed clinical trials (phase IIa and IIb) which exposed over 70 patients to simufilam. Cassava Sciences is currently recruiting 200 additional patients for a follow-up open-label trial.

This report raises concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate. To preface the analysis that follows, no other labs have confirmed this research connecting Filamin A to pain or AD. No other labs have confirmed that simufilam binds or modifies Filamin A or has effects in AD models.

In this document, three primary concerns are raised:

- The validity of clinical biomarker data: Biomarker analysis from patients treated with simufilam in Cassava's double-blind study forms a primary basis of Cassava's claim that simufilam engages its target in the central nervous system, but there are concerns about the integrity of this data. The CSF samples in this study were analyzed by an outside lab, which found that simufilam was ineffective in improving the primary biomarker end point and showed high variability in other biomarkers. However, Cassava Science had these samples bioanalyzed again and the data were finalized in

an academic lab, which apparently refers to Dr. Wang. This re-analysis showed that simufilam rapidly and robustly improved a wide array of CSF biomarkers. Whereas Cassava has not fully published this reanalysis, Cassava's 26 July 2021 poster presumably describing aspects of that work shows signs of data manipulation.

- The integrity of western blot analyses: Western blotting was extensively used by Drs. Wang and Burns over the past 15 years to support their foundational scientific claims and underscores their SavaDx clinical plasma biomarker. Detailed analysis of the western blots in the published journal articles from Drs. Wang and Burns shows a series of anomalies. The extent of these anomalies forms a 15-year pattern that strongly suggests systematic data manipulation and misrepresentation.
- The integrity of analyses involving human brain tissue: Simufilam is reported to bind to its target and modify a range of downstream molecules in experiments conducted on post-mortem human brain tissue from subjects with Alzheimer's disease and neurological controls. The same human brain specimens are used across the studies from 2008-2017, so the results are premised on human neurons remaining viable up to 13 hours after death, then being successfully reanimated after nearly 10 years in frozen archival without any advanced cryopreservative techniques. The complex, multi-step cellular processes the authors claim to observe in tissue that has been dead for a decade are contrary to a basic understanding of neurobiology. As with the western blot data, there are anomalies in the presentation of the data which again strongly suggest manipulation.

In the appendix, six additional areas of concern are raised. These frequent errors and anomalies occur in a pattern which is frequently favorable to the authors' hypotheses and is of

sufficient magnitude to strongly suggest scientific misconduct. This scientific work is foundational to the link between simufilam and its supposed target Filamin A in AD. Consequently, urgent action is advisable to limit patient exposure to this drug, until an appropriate investigation is completed.

Finally, we make six specific recommendations:

- The NIH and CUNY should audit the publications and lab of Dr. Wang to determine the existence and extent of data manipulation and possible fraud in all papers and grant applications from Drs. Wang and Burns.
- The FDA should audit both these publications and the IND application for simufilam's use in AD.
- The FDA should audit all clinical biomarker studies of simufilam in AD.
- The FDA should oversee 3rd party reanalysis of all clinical biomarker studies of simufilam in AD.
- The FDA should pause ongoing trials with simufilam pending these investigations.
- The academic journals which published the studies discussed herein should review and retract them to correct the public record, if the concerns remain after adequate investigation.

B. Background

This letter details a long-standing pattern of seemingly intentional data manipulation and misrepresentation in scientific papers and corporate disclosures authored primarily by Drs. Hoau-Yan Wang, Associate Medical Professor, City University of New York, and Lindsay A Burns, Sr. Vice President of Neuroscience at Cassava Sciences. All the information detailed herein was obtained from public, non-proprietary sources. These apparent falsifications have helped garner

>\$5,000,000 in NIH grants for preclinical/clinical studies, attract >\$250,000,000 in public fundraising by Cassava Sciences and misdirect therapeutic studies for patients suffering from Alzheimer's Disease (AD). In the interest of **the safety of patients with Alzheimer's disease enrolled in Cassava Sciences' ongoing clinical trials**, as well as the NIH and other stakeholders, the biomedical and financial communities must be made aware of these apparent falsehoods. The laboratory of Dr. Wang and Cassava Sciences warrant an audit to comprehensively evaluate the integrity of the scientific data.

For >15 years, Dr. Wang has collaborated with Cassava Sciences, formerly known as Pain Therapeutics Incorporated (PTI). Cassava Sciences is developing simufilam, a drug which was initially designated PTI-125, as a disease modifying treatment for Alzheimer's disease. Simufilam is claimed to bind to a cytoskeleton-associated protein called Filamin A and thereby benefit a range of Alzheimer's disease related neuropathologies. This line of research is unique to Dr. Wang and Cassava Sciences.

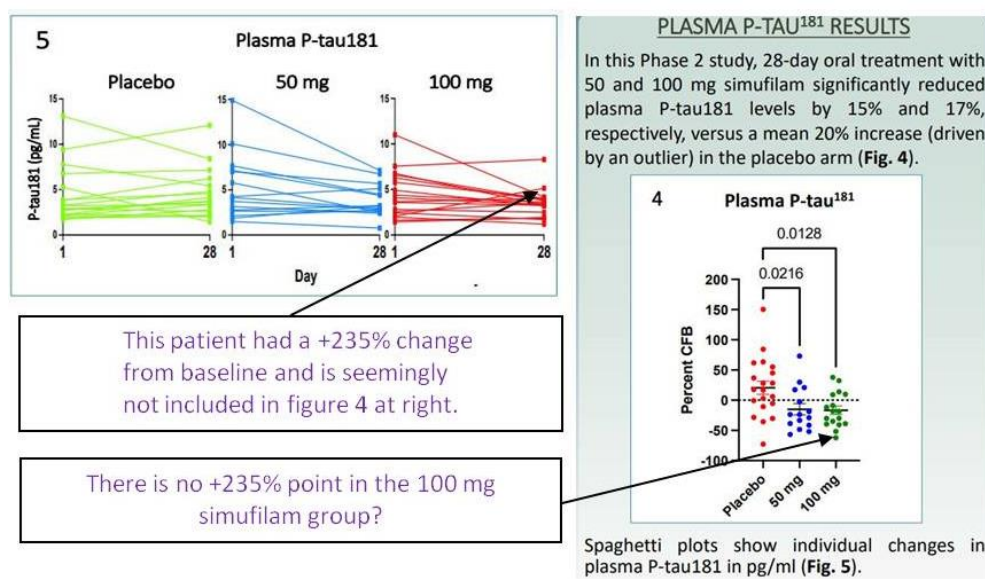
In reviewing this work, several results were encountered that are most unexpected and are probably unique to Drs. Wang, Burns and Cassava Sciences. Consequently, we investigated the published journal articles and other public sources of data underlying the development of simufilam in greater detail. This initial analysis suggests a pattern of clear errors and anomalies that are consistent with data manipulation and misrepresentation. These findings undercut the foundational science on which simufilam therapy is based.

C. Major Concerns

C.1. Concern #1: Integrity of Clinical Biomarker Data

NIH STTR grants (AG057329 & AG060878) funded Cassava Sciences' double-blind placebo-controlled phase II trial of PTI-125 (50, 100 mg QD) in 64 AD patients (NCT04079803). The primary end points reported were changes from baseline (day 1 to day 28) for a series of CSF

biomarkers including Abeta42, total tau, P-tau181, neurogranin, neurofilament light chain, and YKL-40. **On 15 May 2020, Cassava Sciences reported that this study missed its primary end points.** However, on 14 September 2020, Cassava Sciences reported that bioassays done by an external group were in error, and that **when patient samples were retested and finalized in what we believe to be Dr. Wang's lab, PTI-125/simufilam was claimed to robustly improve all biomarkers.**



On 26 July 2021, Cassava Sciences presented a poster at the Alzheimer's Association International Conference entitled "SavaDx, a Novel Plasma Biomarker to Detect..." regarding their clinical biomarkers. This poster, featuring Dr. Wang as first author, can be found on their corporate website (<https://www.cassavasciences.com/company-presentations> | "SavaDx, a Novel Plasma Biomarker to Detect Alzheimer's Disease, Confirms Mechanism of Action of Simufilam"). Figures 4 and 5 of this poster describe effects of 28-day treatment with simufilam (PTI-125) on plasma P-Tau181. Figure 4 shows the percent change from baseline (CFB) and figure 5 shows the absolute biomarker values for individuals before and after treatment. However, Figures 4 and 5 cannot be from the same data set. In Figure 5, one patient in the 100

mg group (at the arrow) had a P-Tau181 level which increased from ~1.5 to 5 pg/ml during the 28-day treatment period, ~235% change from baseline. However, in figure 4 there is no data point in the 100 mg treatment groups showing a CFB >40%. If the correct data point (+235%) were averaged in with the other points in figure 4, any beneficial effect of 100 mg simufilam would likely have been negated.

As a side-note, CSF analysis was also performed on the 13 patients in the phase 2a study and was published by Drs. Wang and Burns in early 2020 in the *Journal of Prevention of Alzheimer's Disease* 7;256-264. Remarkably, this manuscript was accepted for publication Nov. 6, 2020 seven days after submission October 31, 2020. If those dates are correct, it seems highly unlikely to have been subjected to rigorous peer review.

These clinical biomarker data present two significant problems. First, it seems that the primary biomarker data set we have with simufilam in Alzheimer's disease that was entirely produced and finalized by an external lab found that the drug had no effect on clinical biomarkers. Cassava replaced this with a reanalysis that was finalized by an academic lab (presumably Dr. Wang) and showed that simufilam showed remarkable benefit. Second, plasma biomarker data from these same patients, which were just presented by Cassava Sciences, contains evidence of manipulation. If there's no biomarker signal, and there is apparent misrepresentation of clinical data the **continuation of the ongoing Cassava trials may put patients at risk without the claimed evidence of biomarker benefit**. All the clinical biomarker results should be audited and replicated by an independent third party.

C.2. Concern #2: Integrity of Western Blot Data

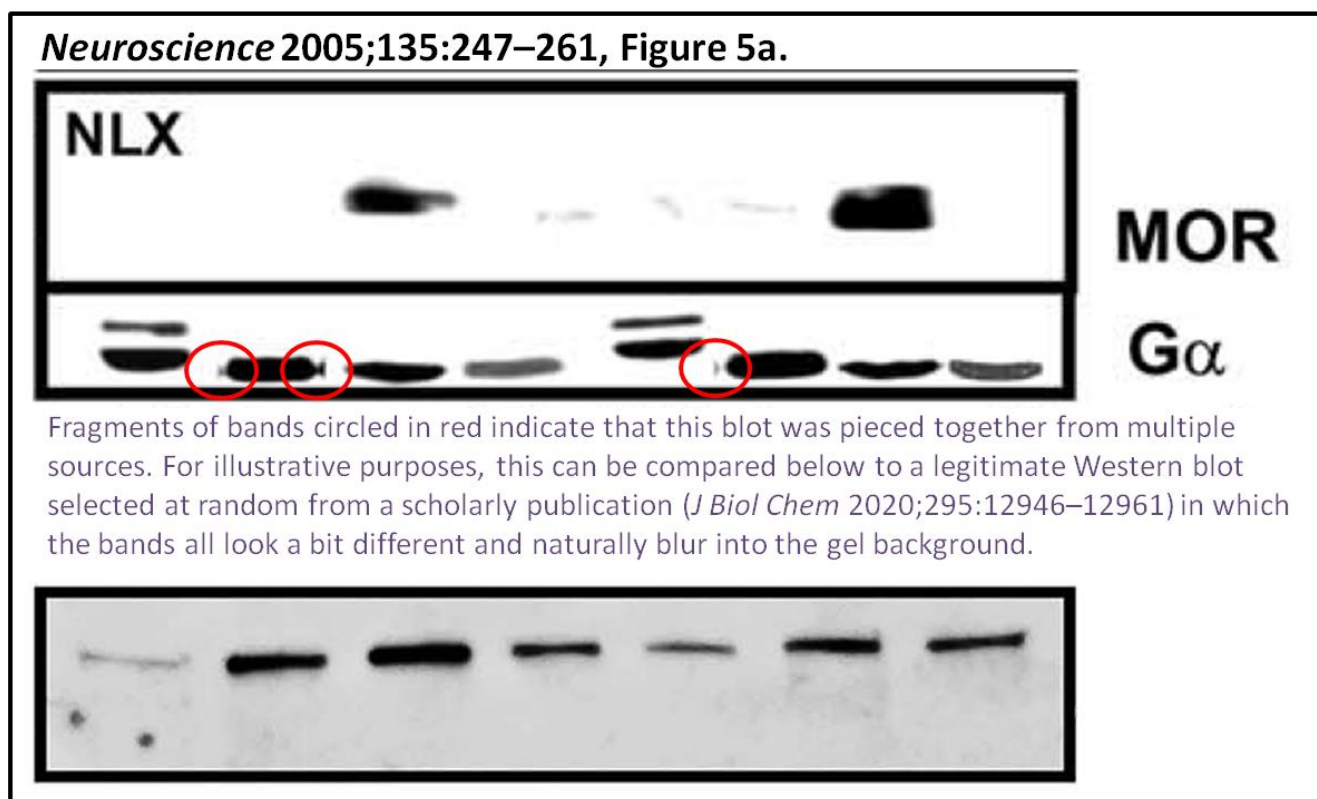
Many experiments in the work by Drs. Wang and Burns involve western blotting. Using this technique, proteins from tissue samples are separated on "gels" in a series of vertical lanes; the proteins are then transferred to a paper-like membrane, and antibodies are used to detect

specific proteins on the membrane, producing an image of specific proteins or “bands”.

Each band generally has a slightly different shape. As noted in an article posted on Retraction Watch about data manipulation and focused on Western blots (<https://retractionwatch.com/2016/04/19/one-in-25-papers-contains-inappropriately-duplicated-images-screen-finds/>), “In Western blots, every band has their own characteristics, they’re like faces.” That article further noted the significant number of cases of inappropriately duplicated or manipulated Western Blots: “... in no way suggest that Western blotting is a flawed method. Indeed, it suggests that Western blots are harder to fake in an undetectable way than other experimental data.” The western blot data presented by Wang and Burns are almost always overexposed and highly processed, which has been repeatedly seen in previously reported examples of image manipulation. In the following sections, we present a series of examples with strong evidence of image manipulation. In the appendix, we include additional examples which raise red flags.

C.2.1. Example #1: Manipulated Western Blot; *Neuroscience* 2005,135:247-261 – Figure 5a.

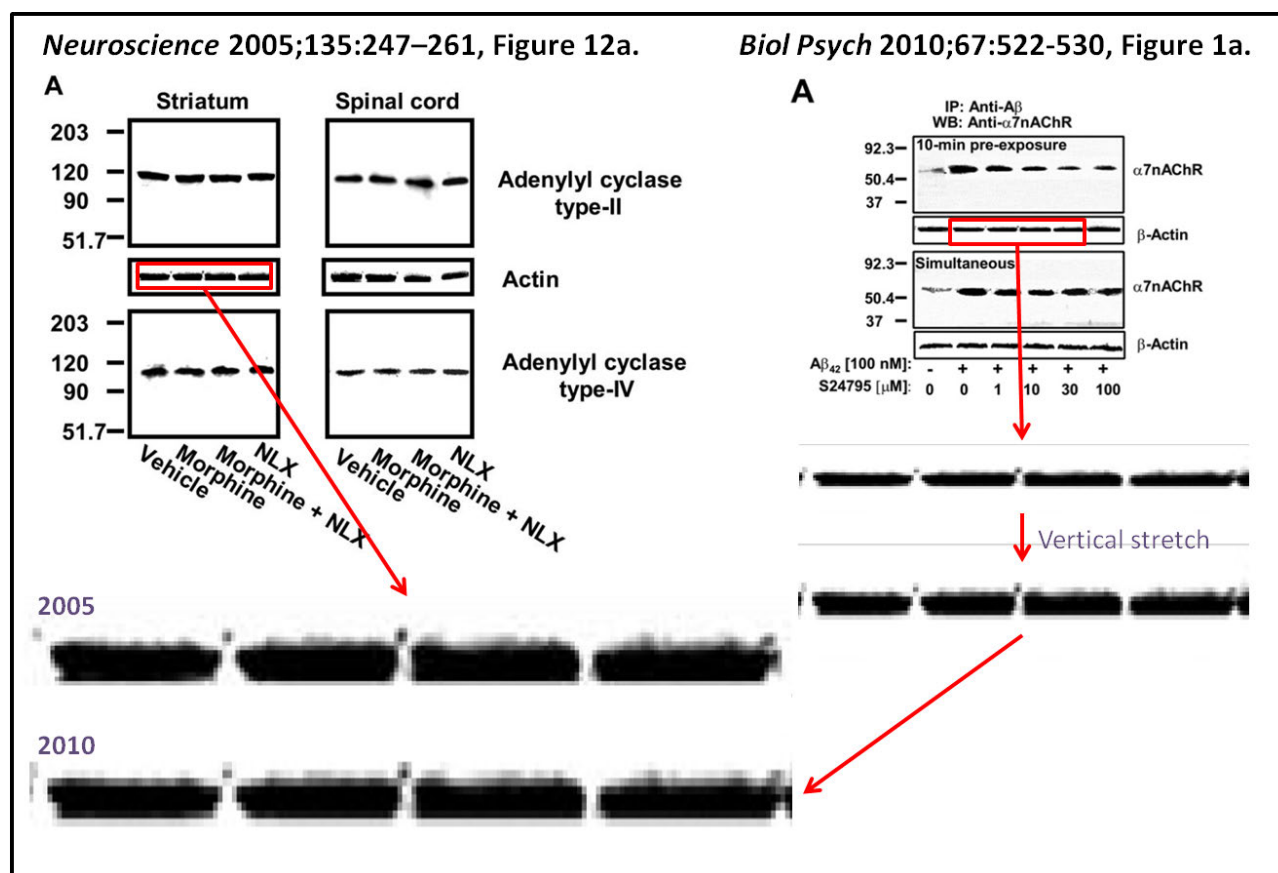
In figure 5a of their 2005 paper *Neuroscience* 135;247–261, the authors appear to have “spliced together” gels from different experiments. Telltale signs that the Gα bands in Figure 5a likely come from different gels are circled in red below. The cropped borders of an adjacent protein band are present indicating the bands were taken from another blot.



C.2.2. Example #2. Falsified Western Blot; *Biol Psych* 2010,67:522 – Figure 1a.

The western blot in Figure 1a (below right) of Dr. Wang’s 2010 paper in *Biological Psychiatry* 67:522 contains four bands that closely resemble an image published in Figure 12a (left) of the Wang and Burns 2005 *Neuroscience* 135: 247 paper mentioned in C.2.1. These eight boxed bands come from different experimental conditions that were allegedly conducted many years apart, using different samples. The authors appear to have vertically compressed the bands

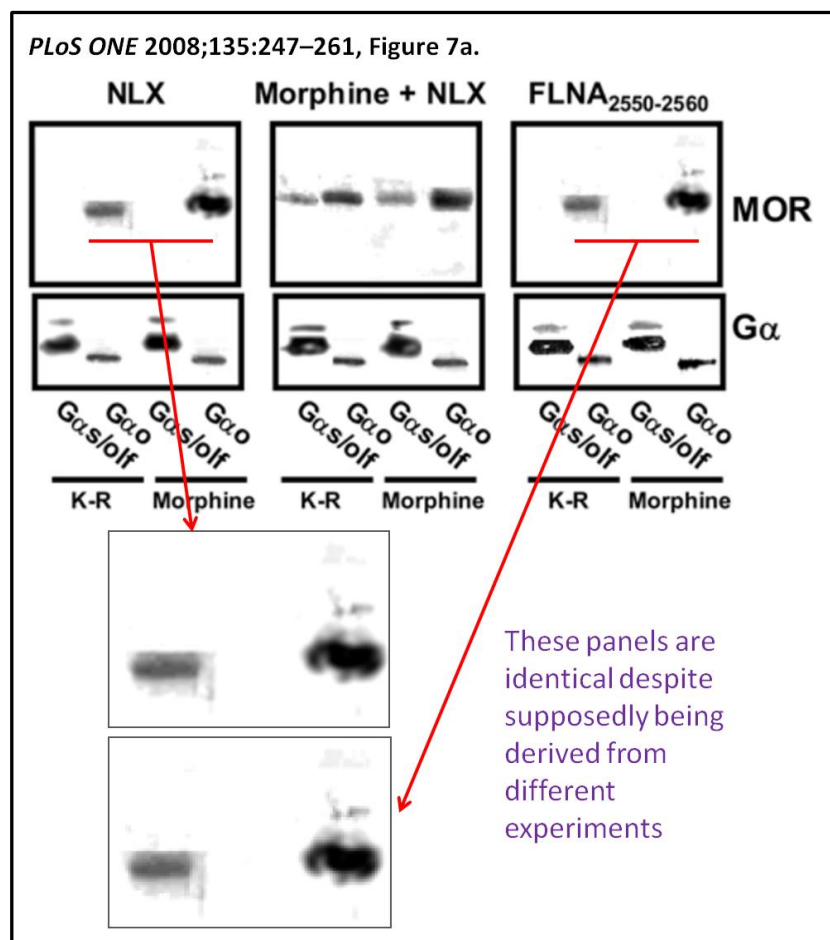
in the 2010 paper, but expanding them here shows they are strikingly similar to those in the 2005 paper. As the sample passes through the gel, it creates a small amount of streaking which causes a distinctive irregular shape in the upper portion of each band; the pattern of this streaking is identical in the two images. This degree of congruence could not have occurred by chance or error; it suggests a complex cross-publication dimension to Cassava Science's band duplication behavior and, in this case, it is hard to imagine that the duplication was not intentional. It is recommended that the original full-length images **with appropriate molecular weight markers are obtained to validate band migration** from both the 2005 and 2010 papers for independent review. Because of the seriousness of this duplication, if the original materials are not available, both of these papers must be retracted.



As a side-note, this western blot was produced on x-ray film, not as a digital image.

C.2.3. Example #3: Reused/Misrepresented Western Blot; *PLoS ONE* 2008;3:e1554 – Figure 7a.

In their 2008 paper *PLoS ONE* 3:e1554, Drs. Wang and Burns again present a series of overexposed and selectively cropped gels that appear to show spliced experiments (i.e., two separate experiments combined as if they were done simultaneously). Suggestive signs include the sharp upper and right border for the band in the Gao lane (lane 2 from the left in both panels; light blue dashed boxes). Further, Figure 7a of that paper appears to show two IDENTICAL panels (red arrows) for what are reported as different experiments. The similarity in these images could not have occurred by chance. All original full-length gel images **with appropriate molecule weight markers to validate band migration**, from this paper should be requested and analyzed. If they are not available, this paper should be retracted.



C.2.3. Example #4: Band Insertion Into Western Blots. Numerous publications.

The foundational paper from Drs. Wang and Burns that links Filamin A and PTI-125 to Alzheimer's disease is *The Journal of Neuroscience*, 2012 32:9773–9784. This paper appears to contain a collection of questionable western blots. Most of the paper comprises western blots that are of low quality, over exposed and selectively cropped. In this paper, the authors appear to have duplicated and transposed bands. There are dozens of questionable image features in this paper, only a small sampling is presented here. Numerous additional examples of this pattern of behavior in other manuscripts are included in the appendix.

In Figure 1a, the four Filamin A bands in the top set are more similar to each than can be expected by chance and appear to be duplicates. The images at right are magnified, showing that the pixels containing the bands are essentially identical. Additionally, the blots are not aligned and the spacing is irregular. Because FLNA is a large protein (~290kDa), it does not migrate in the gel very far; therefore, this degree of misalignment is suspicious. Moreover, the thin white halos surrounding each band are concerning. There are optical reasons why a halo (or ringing artifact) could occur, but this artifact is most common when components from multiple images are combined using photo editing software. This halo artifact is more prominent in the questionable blots, and extends in some cases into the frame around the blot which is hard to explain as an optical phenomenon.

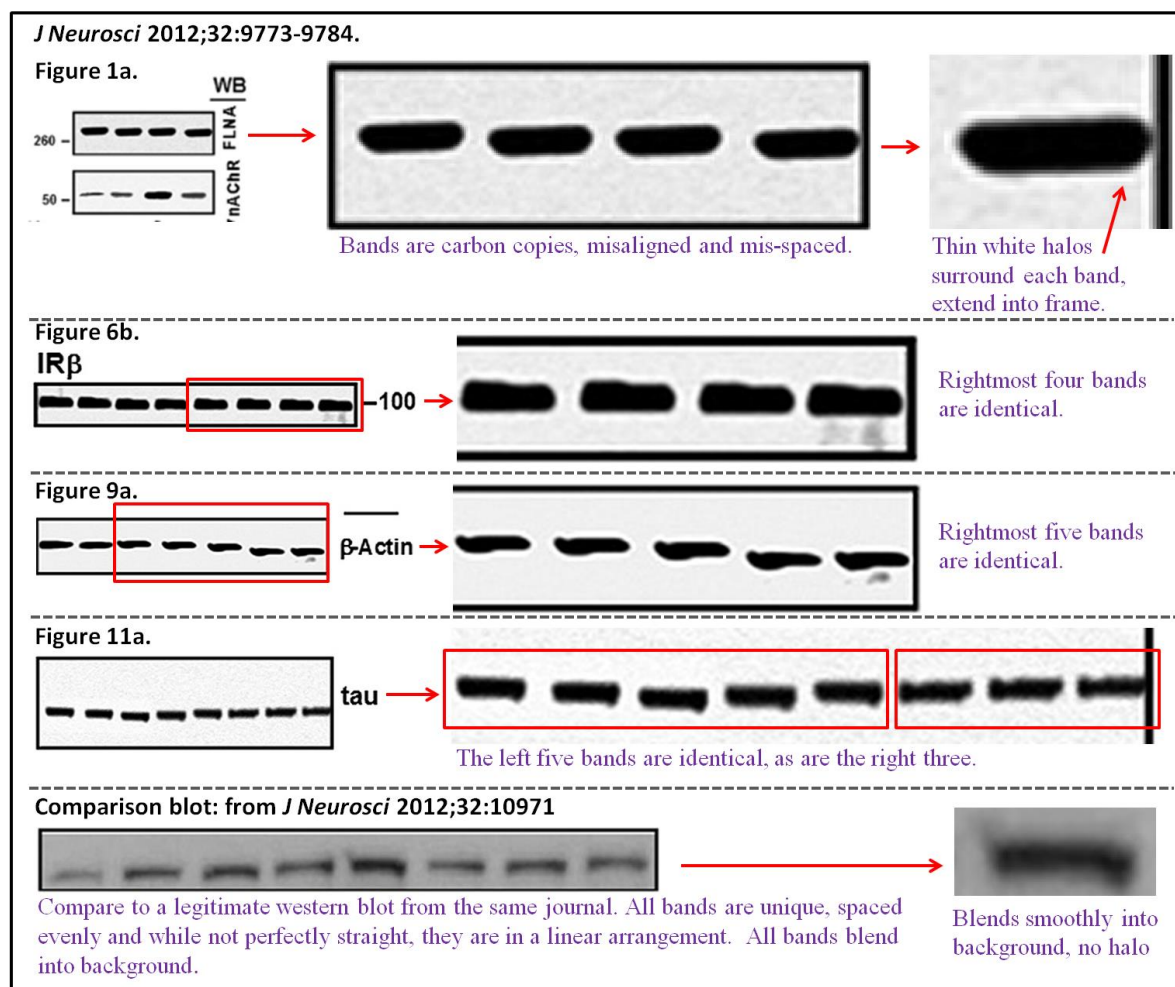


Figure 6b: The four rightmost bands appear to be identical to each other. This degree of similarity is unlikely to occur by chance.

Figure 9a: The five rightmost actin bands have a distinctive shape, but are nevertheless identical to each other. That these bands all have apparently identical “dipper” shapes cannot occur by chance. As above, the thin white border surrounding each band is prominently seen again.

Figure 11a: The five leftmost tau bands appear to be identical to each other, AND the 3 rightmost tau bands appear to be identical to each other. These degrees of similarity are unlikely occur by chance.

There are many other examples that strongly suggest data manipulation in this *Journal of*

Neuroscience paper. Individually, each of these examples is concerning, but together they form a pattern that strongly calls into question the integrity of this publication (and the other publications from these authors with similar patterns of band insertion). The work in question here serves as THE foundational research linking PTI-125 (Simufilam) to Alzheimer's disease. Unless the authors can produce full length unaltered gels with appropriate molecule weight markers to validate band migration, for all experiments in this paper, it should be retracted.

Importantly, data in this paper were part of the package used to garner NIH grant AG060878 and open an FDA investigational new drug application to study PTI-125 (Simufilam) in Alzheimer's disease patients.

C.3. Concern #3: Integrity of Analyses Involving Human Brain Tissue

C.3.1. Implausibility of Reported Pharmacology in Postmortem Human Brain Tissue.

PTI-125/Simufilam is reported to bind to Filamin and alter its conformation. In so doing, it allegedly blocks the interaction between β -amyloid and the $\alpha 7$ -nicotinic acetylcholine receptor. This supposedly modifies a range of downstream molecules and signaling pathways including NMDA signaling, Toll-like receptor signaling (causing an anti-inflammatory effect) and decreasing tau phosphorylation.

This is a complex mechanism. In one key line of experiments, the authors report that this entire mechanism can be observed in post-mortem human brain tissue from subjects with Alzheimer's disease and neurological controls. This data is contained in *Neurobiology of Aging* 2017;55:99-114. This builds on similar experiments in *The Journal of Neuroscience* 2009;29:10961-10973 and *The Journal of Neuroscience* 2012;32:9773-9784.

In these experiments, post-mortem human brain tissue is warmed from -80°C to -20°C and chopped into 200micron x 200micron x 3mm blocks with a McIlwain chopper (as a side note, a McIlwain chopper doesn't effectively cut frozen tissue). The resulting chopped tissue is treated with β -amyloid and the experimental drug for 1 hour. They then report a massive increase in tau phosphorylation (modification of the tau protein by enzymatic addition of a phosphate group to the protein; up to 10 fold) from β -amyloid treatment in untreated samples; and that tau phosphorylation was blocked by addition of PTI-125. It is unlikely that the enzyme responsible for phosphorylation would survive the initial -80°C freezing step. Moreover, the phosphorylation experiments are reported to have been performed at 4°C , but it is unlikely that the enzyme responsible for phosphorylation would be active at 4°C (enzymes generally work best at body temperature— 37°C).

In a similar experiment, NMDA-receptor signaling was evaluated after incubating minced human brain from patients with AD and neurological controls with NMDA/glycine along with β -amyloid and the experimental drug for 1 hour. NMDA signaling was reported blocked by β -amyloid and in AD and rescued in both cases by the experimental drug. For similar reasons, these reported results are unlikely.

The methodology for the post-mortem human brain experiments among the three studies are virtually word-for-word identical. The age and post-mortem interval for the groups of subjects are the same (down to the decimal points) in each of the three papers. It is therefore reasonable to assume the same human brain specimens were used across the studies from 2008-2017, so the results are premised on the enzymes in the human brain extracts remaining active up to 13 hours post-mortem before freezing, remaining active after nearly 10 years in frozen archival without any advanced cryopreservative techniques, and being active at 4°C.

Importantly, the authors report that there was a marked, rapid increase in the Arc protein observed as evidence of NMDA receptor activity with this approach. The suggestion is that post-mortem human brain tissue, frozen for a decade, thawed and chopped, (1) has intact NMDA receptor signaling, (2) is able to transmit that signal to the cell body through an intact dendrite, (3) has the functioning cellular apparatus to rapidly produce the Arc protein and (4) enough intact neurons are present to mediate a >4 fold rise in Arc levels in this tissue. In reality, neurons in the human brain do not survive extended post-mortem intervals and long-term freezing.

The complex, multi-step cellular processes the authors claim to observe in tissue that has been dead for a decade are contrary to a basic understanding of neurobiology. Claims of this magnitude require extensive, detailed verification, but the authors provide no evidence of tissue

viability. We are not aware of any other research group which has effectively used this technique. As with the western blot data, there are anomalies in the presentation of the data from this human tissue, which again strongly suggest manipulation.

C.3.2. Evidence of Manipulation in Data from Human Tissue

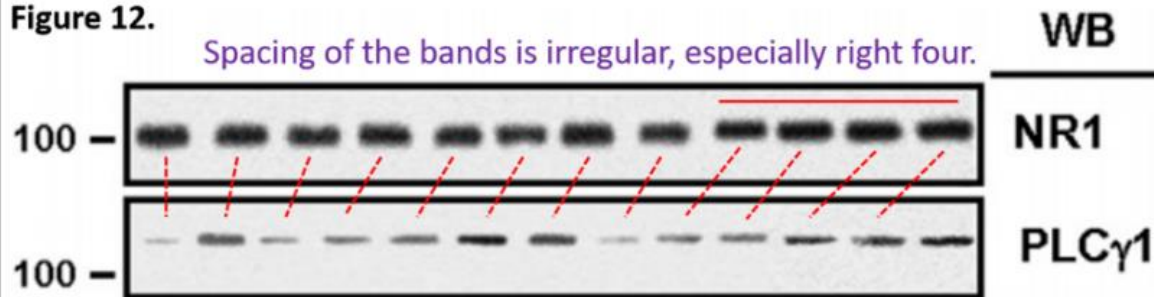
Figure 12 of *Neurobiology of Aging* 2017;55:99-114 uses Western blotting to support their conclusion that PTI-125 improves NMDAR (NR1) function. Their analysis includes a normalization step. In figure 12a (top portion), the NR1 blot that that is used for normalization contains 12 bands whereas all the other blots in this figure contain 13 bands.

Also, the NR1 bands show different spacing than do bands in the PLC γ 1 blot, **which strongly suggests that the NR1 and PLC γ 1 Western blots could not have derived from the same gel.** This directly conflicts with the author's claim in the method section of this paper that, "Proteins were transferred to nitrocellulose membrane and the levels of PSD-95, and signaling proteins were measured using Western blotting with specific antibodies for PSD-95, nNOS, phospholipase C- γ 1, protein kinase C, pY402PyK2, and pY416Src. *Blots were stripped and reprobed with anti-NR1 to assess loading.*" The italicized sentence indicates that the gel membrane was analyzed for PLC γ 1, and the same membrane was re-analyzed for NR1. This process does not introduce or remove band lanes.

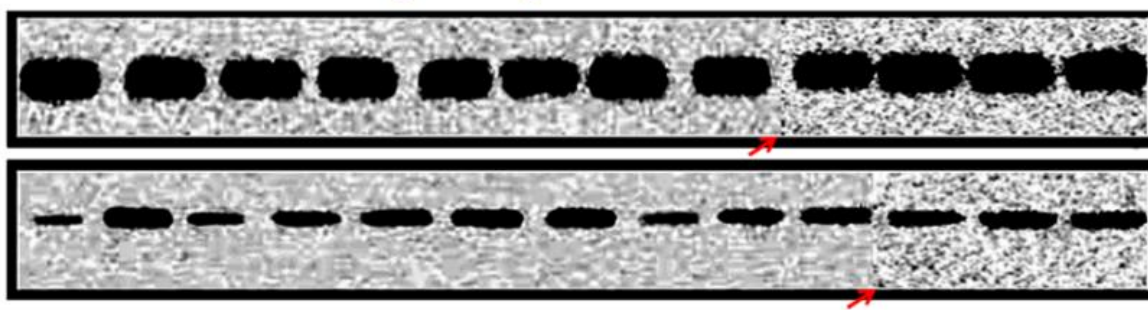
Neurobiol Aging 2017;55:99-114

Figure 12.

Spacing of the bands is irregular, especially right four.



The methods indicate these blots were stripped and reprobbed to assess the ratio of the proteins. The blots above have different number of bands (12 on the upper, 13 on the lower) and the spacing indicates they were not produced as the methods describe. Increasing the contrast in the image makes the piecing of this blot unmistakable due to the change in background texture.



Another major problem with the 12-band blot is that the spacing of the bands is irregular. This is particularly obvious on the right half (lanes 7-12). This asymmetry in band spacing is incompatible with the regular shape of the combs used for gel loading. Therefore, the 12-band blot was almost certainly pasted together from different sources. Further evidence that the bands likely derive from different sources is apparent when the contrast of the image is adjusted. As shown in the magnified panels in the figure below, in the NR1 (top row) there is a sharp contrast between the background for the leftmost 8 bands and the background for the rightmost 4 bands, marked with a red arrow. In the magnified panel for PLC γ 1 (bottom row), there is also evidence of splicing. Again, the red arrow denotes a sharp background contrast between the leftmost 9 bands and the rightmost 3 bands.

For these reasons, the primary data for this paper should be audited. If the primary data

do not support the authors' highly unlikely claims, the paper should be retracted. These questionable experiments used donated cadaveric human tissue, which, if the experimental data are shown to be manipulated, is a particularly egregious ethical transgression.

D. Implications and Recommendations

In summary, it appears that Drs. Wang and Burns in published PubMed indexed manuscripts and through disclosures with Cassava Sciences have misrepresented preclinical and clinical research results for more than 15 years. This initial examination of their published western blots identified many dozens of examples of protein bands that appear to have been duplicated and/or misrepresented, a Western blot that was used twice to represent different experimental conditions, and a normalization blot that appears to have been manually constructed. Some bands appear to have been “reused” in papers concerning different research topics that were published five years apart.

The volume of problematic material uncovered in publicly available sources indicates a thorough audit would likely unveil significant additional scientific misconduct and data manipulation. It is essential that the scientific team behind Cassava Sciences' Simuflam provide the original blots with molecular weight markers to validate these published papers and clinical biomarker data, which include SavaDx.

It is worth repeating, the preclinical and clinical foundations linking Filamin A to Alzheimer's disease derive only from the publications of Drs. Wang and Burns. As shown above, ALL of these papers have evidence of apparent intentional scientific misrepresentation. Cassava Sciences' Alzheimer's disease clinical biomarker data with PTI-125/simuflam showed no evidence of efficacy when tested by an outside lab, and only showed apparent efficacy when re-analyzed in an academic lab—likely Dr. Wang's lab as he is listed as the first author on the

poster (26 July 2021) describing the re-analyzed data. Now, Cassava Science's 26 July 2021 analysis of clinical biomarker results with PTI-125/simufilam also shows evidence of data manipulation.

Finally, the methodology allegedly used to evaluate the function of simufilam in postmortem human brain tissue defies logic and the data presented again have clear hallmarks of manipulation.

In the interests of the NIH, Main Street investors, and most importantly Alzheimer's disease patients, **especially those currently taking simufilam in Cassava Sciences clinical trials**, the issues noted above should be investigated with expediency.

Again, we make six specific recommendations:

- NIH and CUNY should audit the publications and lab of Dr. Wang to determine the existence and extent of data manipulation and fraud in all papers and grant applications from Drs. Wang and Burns.
- The FDA should audit both these publications and the IND application for simufilam's use in AD.
- The FDA should audit all clinical biomarker studies of simufilam in AD.
- The FDA should oversee 3rd party reanalysis of all clinical biomarker studies of simufilam in AD.
- The FDA should pause ongoing clinical trials with simufilam immediately pending these investigations.
- The academic journals which published the studies discussed herein should review the manuscripts and retract them to correct the public record, if the concerns remain after adequate investigations.

In particular, there are six papers that require close scrutiny:

- Wang et al. J Prev Alzheimers Dis. 2020;7(4):256-264
- Wang et al. Neurobiol Aging. 2017 Jul;55:99-114
- Wang et al. J Neurosci. 2012 Jul 18;32(29):9773-84
- Wang et al. Biol Psychiatry 2010;67: 522
- Wang, Frankfurt and Burns PLoS One. 2008 Feb 6;3(2):e1554
- Wang et al. Neuroscience. 2005;135(1):247-61

Additionally, the following corporate presentation should be examined:

- (<https://www.cassavasciences.com/company-presentations> | "SavaDx, a Novel Plasma Biomarker to Detect Alzheimer's Disease, Confirms Mechanism of Action of Simufilam").

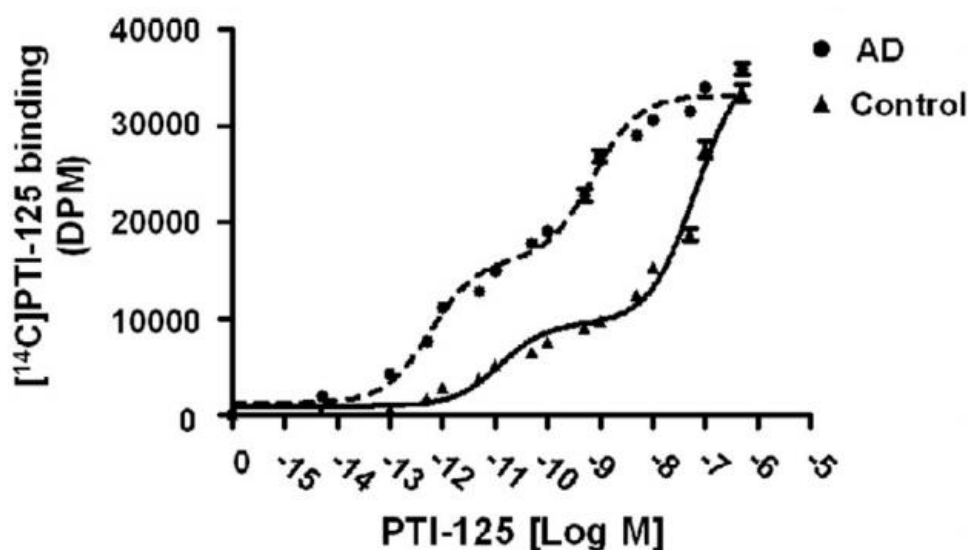
E. Appendix

E.1. Six Additional Areas of Concern

Six further aspects of the research by Drs. Wang and Burns are incompatible with scientific norms, and these claims raise further suspicions. These issues are enumerated below. In addition to the many examples of apparent Western blot manipulation and clinical data misreporting noted above, a number of additional western blots are included at the end of this appendix which raise additional red flags.

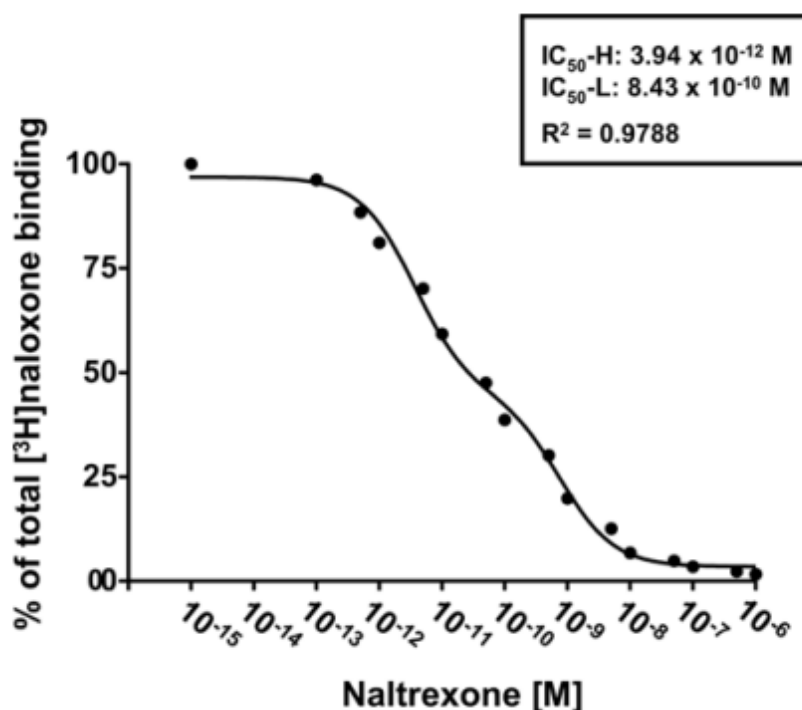
Suspicious Claim #1: Remarkably High Affinity Binding Between PTI-125 and Filamin A

Figure 1B (below) in the *Neurobiology of Aging* 2017;55:99-114 paper claims that PTI-125 has *femtomolar* binding affinity for filamin A in Alzheimer's disease brain. There is scant precedent for a small molecule to bind so potently to a cytoskeletal protein. The claimed affinity seems higher than that of any other small molecule binding to any cytoskeletal protein. Figure 1b in this paper also shows that PTI-125 displacement occurs over 7 orders of magnitude. This "shallow" displacement is highly unusual/unprecedented. An experienced pharmacologist could advise that this is suspicious / implausible. The authors should be asked for the raw data.



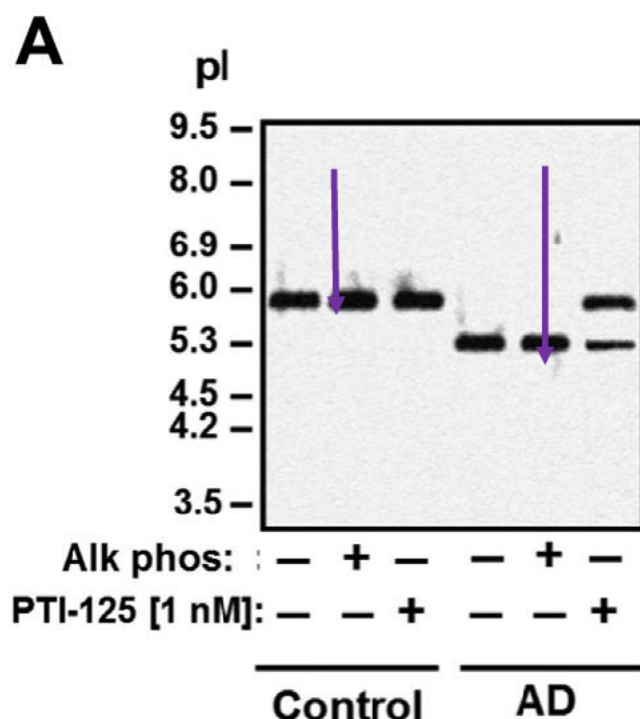
Suspicious Claim #2: Remarkably High Affinity Binding Between Naloxone and Filamin A

Naloxone is an old and intensively studied drug that binds with nanomolar affinity to opiate receptors. Figure 3 (below) of the *PLoS ONE* 2008;3:e1554 paper claims that Naloxone [^3H]NLX binds with low *picomolar* affinity to Filamin A. As Filamin A is present in brain, it is puzzling why previous studies have not reported picomolar binding affinity for naloxone in brain. Also unusual is the “shallow” displacement curve in figure 3 that spans 4-5 orders of magnitude. An experienced opiate receptor pharmacologist could advise that this figure is suspicious / implausible. The authors should be asked for the raw data.



Suspicious Claim #3: Isoelectric Focusing Experiments in Multiple Papers Indicate 100% of Filamin in Altered Conformation in Alzheimer's Disease and largely Restored to Correct Conformation by PTI-125

In Figure 2 (below) of the 2017 *Neurobiology of Aging* 2017 55:99-114 paper, the authors present a gel showing that Filamin A isoelectric point shifts from 5.9 in control to 5.3 in Alzheimer's disease (purple arrows for lanes 1 and 4). This is suspicious for two reasons. First, Alzheimer's disease affects only a small subset of neurons in a diseased brain, so it is scientifically unclear how 100% of Filamin A could shift. Second, isoelectric focusing gels do not typically "look" like the image below. Especially for a 290 kD protein like Filamin A, one would not expect such crisp bands in isoelectric focusing. An experienced biochemist could advise that this figure is suspicious / implausible. This is especially suspect considering the apparent pattern of band manipulation by Drs. Wang and Burns on Western blots. Similar experiments are shown in other publications. The authors should be asked for the raw data.



Suspicious Claim #5: PTI-125/Simufilam Improves Memory in a Mouse Model of Alzheimer's Disease

In *Neurobiol Aging* 2017;55:99-114, figure 9 shows a pre-clinical study of simufilam in a mouse model of AD and misinterprets the data as showing “improvements in memory.” It is dubious that any legitimate experiment approximating the methodology described could yield the reported result.

For instance, the third panel (shown below) shows data from a Y-maze which is used to assess memory in mice. Animals are placed in an apparatus made of three tubes which interlock in the middle, like a Mercedes Benz emblem. The test is based on two observations about mouse behavior – (1) when they are put in a new environment, they will explore it and (2) they prefer to explore a new area rather than areas recently explored. After a mouse explores one arm of the y-maze and returns to the center, they must decide which of the other two tubes to enter next. A normal mouse will generally avoid the tube that was most recently explored resulting in a pattern where they spontaneously alternate between each of the tubes. Normal mice would be expected to follow this pattern 70-80% of the time as a rough estimate. If a mouse has memory impairment, the selection of which tube to enter will be random, and the alternation rate should be about 50%. Remarkably, wild type mice and transgenic mice in Wang's study spontaneously alternated less than 20% of the time, which is an atypical result. Drug treatment in 6 month old transgenic mice, increased the rate of alternation to over 30%. This raises a number of issues: (1) this pattern of results is unlikely to occur and suggests, at the least, the experiment was conducted incorrectly, and (2) if the result were legitimate, the drug treatment changing the mice's behavior to closer to 50% spontaneous alternation (i.e., closer to random) would be more accurately interpreted as evidence of *worse* memory performance.

A mouse neurobehavioral specialist would likely advise that there are significant

problems with all of the behavioral and memory data presented in the paper. Importantly, this is the only pre-clinical cognitive/memory data that has been published supporting simufilam's efficacy as a cognitive enhancer. This data should be audited.

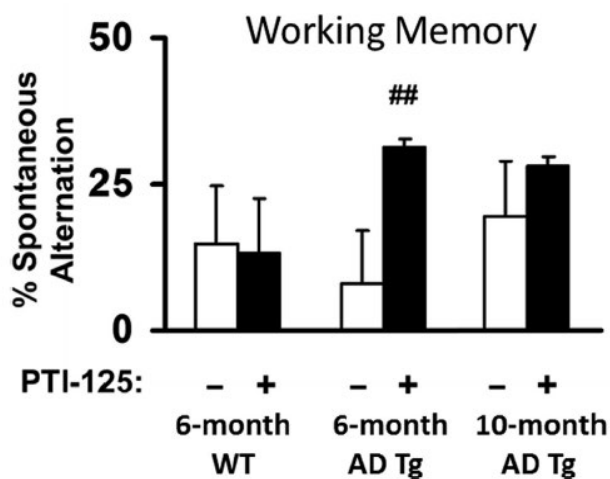
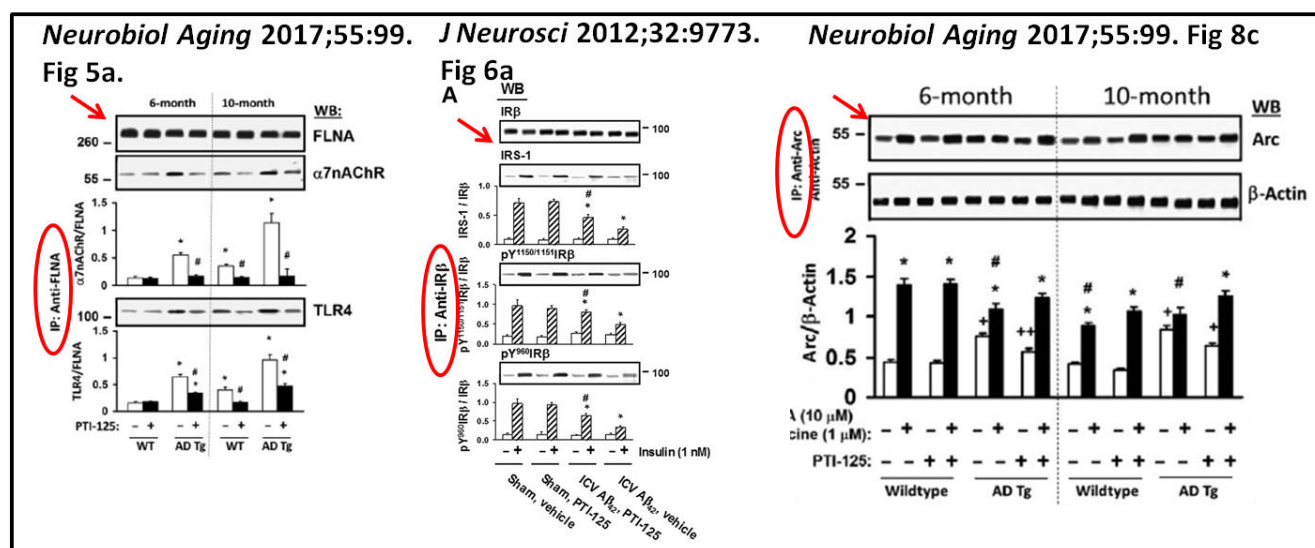


Fig. 9. PTI-125 via drinking water improved nesting behavior in 6-month 3xTg AD mice. Compared to 6-month wildtypes, spatial memory assessed using Y-maze with extra-maze visual cues was impaired in 3xTg AD mice of both ages but not in 3xTg AD mice of either age treated with PTI-125. Additionally, PTI-125 significantly improved spatial memory in 10-month 3xTg AD mice. PTI-125 significantly improved working memory assessed by Y-maze spontaneous alternation paradigm in the 10-month but not 6-month 3xTg AD mice. $n = 5$. * $p < 0.01$, ** $p < 0.05$ versus 6-month-old vehicle-treated wild-type group; # $p < 0.01$, ## $p < 0.05$ versus respective vehicle-treated group. Abbreviations: AD, Alzheimer's disease; 3xTg, triple-transgenic.

Suspicious Claim #6: PTI-125/Simufilam Blocks the Interaction Between β -amyloid and $\alpha 7$ - Nicotinic Acetylcholine Receptors.

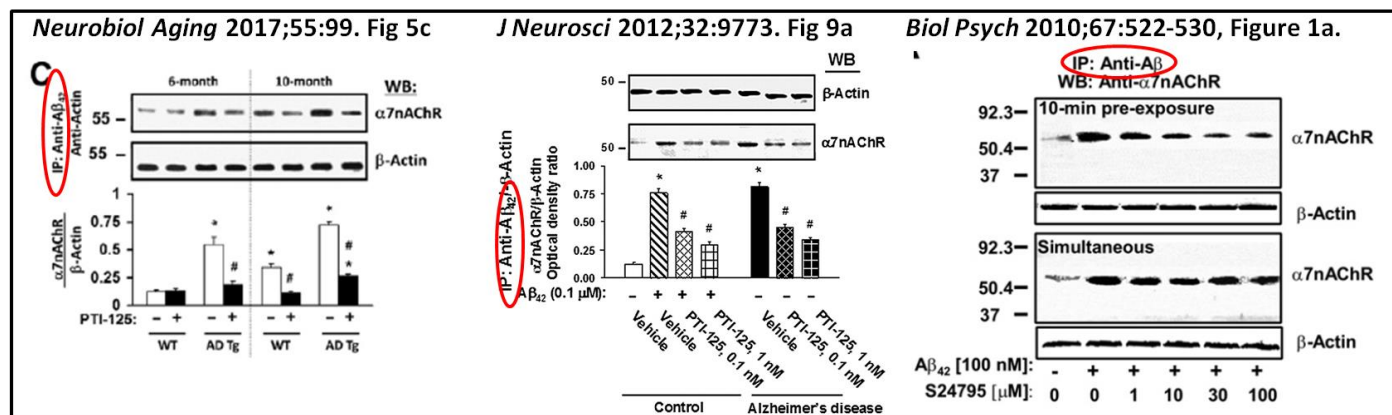
Most of the western blots in these papers take advantage of a process known as co-immunoprecipitation. In this technique, tissue is ground up until it is liquefied and an antibody is used to catch a protein of interest. When the antibody and the protein it binds are isolated, any other proteins that bind to the target protein will also be isolated. This approach enables scientists to evaluate if two proteins interact with each other.

As a standard laboratory practice, the first step in evaluating a co-immunoprecipitation sample is to perform a western blot to confirm that the target protein was captured. It obviously makes little sense to proceed to analyze other proteins, if the target protein was not captured. Drs. Wang and Burns consistently follow this convention. Examples are shown below.

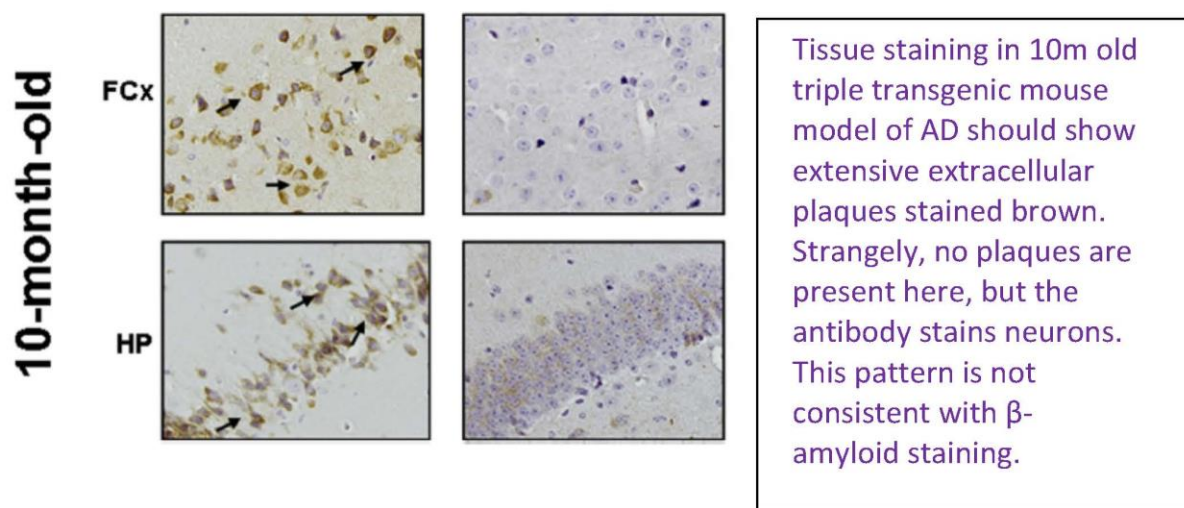


However, there is one exception. The control blot demonstrating efficient capture of the target protein is omitted every time co-immunoprecipitation of β -amyloid is presented. A series of these co-immunoprecipitation experiments is shown below, each omitting this necessary blot. There are numerous other examples throughout the publications. The authors used this technique to build the case that β -amyloid interacts with $\alpha 7$ -nicotinic acetylcholine receptors. The fact that

they deviated from a standard of practice they strictly follow in other settings is suspicious. It is also noteworthy that a significant fraction of the western blots shown elsewhere in the document to have been manipulated are associated with β -amyloid co-immunoprecipitation experiments (the center and right example in the figure following also contain two of the more-egregious examples of western blot falsification).



The authors appear to have used the same β -amyloid antibody to perform tissue staining in a transgenic mouse model of AD. Despite the authors' claims, this staining does not show any extracellular β -amyloid plaques (see following figure). It is clear that this antibody is malfunctioning in the tissue staining. Consequently, it is reasonable to be concerned that it is non-functional in the co-immunoprecipitation as well.



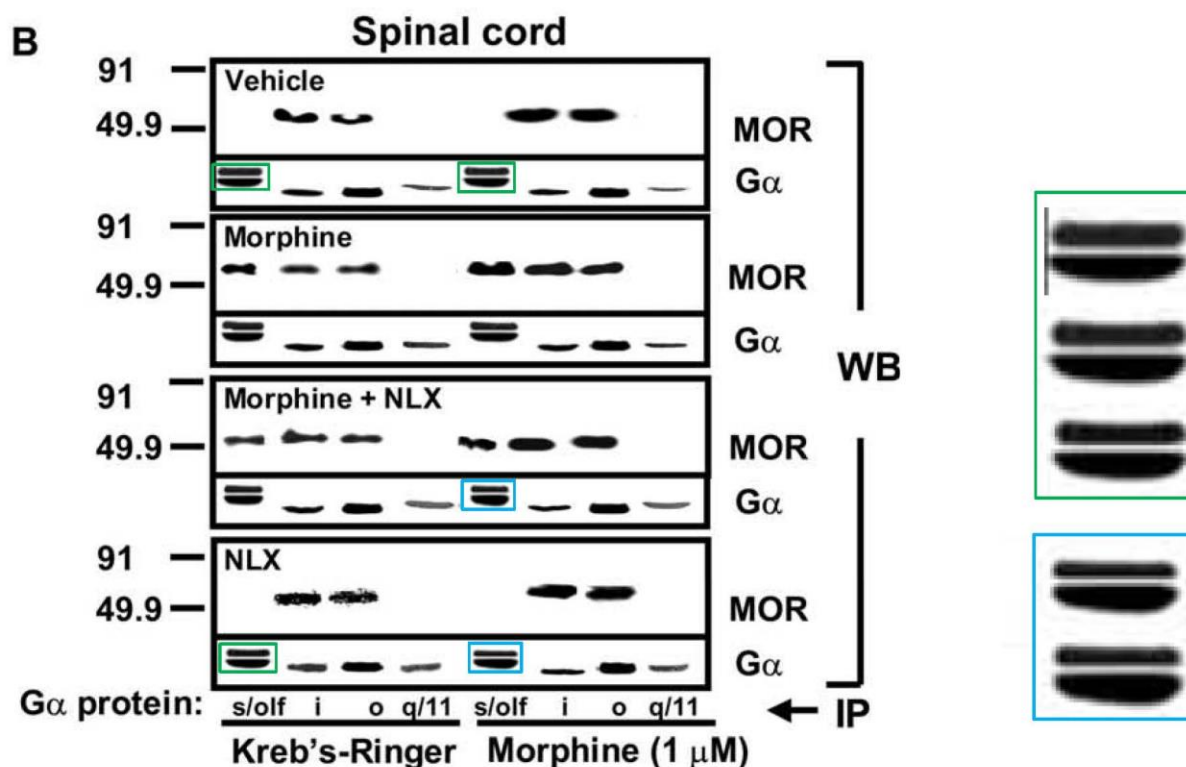
These observations strongly call into question the assertion that PTI-125/simufilam alters the interaction between β -amyloid and any of its supposed targets. The authors should show clear validation of effective immunoprecipitation of β -amyloid in every one of these instances.

E.2. Additional Suspicious Western Blots:

In the 2005 Wang and Burns paper *Neuroscience* 135 247–261, one can see bands with unique features that appear spliced into multiple gels. This suggests that experiments were not conducted as described. One example of this is Figure 5B (below).

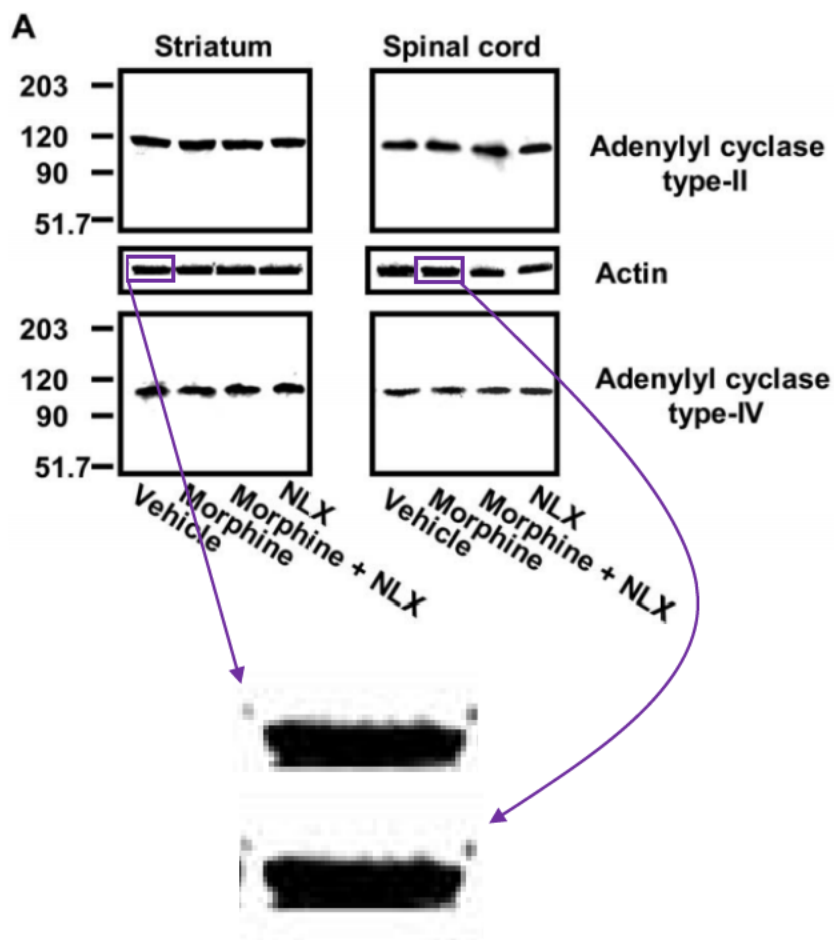
In this Western blot, the $G\alpha$ bands in the s/olf lanes have peculiar “double decker” shapes. Close inspection reveals that three of these double decker bands (green) are more similar to each other than would be expected AND another two of these double deckers (blue) are also more similar to each other than would be expected.

The congruence of these oddly shaped bands are unlikely to have occurred by chance and raises the possibility of band duplication and data manipulation.



Another striking example of probable band duplication occurs in Figure 12a of this paper. Here, the actin band from the striatum brain region treated with “Vehicle” is indistinguishable

from the actin band from the spinal cord region treated with Morphine. The uncanny resemblance of these “battleship” shaped bands and the precise alignment of the dot artifacts suggest that one or both were intentionally inserted, perhaps with the intention of misrepresenting the results.

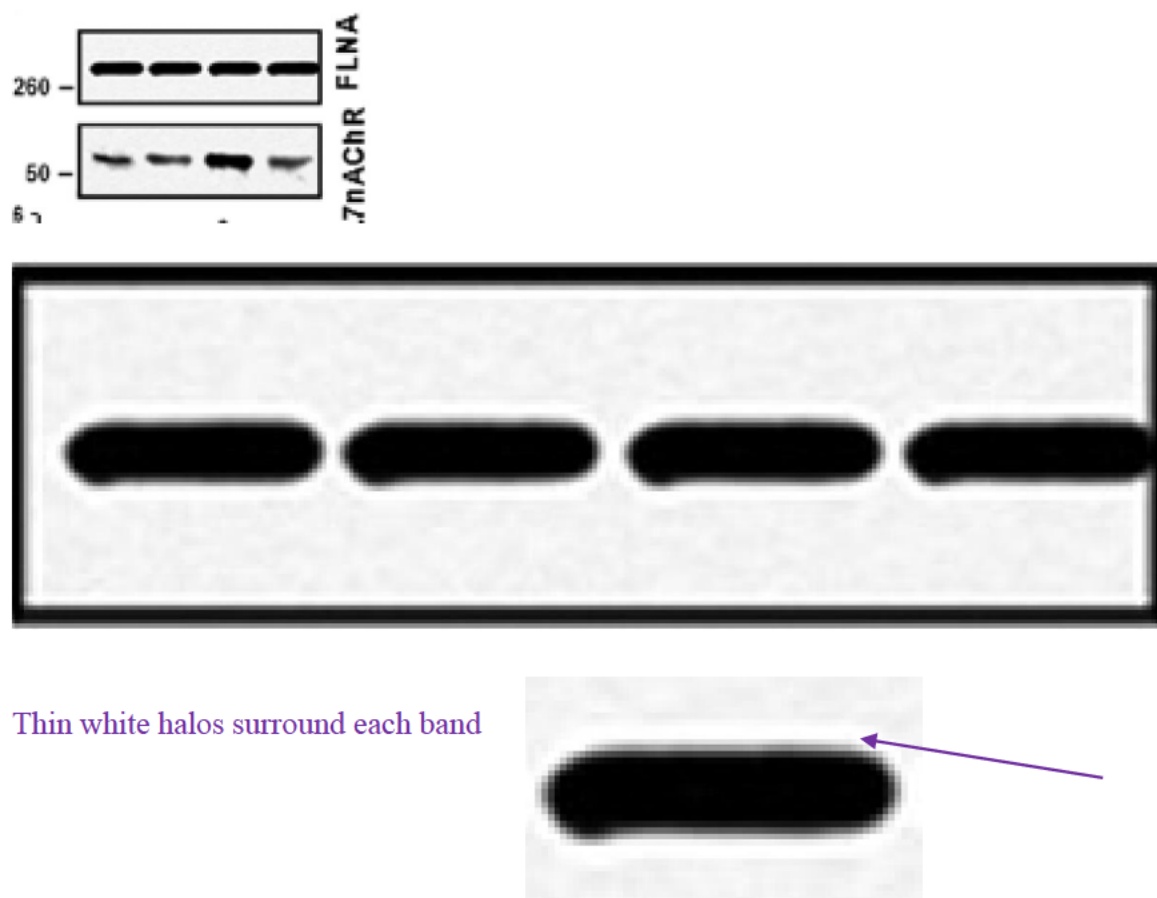


The seemingly identical battleship shape of these protein bands from different

It is recommended that the original full-length images **with appropriate molecule weight markers to validate band migration** from this paper be requested and analyzed. If they are not available, this paper should be retracted.

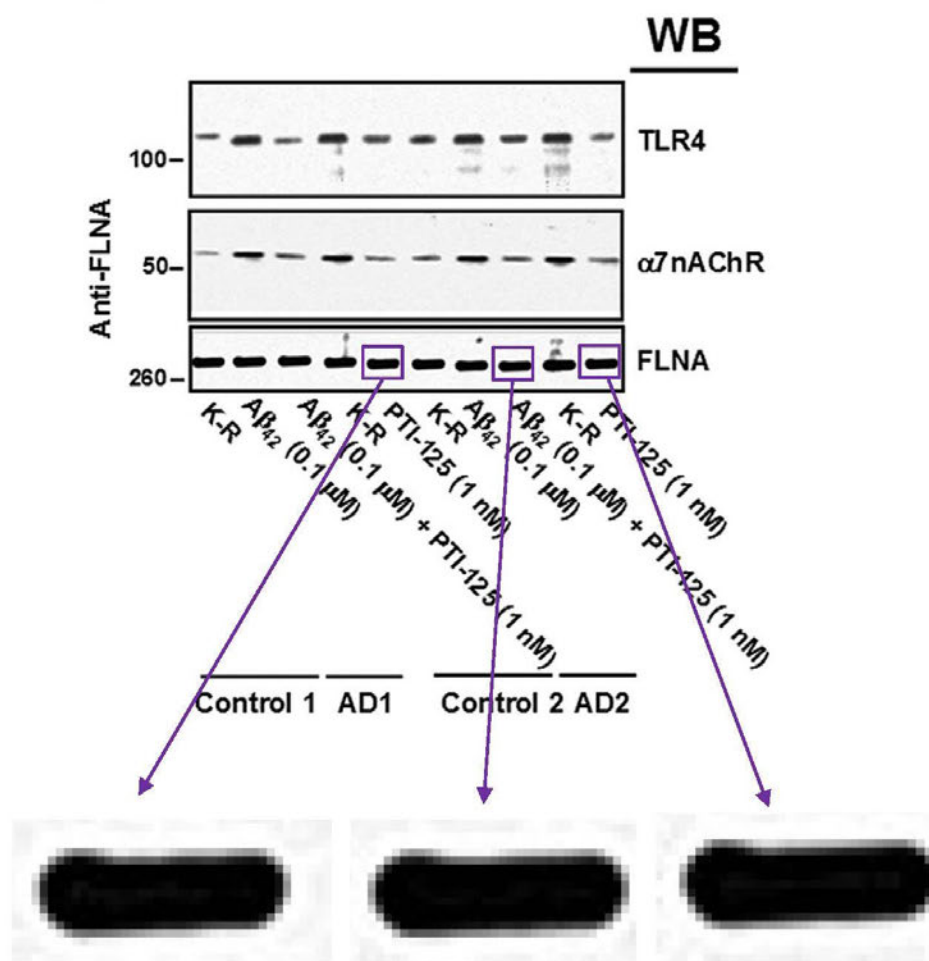
Additional examples of probable band duplication in *J Neurosci* 2012;32:9773-9784.

One can see that the four Filamin A bands in the bottom set of Figure 1A appear to be identical to each other. This degree of similarity is unlikely to occur by chance, and the thin white borders surrounding each band could be due to merging multiple images in a photo editing software.



Another important consideration is that the Wang and Burns 2012 Journal of Neuroscience paper uses human specimens from Alzheimer's disease patients. Any intentional misuse of such material violates the World Medical Association Declaration of Helsinki regarding ethical use of donated human tissue.

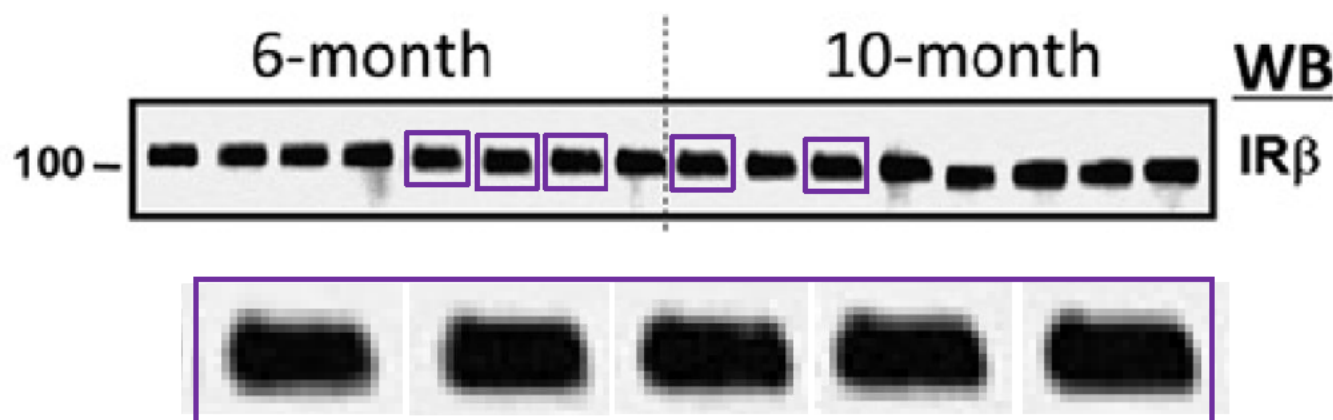
Figure 12A (below) of the Journal of Neuroscience paper, used human Alzheimer's disease tissue to establish the SavaDx biomarker and effects of PTI-125/simufilam. The ten filamin A (FLNA) bands appear identical in size and shape. As protein bands on Western blots typically have unique features, ten consecutive indistinguishable bands are exceedingly unlikely to occur by chance and were probably manually duplicated.



All ten virtually indistinguishable FLNA bands are exactly 11 pixels high and 32 pixels wide. Three examples are magnified here for illustration.

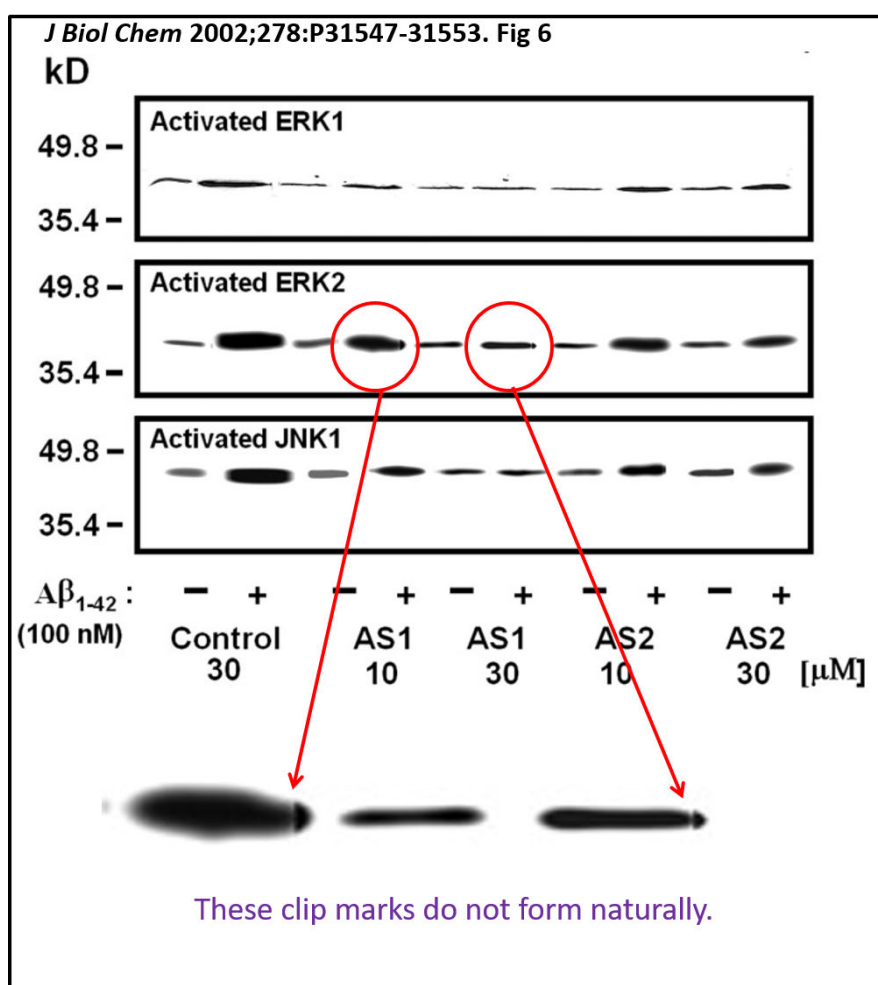
A subsequent paper alleging to connect PTI-125 with Alzheimer's disease is 2017 Neurobiol Aging 55: 99-114. Again, this paper largely comprises a series of overexposed, and apparently manipulated and cropped Western blots. Band duplication appears to occur throughout this paper.

As just one of many examples, Figure 8B contains Western blots from mice treated with PTI-125. The top blot displays a western blot using an antibody for IR β (see label on the right). The similarity in size and shape of the bands in the purple boxes seemingly could not have occurred by chance. This and many other blots in this paper appear to have been manipulated.



These five indistinguishable bands are all exactly 12 pixels high and 20 pixels wide.

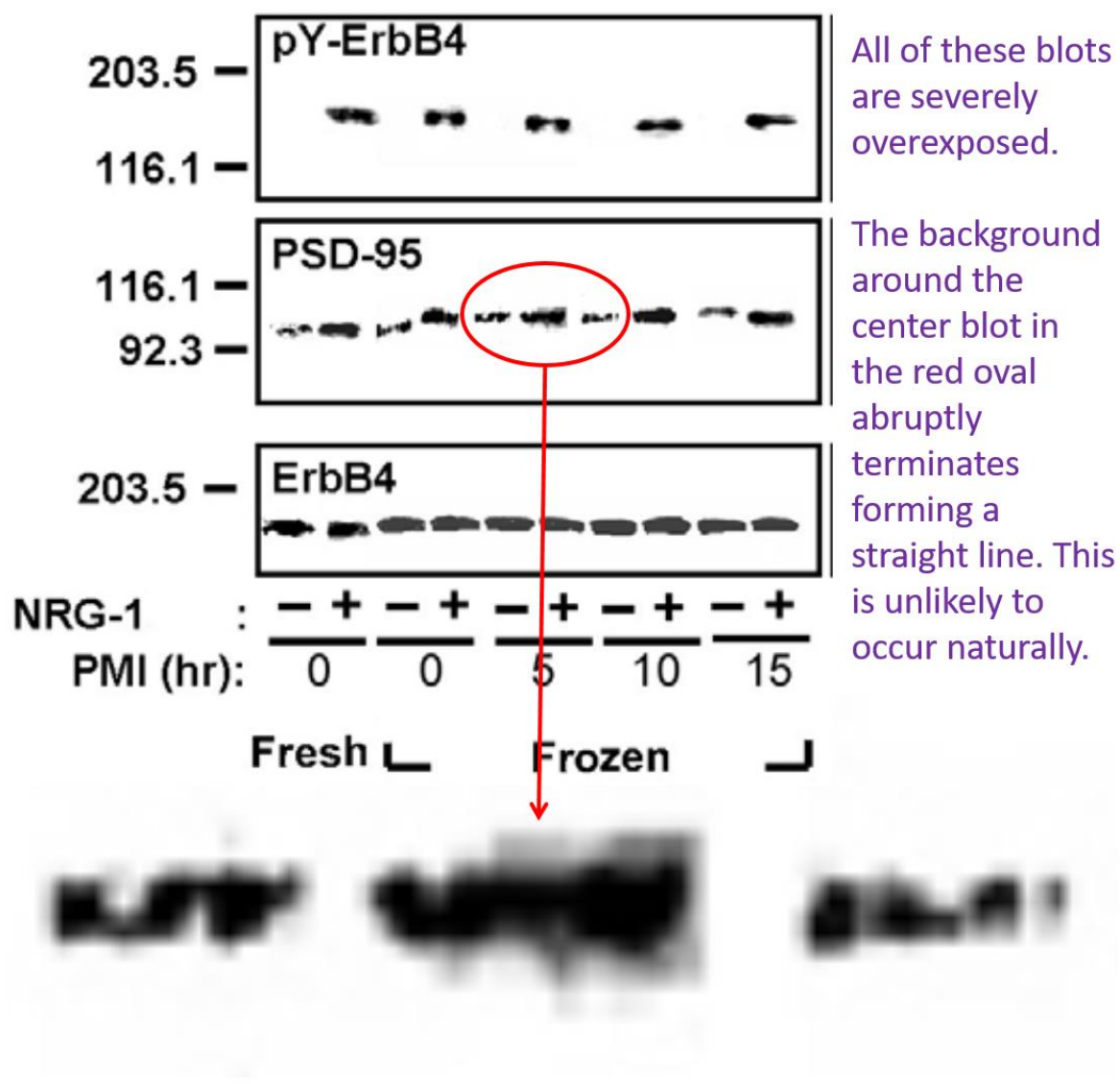
The following example of a manipulated western blot occurred earlier than the examples referenced in the primary document. Dr. Wang was the first author of this 2002 paper in the *Journal of Biological Chemistry* 278:P31547-32553 and it is one of the few examples presented in this document without Dr. Burns as a co-author. The apparent manipulation applied to this blot is similar to that shown in C2.2.1. The marks highlighted at the red arrow do not form naturally and are likely produced by clipping multiple blots together. These blots are also severely overexposed. This study purports to establish that β -amyloid binding to the $\alpha 7$ nicotinic acetylcholine receptor induced tau phosphorylation, which is one of the pathways simufilam is supposed to interrupt.



Because of the contemporaneous examples of western blot manipulation, we undertook an evaluation the author's highest profile publication, a 2006 publication in *Nature Medicine* 12:824-828. Dr. Wang is the co-first author of this work. There are numerous suspicious appearing blots in this publication, as well. Again, blots are suspiciously over-exposed. In the supplementary material accompanying that published manuscript, we encounter the blot shown below. The background has more-or-less been obliterated, except for a small area circled in the red oval. Linear termination of the background signal is suspicious for the original blot having been cut and reassembled. Because of the low quality of this image, we evaluated the images in the main manuscript (which are higher quality), to assess for evidence of tampering.

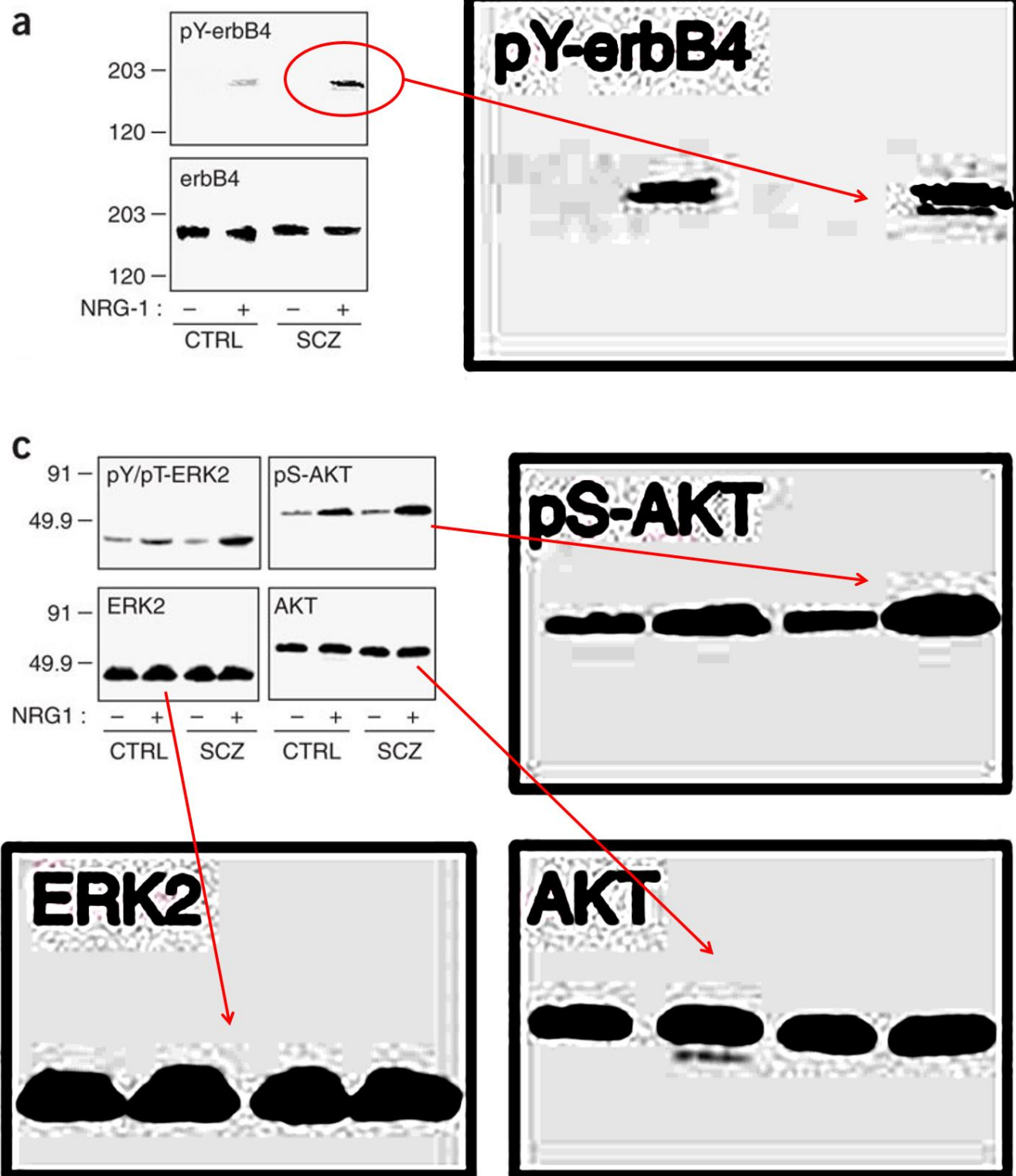
Importantly, this manuscript purports to establish the validity of the functional characterization of NMDA receptor signaling in post-mortem, frozen human brain material which is called into question in section C.3.1. Evidence of tampering with this evidence further calls into question the validity of this unusual technique.

Nature Med. 2006;12:824-828. Supplementary Figure 2



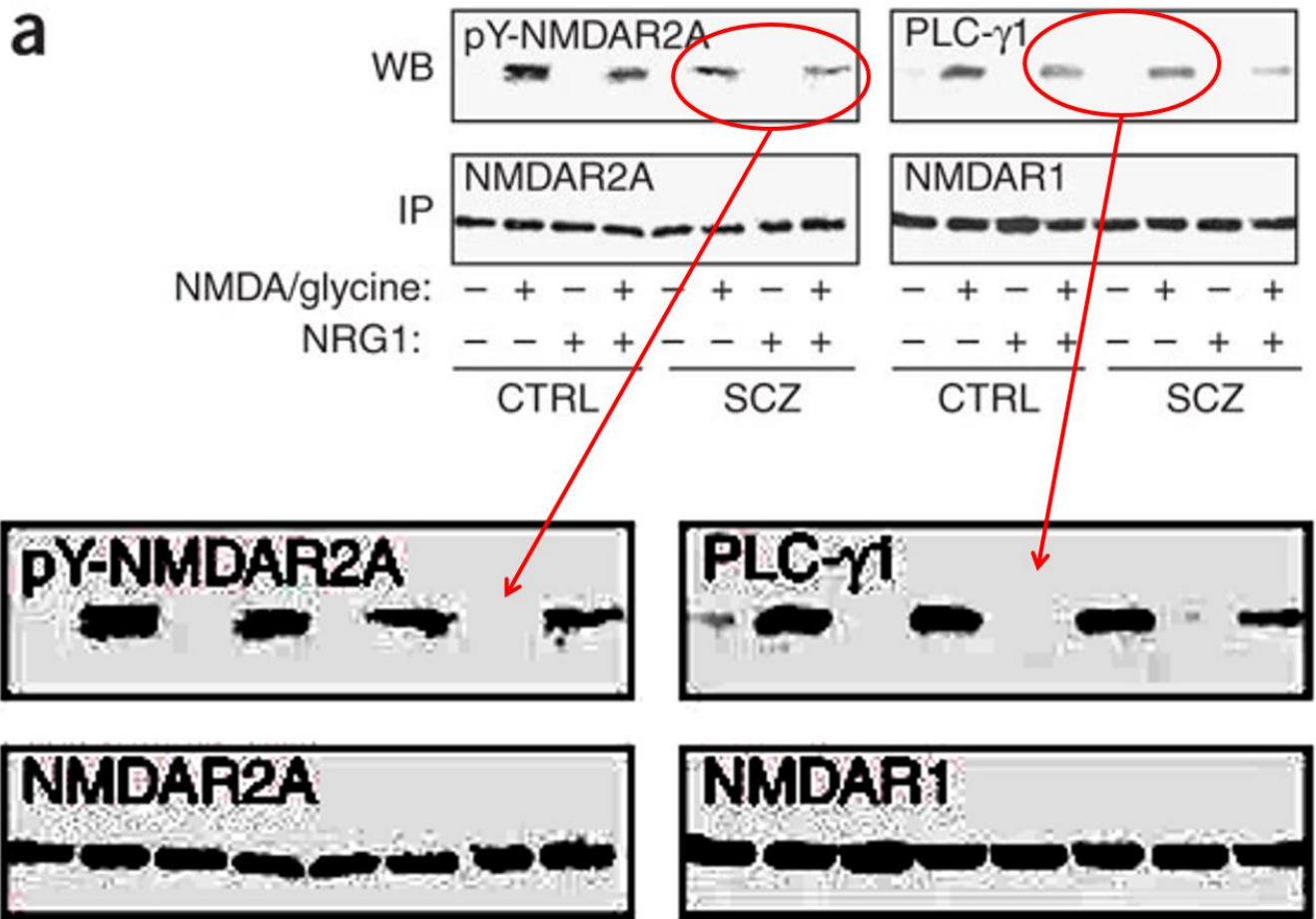
The images in the main text are of higher quality, enabling clearer evaluation. Increasing

Nature Med. 2006;12:824-828. Figure 2.



the contrast in the images published as Figure 4 (below) clearly reveals evidence of linear cuts in the blots. Importantly, there is clearly a smooth background between the two darker bands and a textured background only behind the dark bands. This was not likely done for cosmetic reasons, it strongly suggests a manufactured/fraudulent result. There is no legitimate explanation for this pattern of findings. This high-profile manuscript should be reviewed by the publisher and retracted. All subsequent manuscripts built on this technique should likewise be reviewed.

Nature Med. 2006;12:824-828. Figure 4.



From: Christine Li
Sent time: 08/28/2021 11:18:53 AM
To: Hoau-yan Wang
Subject: Damaging report
Attachments: FDA-2021-P-0930-0004_content.pdf ATT00001.htm

Hello Hoau-Yan,

I received this report from a departmental colleague, who knows that I have a grant with you. You have my complete support, but you should be aware that other CCNY colleagues have also seen this report and be prepared. Sorry I didn't call, but I don't have your number.

Stay strong,
Chris

<https://downloads.regulations.gov/FDA-2021-P-0930-0004/content.pdf>



Statement of Concern Regarding the Accuracy and Integrity of Clinical and Preclinical Data Supporting the Ongoing Clinical Evaluation of Compound PTI-125, Also Known As Simufilam

August 18, 2021

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A. Executive Summary

For over 15 years, Cassava Sciences (previously Pain Therapeutics, Inc, PTI) has funded the lab of Dr. Hoau-Yan Wang at City University of New York (CUNY). Together with Dr. Lindsay Burns at Cassava, Dr. Wang has published nearly a dozen papers connecting Filamin A protein with pain and Alzheimer's disease (AD).

Cassava Sciences created a drug candidate called simufilam (previously PTI-125) that they claim binds Filamin A and has beneficial effects in biochemical and animal models of AD. The studies from Drs. Wang and Burns discussed in this dossier were used by Cassava Sciences to garner NIH grants and to open an investigational new drug (IND) application to study simufilam in AD patients. They form the basic science foundation for two completed clinical trials (phase IIa and IIb) which exposed over 70 patients to simufilam. Cassava Sciences is currently recruiting 200 additional patients for a follow-up open-label trial.

This report raises concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate. To preface the analysis that follows, no other labs have confirmed this research connecting Filamin A to pain or AD. No other labs have confirmed that simufilam binds or modifies Filamin A or has effects in AD models.

In this document, three primary concerns are raised:

- The validity of clinical biomarker data: Biomarker analysis from patients treated with simufilam in Cassava's double-blind study forms a primary basis of Cassava's claim that simufilam engages its target in the central nervous system, but there are concerns about the integrity of this data. The CSF samples in this study were analyzed by an outside lab, which found that simufilam was ineffective in improving the primary biomarker end point and showed high variability in other biomarkers. However, Cassava Science had these samples bioanalyzed again and the data were finalized in

an academic lab, which apparently refers to Dr. Wang. This re-analysis showed that simufilam rapidly and robustly improved a wide array of CSF biomarkers. Whereas Cassava has not fully published this reanalysis, Cassava's 26 July 2021 poster presumably describing aspects of that work shows signs of data manipulation.

- The integrity of western blot analyses: Western blotting was extensively used by Drs. Wang and Burns over the past 15 years to support their foundational scientific claims and underscores their SavaDx clinical plasma biomarker. Detailed analysis of the western blots in the published journal articles from Drs. Wang and Burns shows a series of anomalies. The extent of these anomalies forms a 15-year pattern that strongly suggests systematic data manipulation and misrepresentation.
- The integrity of analyses involving human brain tissue: Simufilam is reported to bind to its target and modify a range of downstream molecules in experiments conducted on post-mortem human brain tissue from subjects with Alzheimer's disease and neurological controls. The same human brain specimens are used across the studies from 2008-2017, so the results are premised on human neurons remaining viable up to 13 hours after death, then being successfully reanimated after nearly 10 years in frozen archival without any advanced cryopreservative techniques. The complex, multi-step cellular processes the authors claim to observe in tissue that has been dead for a decade are contrary to a basic understanding of neurobiology. As with the western blot data, there are anomalies in the presentation of the data which again strongly suggest manipulation.

In the appendix, six additional areas of concern are raised. These frequent errors and anomalies occur in a pattern which is frequently favorable to the authors' hypotheses and is of

sufficient magnitude to strongly suggest scientific misconduct. This scientific work is foundational to the link between simufilam and its supposed target Filamin A in AD. Consequently, urgent action is advisable to limit patient exposure to this drug, until an appropriate investigation is completed.

Finally, we make six specific recommendations:

- The NIH and CUNY should audit the publications and lab of Dr. Wang to determine the existence and extent of data manipulation and possible fraud in all papers and grant applications from Drs. Wang and Burns.
- The FDA should audit both these publications and the IND application for simufilam's use in AD.
- The FDA should audit all clinical biomarker studies of simufilam in AD.
- The FDA should oversee 3rd party reanalysis of all clinical biomarker studies of simufilam in AD.
- The FDA should pause ongoing trials with simufilam pending these investigations.
- The academic journals which published the studies discussed herein should review and retract them to correct the public record, if the concerns remain after adequate investigation.

B. Background

This letter details a long-standing pattern of seemingly intentional data manipulation and misrepresentation in scientific papers and corporate disclosures authored primarily by Drs. Hoau-Yan Wang, Associate Medical Professor, City University of New York, and Lindsay A Burns, Sr. Vice President of Neuroscience at Cassava Sciences. All the information detailed herein was obtained from public, non-proprietary sources. These apparent falsifications have helped garner

>\$5,000,000 in NIH grants for preclinical/clinical studies, attract >\$250,000,000 in public fundraising by Cassava Sciences and misdirect therapeutic studies for patients suffering from Alzheimer's Disease (AD). In the interest of **the safety of patients with Alzheimer's disease enrolled in Cassava Sciences' ongoing clinical trials**, as well as the NIH and other stakeholders, the biomedical and financial communities must be made aware of these apparent falsehoods. The laboratory of Dr. Wang and Cassava Sciences warrant an audit to comprehensively evaluate the integrity of the scientific data.

For >15 years, Dr. Wang has collaborated with Cassava Sciences, formerly known as Pain Therapeutics Incorporated (PTI). Cassava Sciences is developing simufilam, a drug which was initially designated PTI-125, as a disease modifying treatment for Alzheimer's disease. Simufilam is claimed to bind to a cytoskeleton-associated protein called Filamin A and thereby benefit a range of Alzheimer's disease related neuropathologies. This line of research is unique to Dr. Wang and Cassava Sciences.

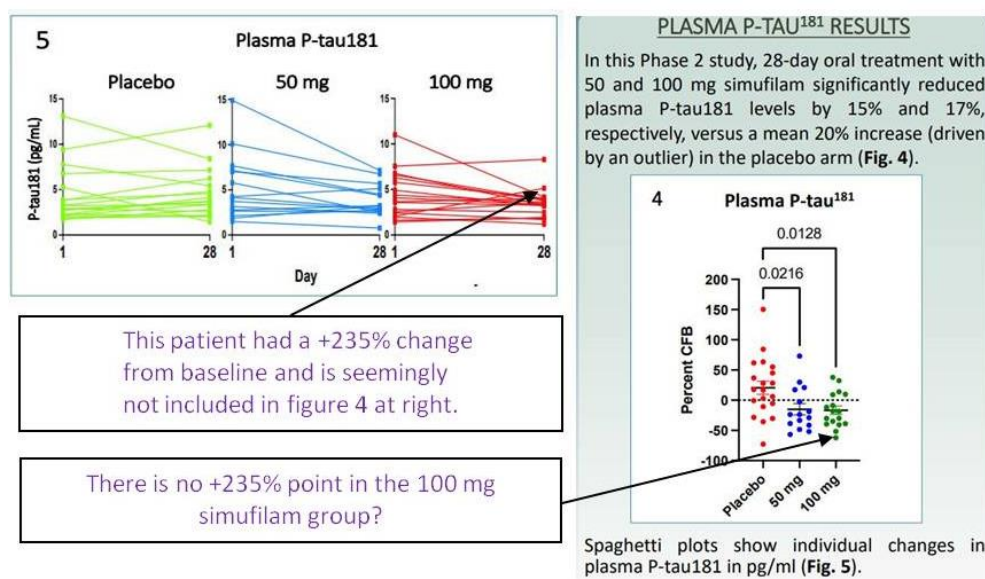
In reviewing this work, several results were encountered that are most unexpected and are probably unique to Drs. Wang, Burns and Cassava Sciences. Consequently, we investigated the published journal articles and other public sources of data underlying the development of simufilam in greater detail. This initial analysis suggests a pattern of clear errors and anomalies that are consistent with data manipulation and misrepresentation. These findings undercut the foundational science on which simufilam therapy is based.

C. Major Concerns

C.1. Concern #1: Integrity of Clinical Biomarker Data

NIH STTR grants (AG057329 & AG060878) funded Cassava Sciences' double-blind placebo-controlled phase II trial of PTI-125 (50, 100 mg QD) in 64 AD patients (NCT04079803). The primary end points reported were changes from baseline (day 1 to day 28) for a series of CSF

biomarkers including Abeta42, total tau, P-tau181, neurogranin, neurofilament light chain, and YKL-40. **On 15 May 2020, Cassava Sciences reported that this study missed its primary end points.** However, on 14 September 2020, Cassava Sciences reported that bioassays done by an external group were in error, and that **when patient samples were retested and finalized in what we believe to be Dr. Wang's lab, PTI-125/simufilam was claimed to robustly improve all biomarkers.**



On 26 July 2021, Cassava Sciences presented a poster at the Alzheimer's Association International Conference entitled "SavaDx, a Novel Plasma Biomarker to Detect..." regarding their clinical biomarkers. This poster, featuring Dr. Wang as first author, can be found on their corporate website (<https://www.cassavasciences.com/company-presentations> | "SavaDx, a Novel Plasma Biomarker to Detect Alzheimer's Disease, Confirms Mechanism of Action of Simufilam"). Figures 4 and 5 of this poster describe effects of 28-day treatment with simufilam (PTI-125) on plasma P-Tau181. Figure 4 shows the percent change from baseline (CFB) and figure 5 shows the absolute biomarker values for individuals before and after treatment. However, Figures 4 and 5 cannot be from the same data set. In Figure 5, one patient in the 100

mg group (at the arrow) had a P-Tau181 level which increased from ~1.5 to 5 pg/ml during the 28-day treatment period, ~235% change from baseline. However, in figure 4 there is no data point in the 100 mg treatment groups showing a CFB >40%. If the correct data point (+235%) were averaged in with the other points in figure 4, any beneficial effect of 100 mg simufilam would likely have been negated.

As a side-note, CSF analysis was also performed on the 13 patients in the phase 2a study and was published by Drs. Wang and Burns in early 2020 in the *Journal of Prevention of Alzheimer's Disease* 7;256-264. Remarkably, this manuscript was accepted for publication Nov. 6, 2020 seven days after submission October 31, 2020. If those dates are correct, it seems highly unlikely to have been subjected to rigorous peer review.

These clinical biomarker data present two significant problems. First, it seems that the primary biomarker data set we have with simufilam in Alzheimer's disease that was entirely produced and finalized by an external lab found that the drug had no effect on clinical biomarkers. Cassava replaced this with a reanalysis that was finalized by an academic lab (presumably Dr. Wang) and showed that simufilam showed remarkable benefit. Second, plasma biomarker data from these same patients, which were just presented by Cassava Sciences, contains evidence of manipulation. If there's no biomarker signal, and there is apparent misrepresentation of clinical data the **continuation of the ongoing Cassava trials may put patients at risk without the claimed evidence of biomarker benefit**. All the clinical biomarker results should be audited and replicated by an independent third party.

C.2. Concern #2: Integrity of Western Blot Data

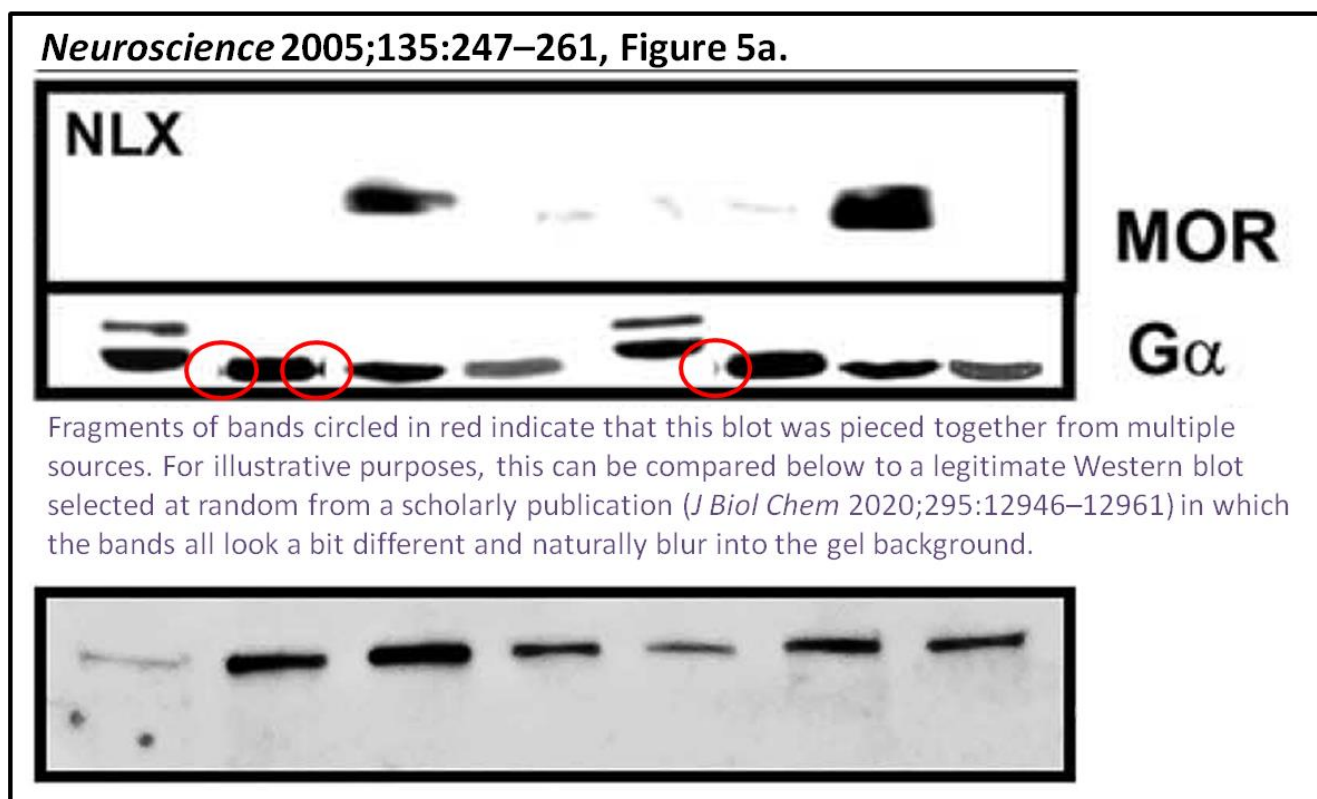
Many experiments in the work by Drs. Wang and Burns involve western blotting. Using this technique, proteins from tissue samples are separated on "gels" in a series of vertical lanes; the proteins are then transferred to a paper-like membrane, and antibodies are used to detect

specific proteins on the membrane, producing an image of specific proteins or “bands”.

Each band generally has a slightly different shape. As noted in an article posted on Retraction Watch about data manipulation and focused on Western blots (<https://retractionwatch.com/2016/04/19/one-in-25-papers-contains-inappropriately-duplicated-images-screen-finds/>), “In Western blots, every band has their own characteristics, they’re like faces.” That article further noted the significant number of cases of inappropriately duplicated or manipulated Western Blots: “... in no way suggest that Western blotting is a flawed method. Indeed, it suggests that Western blots are harder to fake in an undetectable way than other experimental data.” The western blot data presented by Wang and Burns are almost always overexposed and highly processed, which has been repeatedly seen in previously reported examples of image manipulation. In the following sections, we present a series of examples with strong evidence of image manipulation. In the appendix, we include additional examples which raise red flags.

C.2.1. Example #1: Manipulated Western Blot; *Neuroscience* 2005,135:247-261 – Figure 5a.

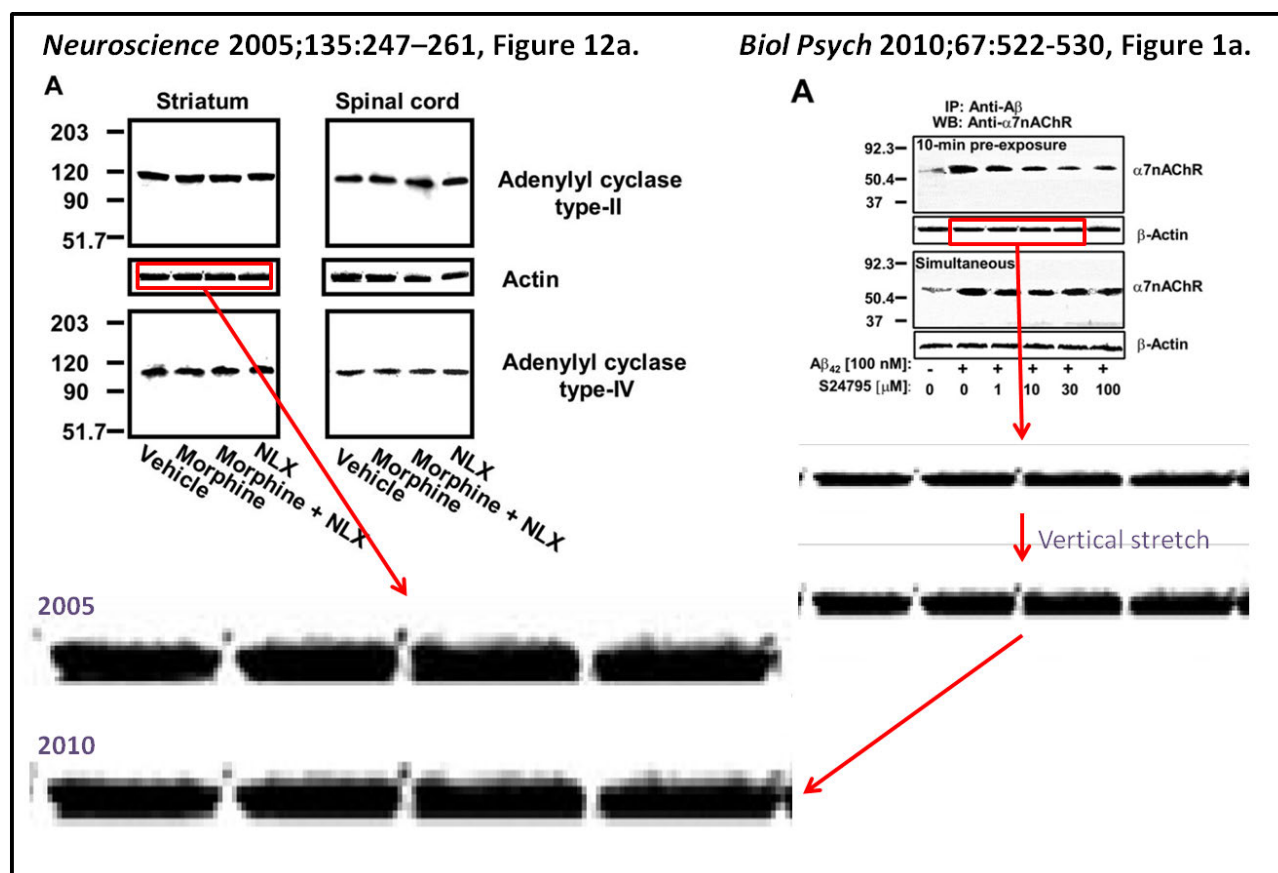
In figure 5a of their 2005 paper *Neuroscience* 135;247–261, the authors appear to have “spliced together” gels from different experiments. Telltale signs that the Gα bands in Figure 5a likely come from different gels are circled in red below. The cropped borders of an adjacent protein band are present indicating the bands were taken from another blot.



C.2.2. Example #2. Falsified Western Blot; *Biol Psych* 2010,67:522 – Figure 1a.

The western blot in Figure 1a (below right) of Dr. Wang’s 2010 paper in *Biological Psychiatry* 67:522 contains four bands that closely resemble an image published in Figure 12a (left) of the Wang and Burns 2005 *Neuroscience* 135: 247 paper mentioned in C.2.1. These eight boxed bands come from different experimental conditions that were allegedly conducted many years apart, using different samples. The authors appear to have vertically compressed the bands

in the 2010 paper, but expanding them here shows they are strikingly similar to those in the 2005 paper. As the sample passes through the gel, it creates a small amount of streaking which causes a distinctive irregular shape in the upper portion of each band; the pattern of this streaking is identical in the two images. This degree of congruence could not have occurred by chance or error; it suggests a complex cross-publication dimension to Cassava Science's band duplication behavior and, in this case, it is hard to imagine that the duplication was not intentional. It is recommended that the original full-length images **with appropriate molecular weight markers are obtained to validate band migration** from both the 2005 and 2010 papers for independent review. Because of the seriousness of this duplication, if the original materials are not available, both of these papers must be retracted.



As a side-note, this western blot was produced on x-ray film, not as a digital image.

C.2.3. Example #4: Band Insertion Into Western Blots. Numerous publications.

The foundational paper from Drs. Wang and Burns that links Filamin A and PTI-125 to Alzheimer's disease is *The Journal of Neuroscience*, 2012 32:9773–9784. This paper appears to contain a collection of questionable western blots. Most of the paper comprises western blots that are of low quality, over exposed and selectively cropped. In this paper, the authors appear to have duplicated and transposed bands. There are dozens of questionable image features in this paper, only a small sampling is presented here. Numerous additional examples of this pattern of behavior in other manuscripts are included in the appendix.

In Figure 1a, the four Filamin A bands in the top set are more similar to each than can be expected by chance and appear to be duplicates. The images at right are magnified, showing that the pixels containing the bands are essentially identical. Additionally, the blots are not aligned and the spacing is irregular. Because FLNA is a large protein (~290kDa), it does not migrate in the gel very far; therefore, this degree of misalignment is suspicious. Moreover, the thin white halos surrounding each band are concerning. There are optical reasons why a halo (or ringing artifact) could occur, but this artifact is most common when components from multiple images are combined using photo editing software. This halo artifact is more prominent in the questionable blots, and extends in some cases into the frame around the blot which is hard to explain as an optical phenomenon.

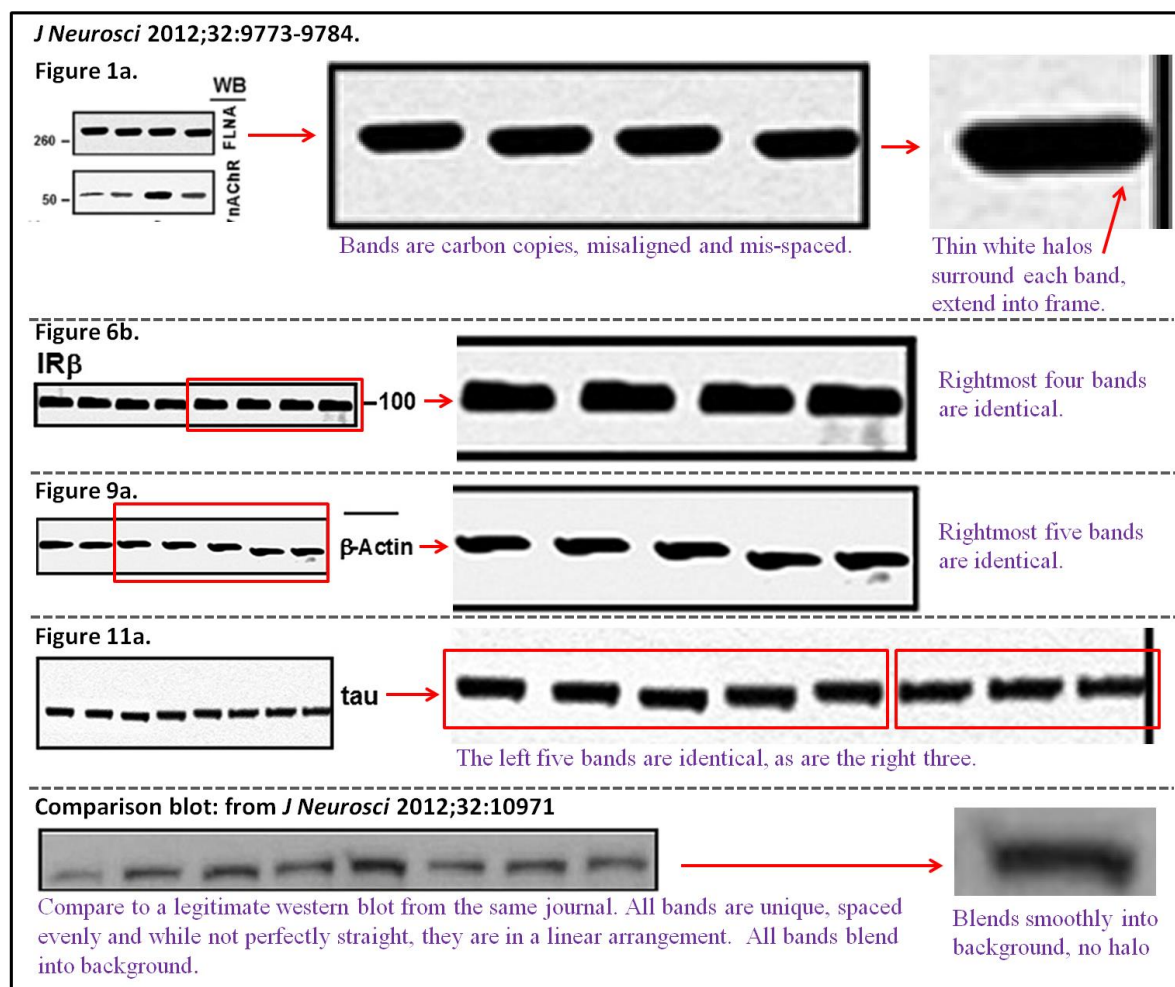


Figure 6b: The four rightmost bands appear to be identical to each other. This degree of similarity is unlikely to occur by chance.

Figure 9a: The five rightmost actin bands have a distinctive shape, but are nevertheless identical to each other. That these bands all have apparently identical “dipper” shapes cannot occur by chance. As above, the thin white border surrounding each band is prominently seen again.

Figure 11a: The five leftmost tau bands appear to be identical to each other, AND the 3 rightmost tau bands appear to be identical to each other. These degrees of similarity are unlikely occur by chance.

There are many other examples that strongly suggest data manipulation in this *Journal of*

Neuroscience paper. Individually, each of these examples is concerning, but together they form a pattern that strongly calls into question the integrity of this publication (and the other publications from these authors with similar patterns of band insertion). The work in question here serves as THE foundational research linking PTI-125 (Simufilam) to Alzheimer's disease. Unless the authors can produce full length unaltered gels with appropriate molecule weight markers to validate band migration, for all experiments in this paper, it should be retracted.

Importantly, data in this paper were part of the package used to garner NIH grant AG060878 and open an FDA investigational new drug application to study PTI-125 (Simufilam) in Alzheimer's disease patients.

C.3. Concern #3: Integrity of Analyses Involving Human Brain Tissue

C.3.1. Implausibility of Reported Pharmacology in Postmortem Human Brain Tissue.

PTI-125/Simufilam is reported to bind to Filamin and alter its conformation. In so doing, it allegedly blocks the interaction between β -amyloid and the $\alpha 7$ -nicotinic acetylcholine receptor. This supposedly modifies a range of downstream molecules and signaling pathways including NMDA signaling, Toll-like receptor signaling (causing an anti-inflammatory effect) and decreasing tau phosphorylation.

This is a complex mechanism. In one key line of experiments, the authors report that this entire mechanism can be observed in post-mortem human brain tissue from subjects with Alzheimer's disease and neurological controls. This data is contained in *Neurobiology of Aging* 2017;55:99-114. This builds on similar experiments in *The Journal of Neuroscience* 2009;29:10961-10973 and *The Journal of Neuroscience* 2012;32:9773-9784.

In these experiments, post-mortem human brain tissue is warmed from -80°C to -20°C and chopped into 200micron x 200micron x 3mm blocks with a McIlwain chopper (as a side note, a McIlwain chopper doesn't effectively cut frozen tissue). The resulting chopped tissue is treated with β -amyloid and the experimental drug for 1 hour. They then report a massive increase in tau phosphorylation (modification of the tau protein by enzymatic addition of a phosphate group to the protein; up to 10 fold) from β -amyloid treatment in untreated samples; and that tau phosphorylation was blocked by addition of PTI-125. It is unlikely that the enzyme responsible for phosphorylation would survive the initial -80°C freezing step. Moreover, the phosphorylation experiments are reported to have been performed at 4°C , but it is unlikely that the enzyme responsible for phosphorylation would be active at 4°C (enzymes generally work best at body temperature— 37°C).

In a similar experiment, NMDA-receptor signaling was evaluated after incubating minced human brain from patients with AD and neurological controls with NMDA/glycine along with β -amyloid and the experimental drug for 1 hour. NMDA signaling was reported blocked by β -amyloid and in AD and rescued in both cases by the experimental drug. For similar reasons, these reported results are unlikely.

The methodology for the post-mortem human brain experiments among the three studies are virtually word-for-word identical. The age and post-mortem interval for the groups of subjects are the same (down to the decimal points) in each of the three papers. It is therefore reasonable to assume the same human brain specimens were used across the studies from 2008-2017, so the results are premised on the enzymes in the human brain extracts remaining active up to 13 hours post-mortem before freezing, remaining active after nearly 10 years in frozen archival without any advanced cryopreservative techniques, and being active at 4°C.

Importantly, the authors report that there was a marked, rapid increase in the Arc protein observed as evidence of NMDA receptor activity with this approach. The suggestion is that post-mortem human brain tissue, frozen for a decade, thawed and chopped, (1) has intact NMDA receptor signaling, (2) is able to transmit that signal to the cell body through an intact dendrite, (3) has the functioning cellular apparatus to rapidly produce the Arc protein and (4) enough intact neurons are present to mediate a >4 fold rise in Arc levels in this tissue. In reality, neurons in the human brain do not survive extended post-mortem intervals and long-term freezing.

The complex, multi-step cellular processes the authors claim to observe in tissue that has been dead for a decade are contrary to a basic understanding of neurobiology. Claims of this magnitude require extensive, detailed verification, but the authors provide no evidence of tissue

viability. We are not aware of any other research group which has effectively used this technique. As with the western blot data, there are anomalies in the presentation of the data from this human tissue, which again strongly suggest manipulation.

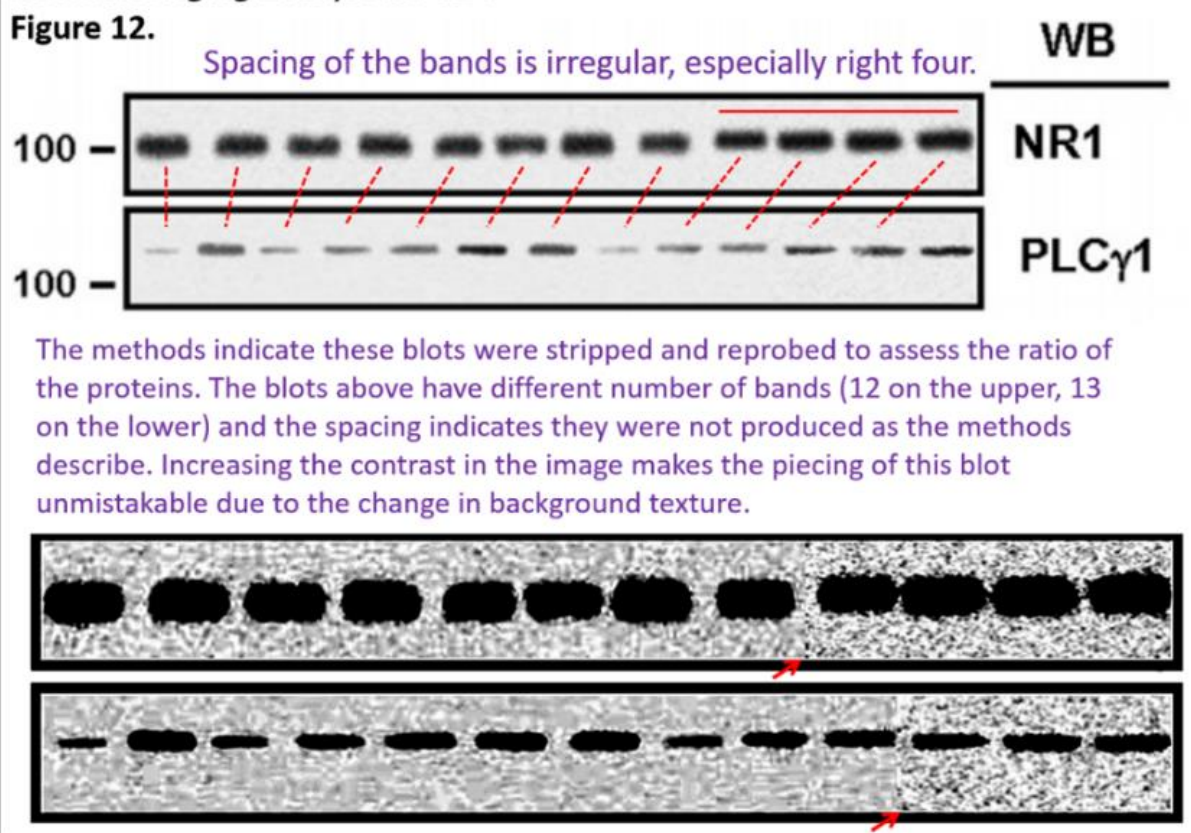
C.3.2. Evidence of Manipulation in Data from Human Tissue

Figure 12 of *Neurobiology of Aging* 2017;55:99-114 uses Western blotting to support their conclusion that PTI-125 improves NMDAR (NR1) function. Their analysis includes a normalization step. In figure 12a (top portion), the NR1 blot that that is used for normalization contains 12 bands whereas all the other blots in this figure contain 13 bands.

Also, the NR1 bands show different spacing than do bands in the PLC γ 1 blot, **which strongly suggests that the NR1 and PLC γ 1 Western blots could not have derived from the same gel.** This directly conflicts with the author's claim in the method section of this paper that, "Proteins were transferred to nitrocellulose membrane and the levels of PSD-95, and signaling proteins were measured using Western blotting with specific antibodies for PSD-95, nNOS, phospholipase C- γ 1, protein kinase C, pY402PyK2, and pY416Src. *Blots were stripped and reprobed with anti-NR1 to assess loading.*" The italicized sentence indicates that the gel membrane was analyzed for PLC γ 1, and the same membrane was re-analyzed for NR1. This process does not introduce or remove band lanes.

Neurobiol Aging 2017;55:99-114

Figure 12.



Another major problem with the 12-band blot is that the spacing of the bands is irregular. This is particularly obvious on the right half (lanes 7-12). This asymmetry in band spacing is incompatible with the regular shape of the combs used for gel loading. Therefore, the 12-band blot was almost certainly pasted together from different sources. Further evidence that the bands likely derive from different sources is apparent when the contrast of the image is adjusted. As shown in the magnified panels in the figure below, in the NR1 (top row) there is a sharp contrast between the background for the leftmost 8 bands and the background for the rightmost 4 bands, marked with a red arrow. In the magnified panel for PLC γ 1 (bottom row), there is also evidence of splicing. Again, the red arrow denotes a sharp background contrast between the leftmost 9 bands and the rightmost 3 bands.

For these reasons, the primary data for this paper should be audited. If the primary data

do not support the authors' highly unlikely claims, the paper should be retracted. These questionable experiments used donated cadaveric human tissue, which, if the experimental data are shown to be manipulated, is a particularly egregious ethical transgression.

D. Implications and Recommendations

In summary, it appears that Drs. Wang and Burns in published PubMed indexed manuscripts and through disclosures with Cassava Sciences have misrepresented preclinical and clinical research results for more than 15 years. This initial examination of their published western blots identified many dozens of examples of protein bands that appear to have been duplicated and/or misrepresented, a Western blot that was used twice to represent different experimental conditions, and a normalization blot that appears to have been manually constructed. Some bands appear to have been “reused” in papers concerning different research topics that were published five years apart.

The volume of problematic material uncovered in publicly available sources indicates a thorough audit would likely unveil significant additional scientific misconduct and data manipulation. It is essential that the scientific team behind Cassava Sciences' Simuflam provide the original blots with molecular weight markers to validate these published papers and clinical biomarker data, which include SavaDx.

It is worth repeating, the preclinical and clinical foundations linking Filamin A to Alzheimer's disease derive only from the publications of Drs. Wang and Burns. As shown above, ALL of these papers have evidence of apparent intentional scientific misrepresentation. Cassava Sciences' Alzheimer's disease clinical biomarker data with PTI-125/simuflam showed no evidence of efficacy when tested by an outside lab, and only showed apparent efficacy when re-analyzed in an academic lab—likely Dr. Wang's lab as he is listed as the first author on the

poster (26 July 2021) describing the re-analyzed data. Now, Cassava Science's 26 July 2021 analysis of clinical biomarker results with PTI-125/simufilam also shows evidence of data manipulation.

Finally, the methodology allegedly used to evaluate the function of simufilam in postmortem human brain tissue defies logic and the data presented again have clear hallmarks of manipulation.

In the interests of the NIH, Main Street investors, and most importantly Alzheimer's disease patients, **especially those currently taking simufilam in Cassava Sciences clinical trials**, the issues noted above should be investigated with expediency.

Again, we make six specific recommendations:

- NIH and CUNY should audit the publications and lab of Dr. Wang to determine the existence and extent of data manipulation and fraud in all papers and grant applications from Drs. Wang and Burns.
- The FDA should audit both these publications and the IND application for simufilam's use in AD.
- The FDA should audit all clinical biomarker studies of simufilam in AD.
- The FDA should oversee 3rd party reanalysis of all clinical biomarker studies of simufilam in AD.
- The FDA should pause ongoing clinical trials with simufilam immediately pending these investigations.
- The academic journals which published the studies discussed herein should review the manuscripts and retract them to correct the public record, if the concerns remain after adequate investigations.

In particular, there are six papers that require close scrutiny:

- Wang et al. J Prev Alzheimers Dis. 2020;7(4):256-264
- Wang et al. Neurobiol Aging. 2017 Jul;55:99-114
- Wang et al. J Neurosci. 2012 Jul 18;32(29):9773-84
- Wang et al. Biol Psychiatry 2010;67: 522
- Wang, Frankfurt and Burns PLoS One. 2008 Feb 6;3(2):e1554
- Wang et al. Neuroscience. 2005;135(1):247-61

Additionally, the following corporate presentation should be examined:

- (<https://www.cassavasciences.com/company-presentations> | "SavaDx, a Novel Plasma Biomarker to Detect Alzheimer's Disease, Confirms Mechanism of Action of Simufilam").

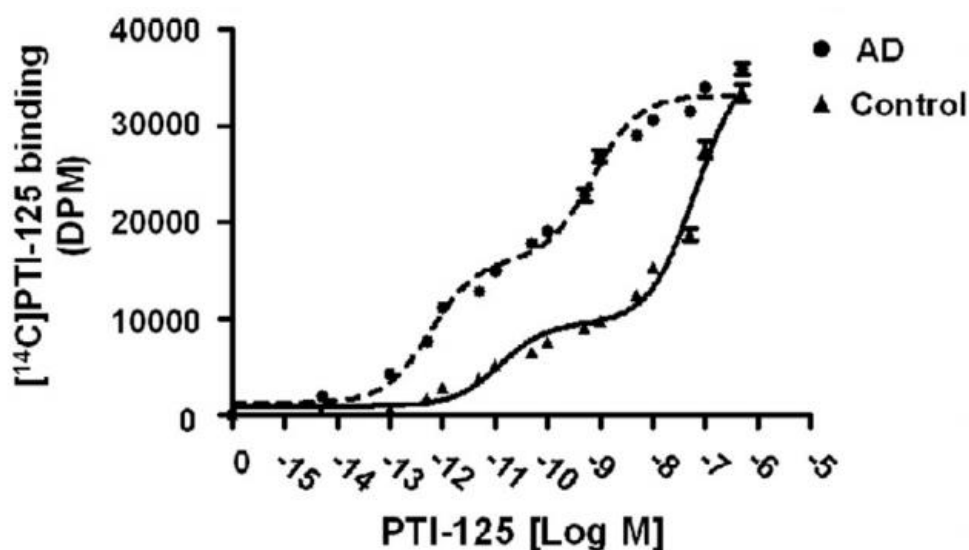
E. Appendix

E.1. Six Additional Areas of Concern

Six further aspects of the research by Drs. Wang and Burns are incompatible with scientific norms, and these claims raise further suspicions. These issues are enumerated below. In addition to the many examples of apparent Western blot manipulation and clinical data misreporting noted above, a number of additional western blots are included at the end of this appendix which raise additional red flags.

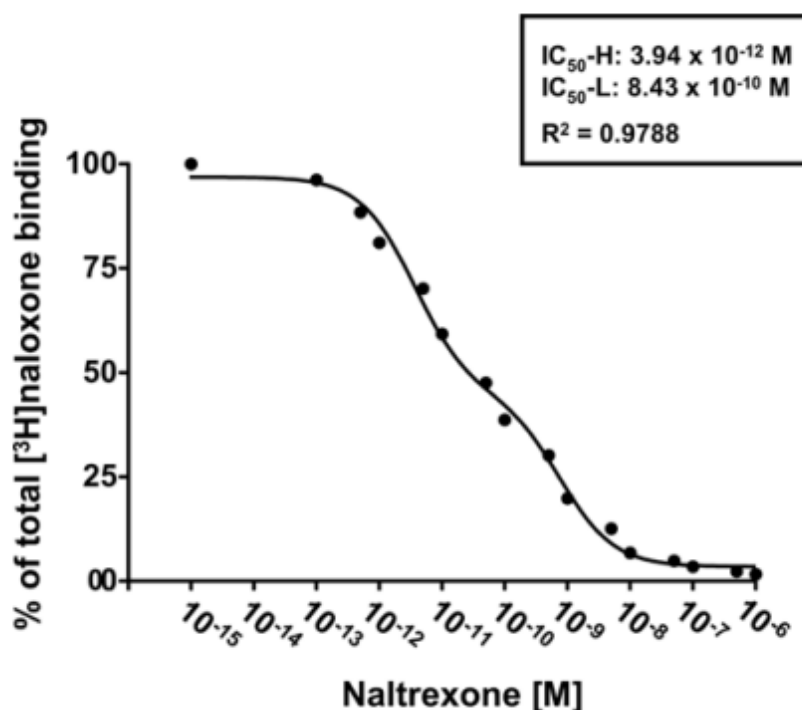
Suspicious Claim #1: Remarkably High Affinity Binding Between PTI-125 and Filamin A

Figure 1B (below) in the *Neurobiology of Aging* 2017;55:99-114 paper claims that PTI-125 has *femtomolar* binding affinity for filamin A in Alzheimer's disease brain. There is scant precedent for a small molecule to bind so potently to a cytoskeletal protein. The claimed affinity seems higher than that of any other small molecule binding to any cytoskeletal protein. Figure 1b in this paper also shows that PTI-125 displacement occurs over 7 orders of magnitude. This "shallow" displacement is highly unusual/unprecedented. An experienced pharmacologist could advise that this is suspicious / implausible. The authors should be asked for the raw data.



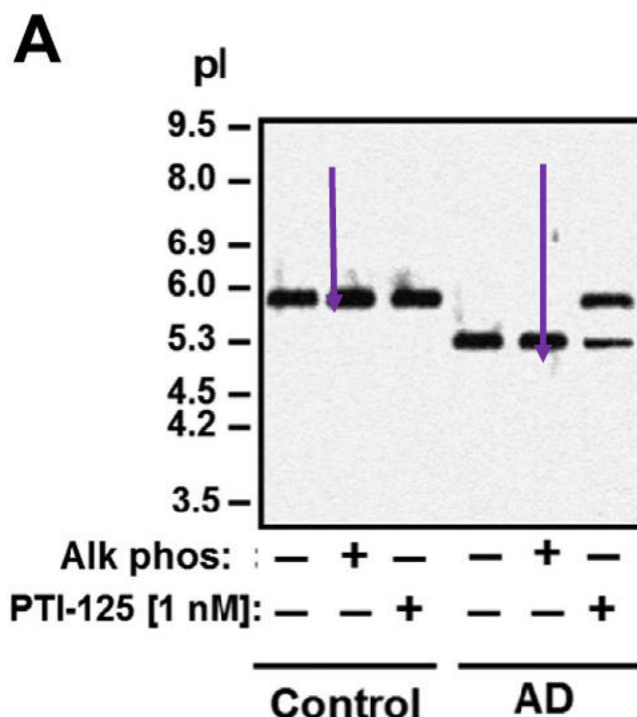
Suspicious Claim #2: Remarkably High Affinity Binding Between Naloxone and Filamin A

Naloxone is an old and intensively studied drug that binds with nanomolar affinity to opiate receptors. Figure 3 (below) of the *PLoS ONE* 2008;3:e1554 paper claims that Naloxone [³H]NLX binds with low *picomolar* affinity to Filamin A. As Filamin A is present in brain, it is puzzling why previous studies have not reported picomolar binding affinity for naloxone in brain. Also unusual is the “shallow” displacement curve in figure 3 that spans 4-5 orders of magnitude. An experienced opiate receptor pharmacologist could advise that this figure is suspicious / implausible. The authors should be asked for the raw data.



Suspicious Claim #3: Isoelectric Focusing Experiments in Multiple Papers Indicate 100% of Filamin in Altered Conformation in Alzheimer's Disease and largely Restored to Correct Conformation by PTI-125

In Figure 2 (below) of the 2017 Neurobiology of Aging 2017 55:99-114 paper, the authors present a gel showing that Filamin A isoelectric point shifts from 5.9 in control to 5.3 in Alzheimer's disease (purple arrows for lanes 1 and 4). This is suspicious for two reasons. First, Alzheimer's disease affects only a small subset of neurons in a diseased brain, so it is scientifically unclear how 100% of Filamin A could shift. Second, isoelectric focusing gels do not typically "look" like the image below. Especially for a 290 kD protein like Filamin A, one would not expect such crisp bands in isoelectric focusing. An experienced biochemist could advise that this figure is suspicious / implausible. This is especially suspect considering the apparent pattern of band manipulation by Drs. Wang and Burns on Western blots. Similar experiments are shown in other publications. The authors should be asked for the raw data.



Suspicious Claim #5: PTI-125/Simufilam Improves Memory in a Mouse Model of Alzheimer's Disease

In *Neurobiol Aging* 2017;55:99-114, figure 9 shows a pre-clinical study of simufilam in a mouse model of AD and misinterprets the data as showing “improvements in memory.” It is dubious that any legitimate experiment approximating the methodology described could yield the reported result.

For instance, the third panel (shown below) shows data from a Y-maze which is used to assess memory in mice. Animals are placed in an apparatus made of three tubes which interlock in the middle, like a Mercedes Benz emblem. The test is based on two observations about mouse behavior – (1) when they are put in a new environment, they will explore it and (2) they prefer to explore a new area rather than areas recently explored. After a mouse explores one arm of the y-maze and returns to the center, they must decide which of the other two tubes to enter next. A normal mouse will generally avoid the tube that was most recently explored resulting in a pattern where they spontaneously alternate between each of the tubes. Normal mice would be expected to follow this pattern 70-80% of the time as a rough estimate. If a mouse has memory impairment, the selection of which tube to enter will be random, and the alternation rate should be about 50%. Remarkably, wild type mice and transgenic mice in Wang's study spontaneously alternated less than 20% of the time, which is an atypical result. Drug treatment in 6 month old transgenic mice, increased the rate of alternation to over 30%. This raises a number of issues: (1) this pattern of results is unlikely to occur and suggests, at the least, the experiment was conducted incorrectly, and (2) if the result were legitimate, the drug treatment changing the mice's behavior to closer to 50% spontaneous alternation (i.e., closer to random) would be more accurately interpreted as evidence of *worse* memory performance.

A mouse neurobehavioral specialist would likely advise that there are significant

problems with all of the behavioral and memory data presented in the paper. Importantly, this is the only pre-clinical cognitive/memory data that has been published supporting simufilam's efficacy as a cognitive enhancer. This data should be audited.

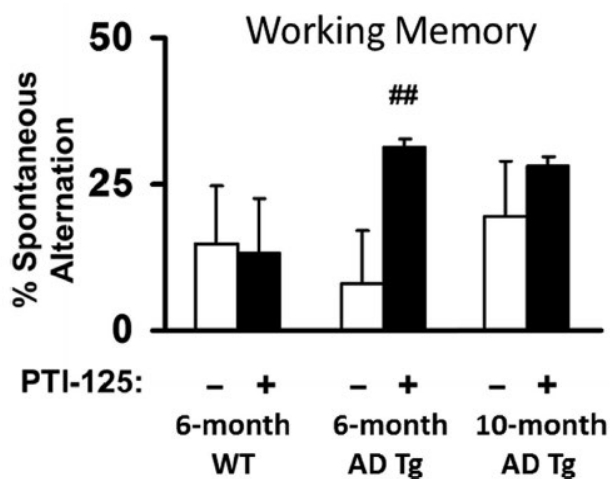
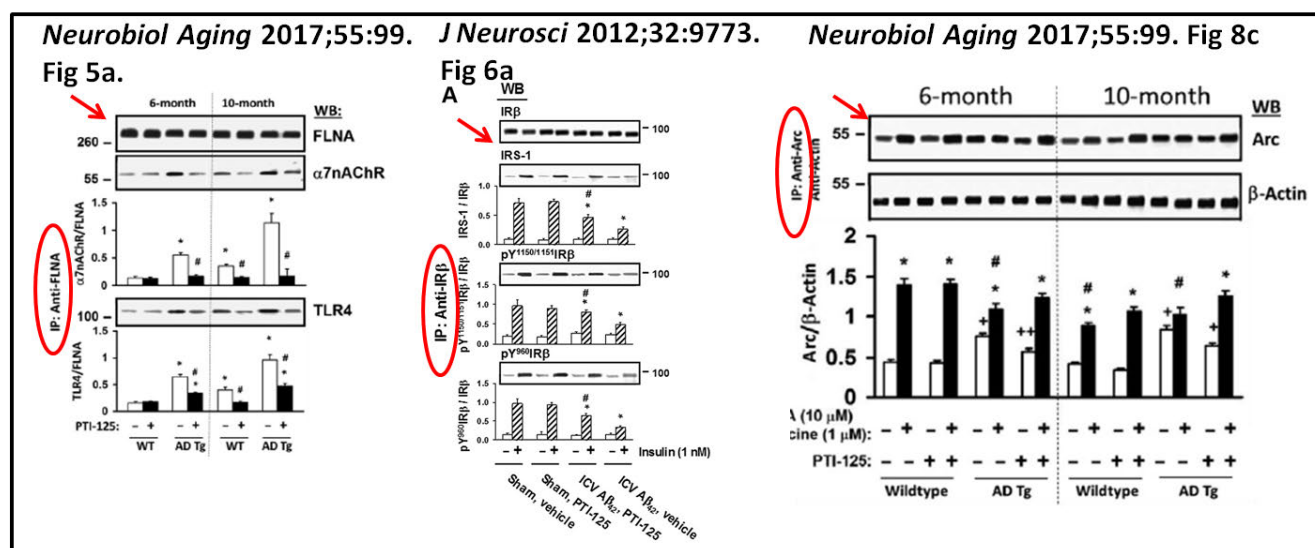


Fig. 9. PTI-125 via drinking water improved nesting behavior in 6-month 3xTg AD mice. Compared to 6-month wildtypes, spatial memory assessed using Y-maze with extra-maze visual cues was impaired in 3xTg AD mice of both ages but not in 3xTg AD mice of either age treated with PTI-125. Additionally, PTI-125 significantly improved spatial memory in 10-month 3xTg AD mice. PTI-125 significantly improved working memory assessed by Y-maze spontaneous alternation paradigm in the 10-month but not 6-month 3xTg AD mice. $n = 5$. * $p < 0.01$, ** $p < 0.05$ versus 6-month-old vehicle-treated wild-type group; # $p < 0.01$, ## $p < 0.05$ versus respective vehicle-treated group. Abbreviations: AD, Alzheimer's disease; 3xTg, triple-transgenic.

Suspicious Claim #6: PTI-125/Simufilam Blocks the Interaction Between β -amyloid and $\alpha 7$ - Nicotinic Acetylcholine Receptors.

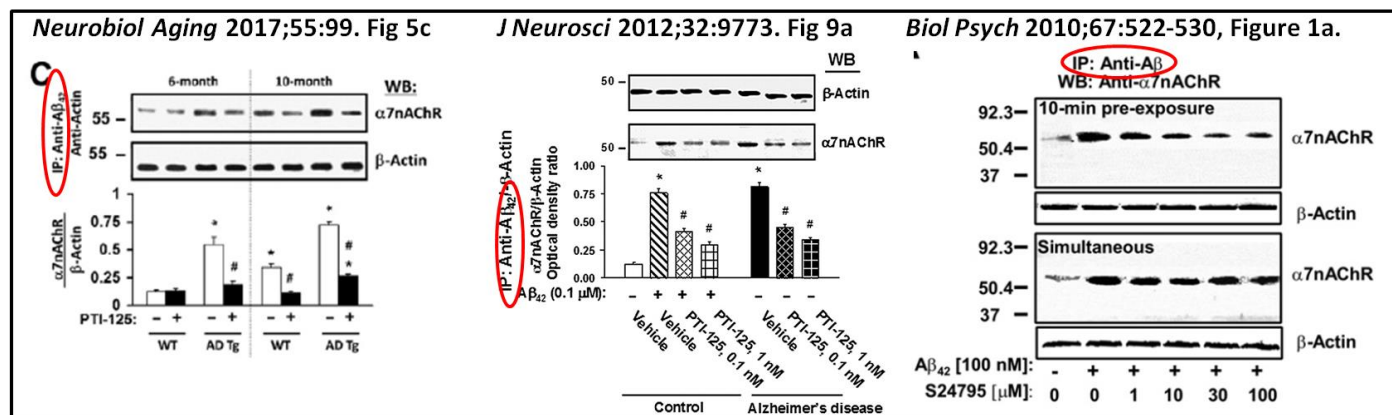
Most of the western blots in these papers take advantage of a process known as co-immunoprecipitation. In this technique, tissue is ground up until it is liquefied and an antibody is used to catch a protein of interest. When the antibody and the protein it binds are isolated, any other proteins that bind to the target protein will also be isolated. This approach enables scientists to evaluate if two proteins interact with each other.

As a standard laboratory practice, the first step in evaluating a co-immunoprecipitation sample is to perform a western blot to confirm that the target protein was captured. It obviously makes little sense to proceed to analyze other proteins, if the target protein was not captured. Drs. Wang and Burns consistently follow this convention. Examples are shown below.

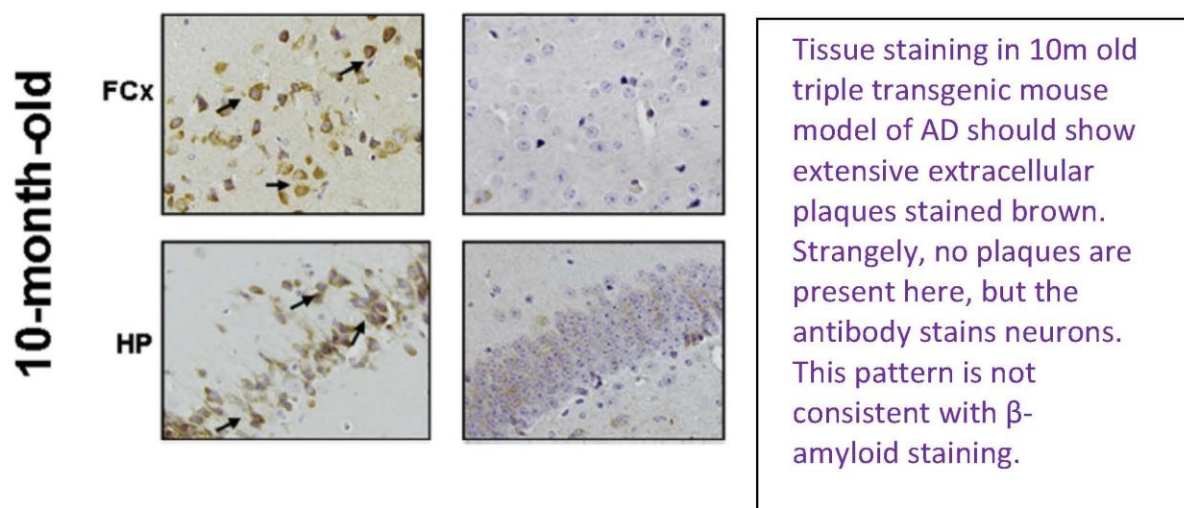


However, there is one exception. The control blot demonstrating efficient capture of the target protein is omitted every time co-immunoprecipitation of β -amyloid is presented. A series of these co-immunoprecipitation experiments is shown below, each omitting this necessary blot. There are numerous other examples throughout the publications. The authors used this technique to build the case that β -amyloid interacts with $\alpha 7$ -nicotinic acetylcholine receptors. The fact that

they deviated from a standard of practice they strictly follow in other settings is suspicious. It is also noteworthy that a significant fraction of the western blots shown elsewhere in the document to have been manipulated are associated with β -amyloid co-immunoprecipitation experiments (the center and right example in the figure following also contain two of the more-egregious examples of western blot falsification).



The authors appear to have used the same β -amyloid antibody to perform tissue staining in a transgenic mouse model of AD. Despite the authors' claims, this staining does not show any extracellular β -amyloid plaques (see following figure). It is clear that this antibody is malfunctioning in the tissue staining. Consequently, it is reasonable to be concerned that it is non-functional in the co-immunoprecipitation as well.



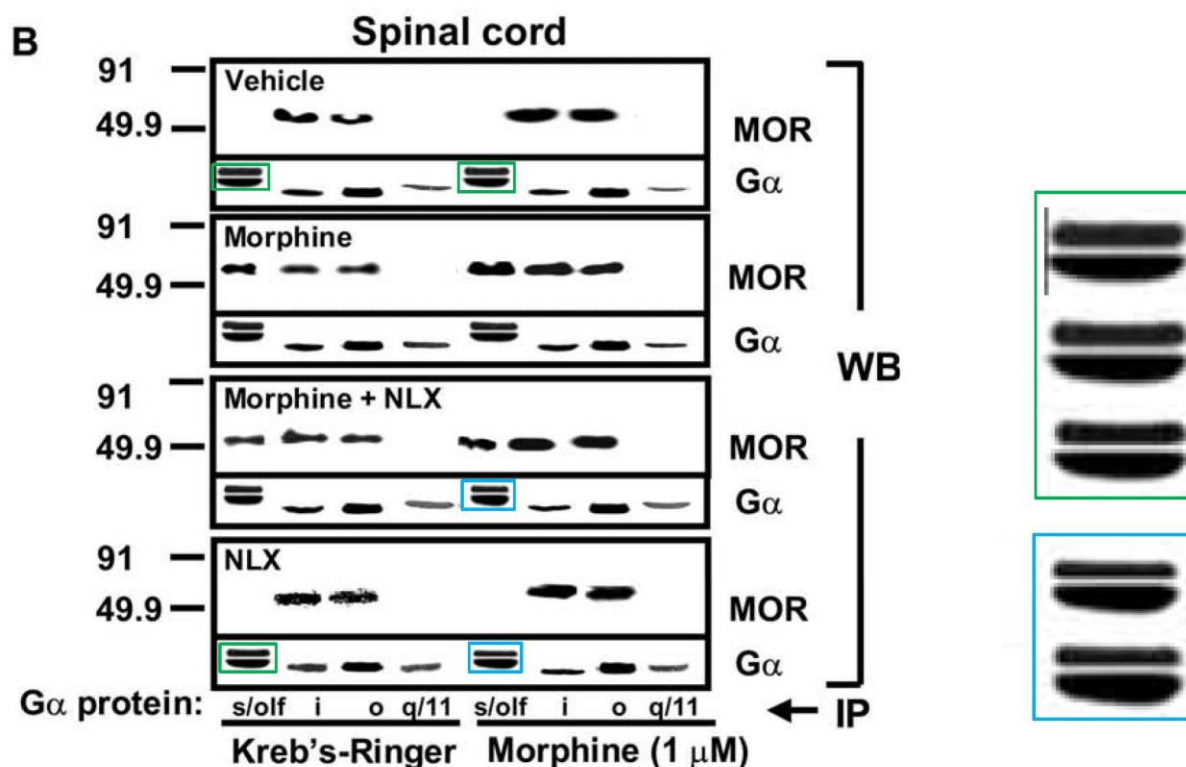
These observations strongly call into question the assertion that PTI-125/simufilam alters the interaction between β -amyloid and any of its supposed targets. The authors should show clear validation of effective immunoprecipitation of β -amyloid in every one of these instances.

E.2. Additional Suspicious Western Blots:

In the 2005 Wang and Burns paper *Neuroscience* 135 247–261, one can see bands with unique features that appear spliced into multiple gels. This suggests that experiments were not conducted as described. One example of this is Figure 5B (below).

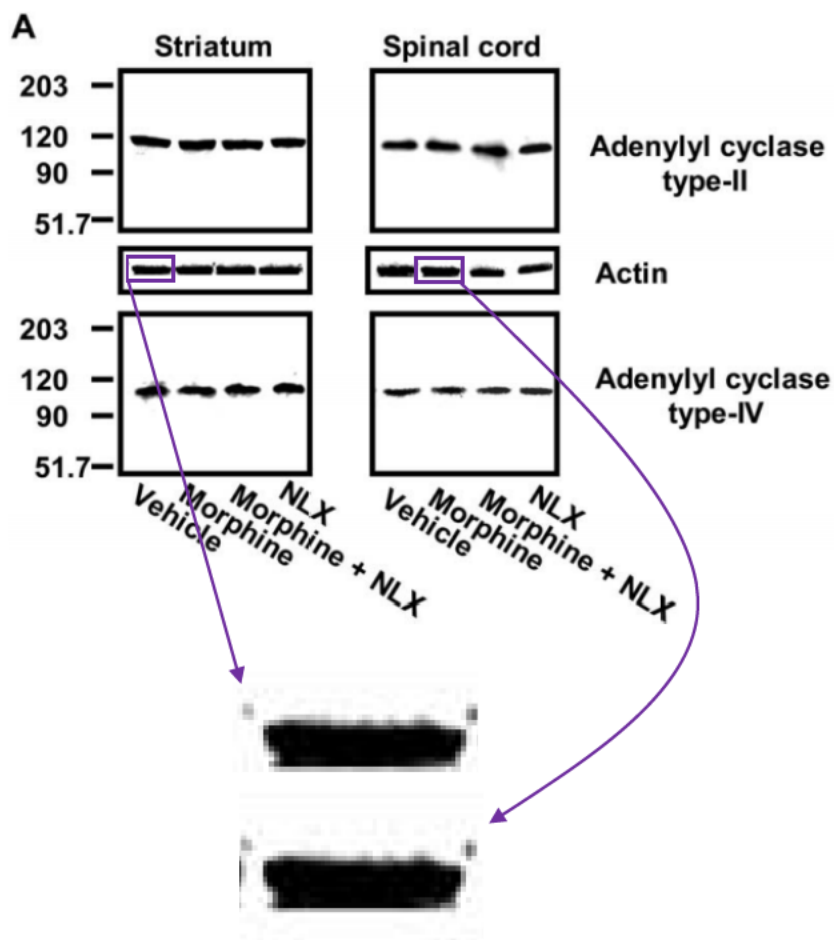
In this Western blot, the $G\alpha$ bands in the s/olf lanes have peculiar “double decker” shapes. Close inspection reveals that three of these double decker bands (green) are more similar to each other than would be expected AND another two of these double deckers (blue) are also more similar to each other than would be expected.

The congruence of these oddly shaped bands are unlikely to have occurred by chance and raises the possibility of band duplication and data manipulation.



Another striking example of probable band duplication occurs in Figure 12a of this paper. Here, the actin band from the striatum brain region treated with “Vehicle” is indistinguishable

from the actin band from the spinal cord region treated with Morphine. The uncanny resemblance of these “battleship” shaped bands and the precise alignment of the dot artifacts suggest that one or both were intentionally inserted, perhaps with the intention of misrepresenting the results.

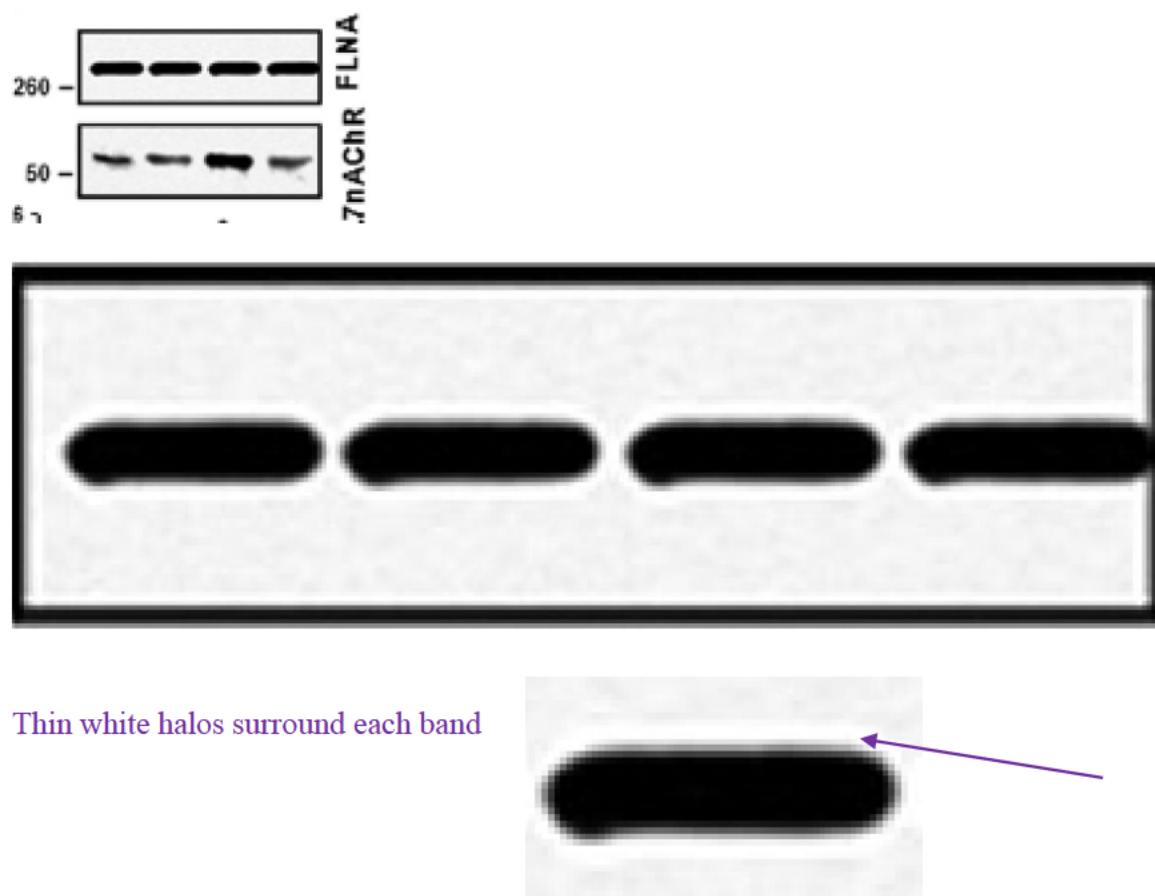


The seemingly identical battleship shape of these protein bands from different

It is recommended that the original full-length images **with appropriate molecule weight markers to validate band migration** from this paper be requested and analyzed. If they are not available, this paper should be retracted.

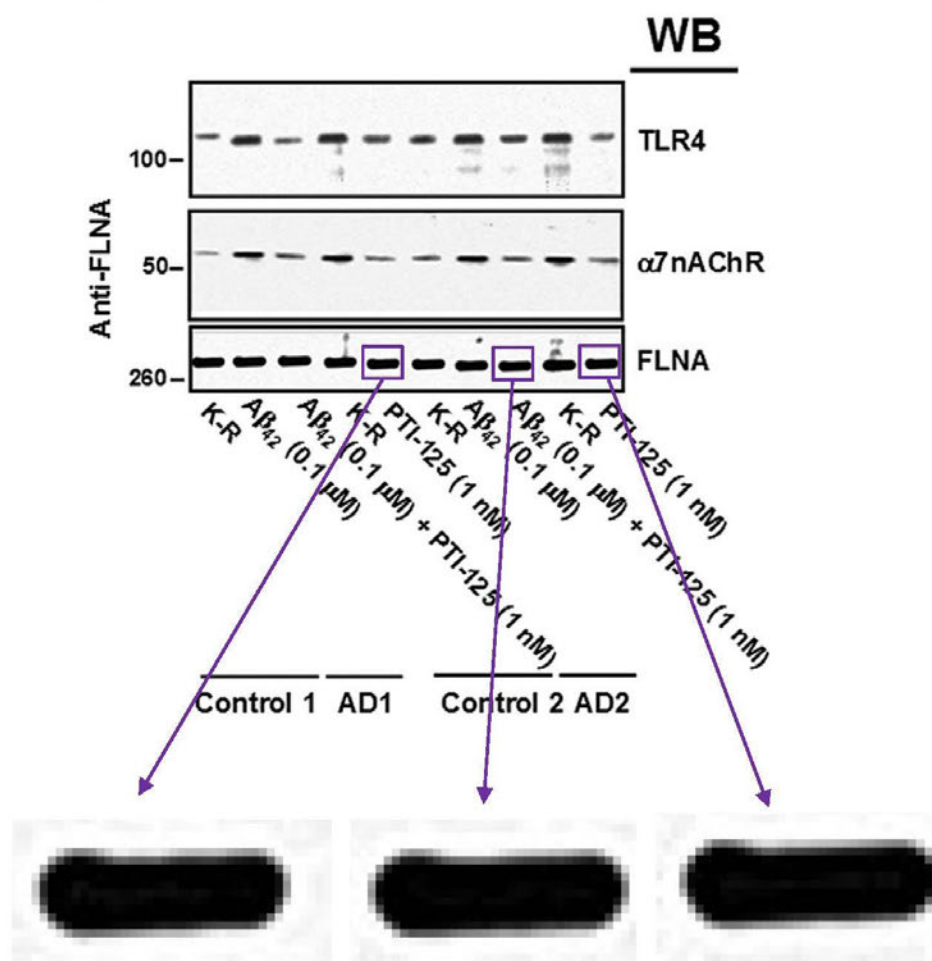
Additional examples of probable band duplication in *J Neurosci* 2012;32:9773-9784.

One can see that the four Filamin A bands in the bottom set of Figure 1A appear to be identical to each other. This degree of similarity is unlikely to occur by chance, and the thin white borders surrounding each band could be due to merging multiple images in a photo editing software.



Another important consideration is that the Wang and Burns 2012 Journal of Neuroscience paper uses human specimens from Alzheimer's disease patients. Any intentional misuse of such material violates the World Medical Association Declaration of Helsinki regarding ethical use of donated human tissue.

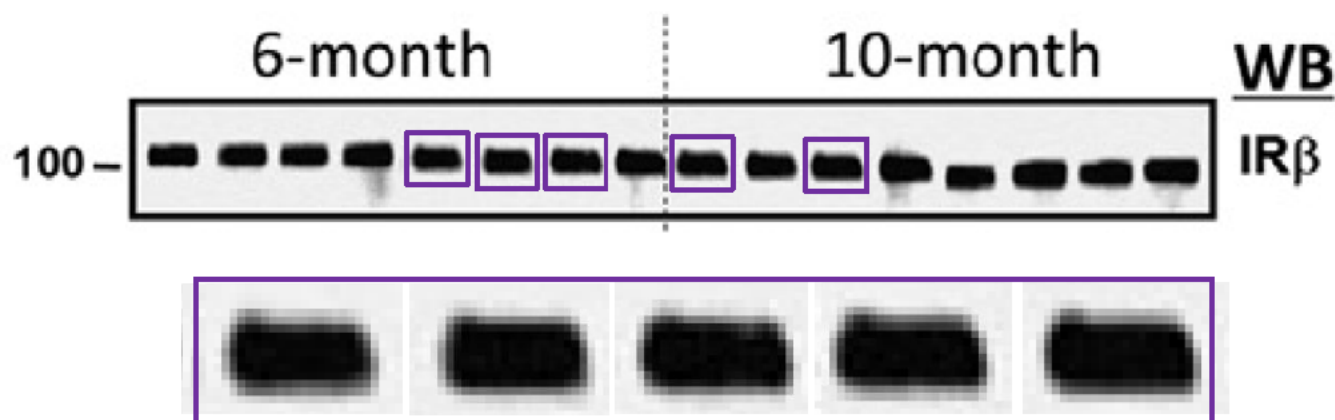
Figure 12A (below) of the Journal of Neuroscience paper, used human Alzheimer's disease tissue to establish the SavaDx biomarker and effects of PTI-125/simufilam. The ten filamin A (FLNA) bands appear identical in size and shape. As protein bands on Western blots typically have unique features, ten consecutive indistinguishable bands are exceedingly unlikely to occur by chance and were probably manually duplicated.



All ten virtually indistinguishable FLNA bands are exactly 11 pixels high and 32 pixels wide. Three examples are magnified here for illustration.

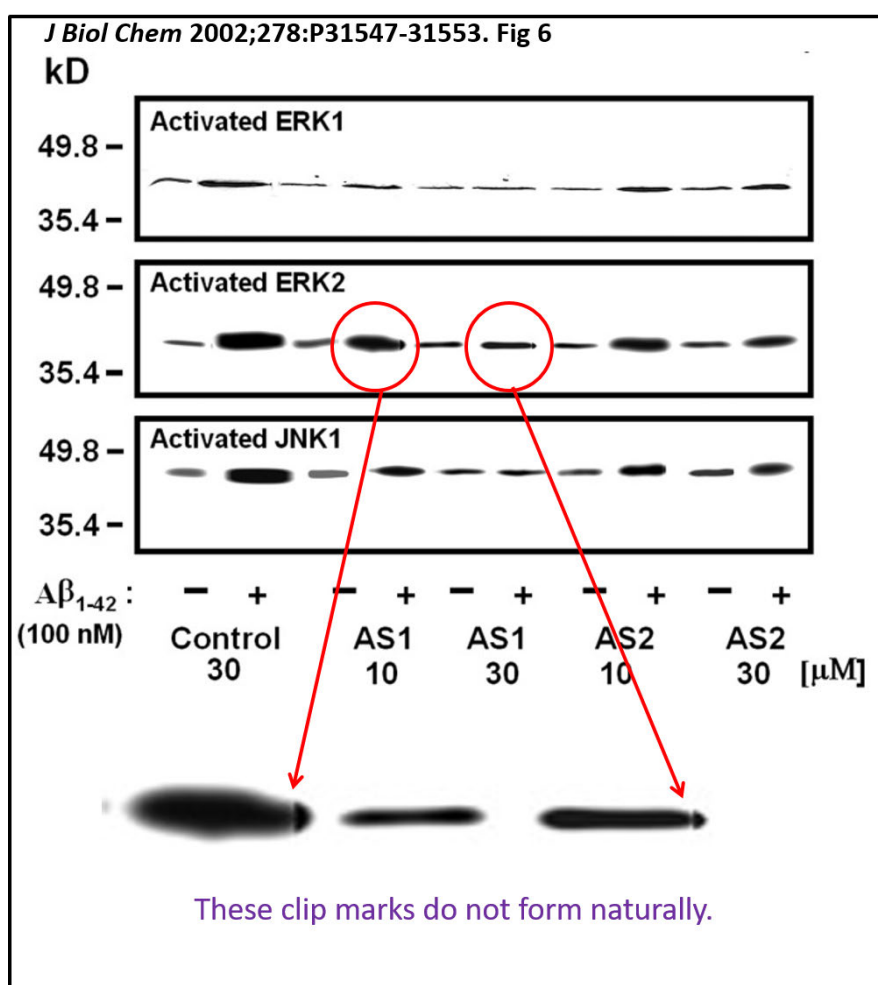
A subsequent paper alleging to connect PTI-125 with Alzheimer's disease is 2017 Neurobiol Aging 55: 99-114. Again, this paper largely comprises a series of overexposed, and apparently manipulated and cropped Western blots. Band duplication appears to occur throughout this paper.

As just one of many examples, Figure 8B contains Western blots from mice treated with PTI-125. The top blot displays a western blot using an antibody for IR β (see label on the right). The similarity in size and shape of the bands in the purple boxes seemingly could not have occurred by chance. This and many other blots in this paper appear to have been manipulated.



These five indistinguishable bands are all exactly 12 pixels high and 20 pixels wide.

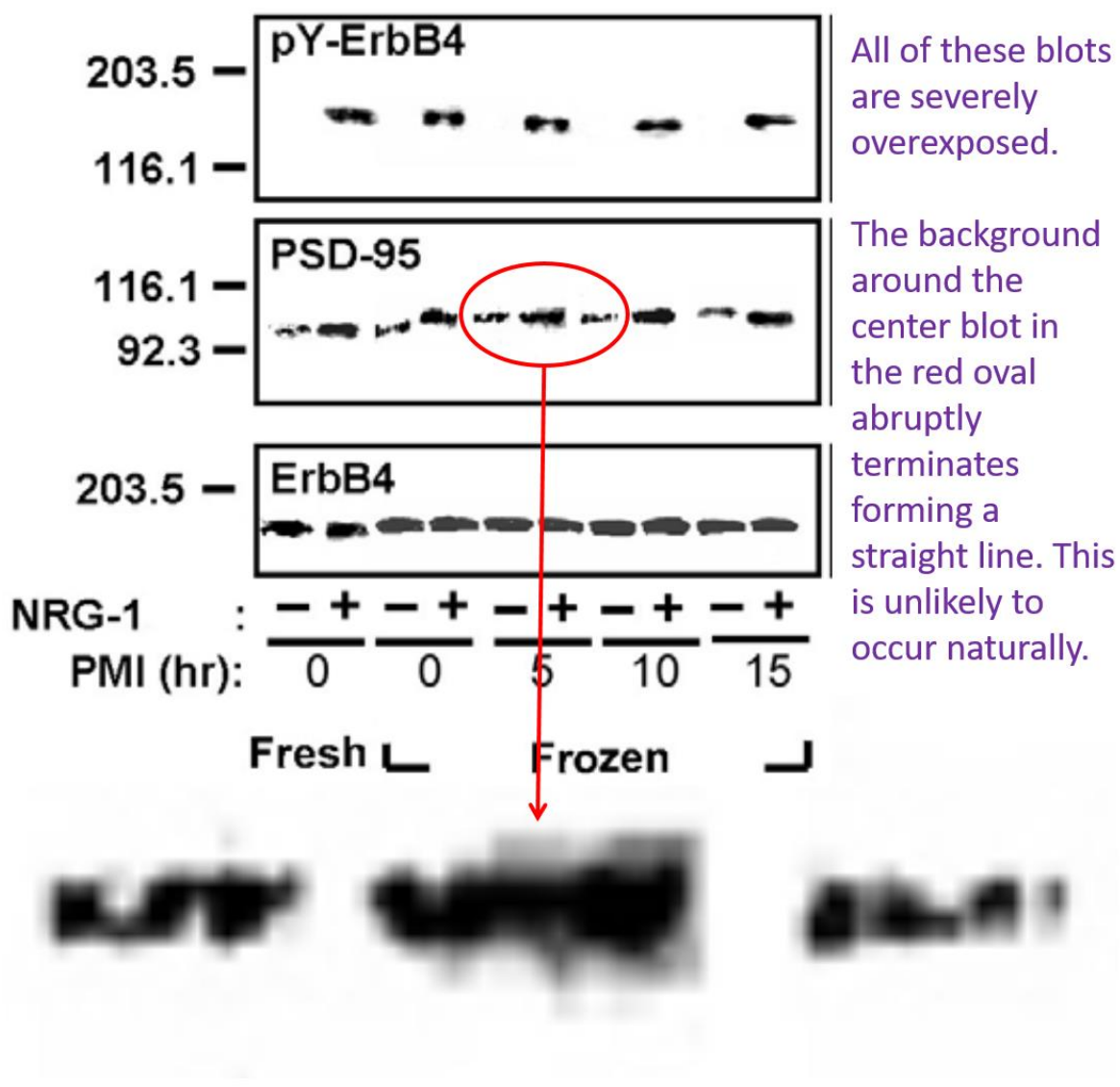
The following example of a manipulated western blot occurred earlier than the examples referenced in the primary document. Dr. Wang was the first author of this 2002 paper in the *Journal of Biological Chemistry* 278:P31547-32553 and it is one of the few examples presented in this document without Dr. Burns as a co-author. The apparent manipulation applied to this blot is similar to that shown in C2.2.1. The marks highlighted at the red arrow do not form naturally and are likely produced by clipping multiple blots together. These blots are also severely overexposed. This study purports to establish that β -amyloid binding to the $\alpha 7$ nicotinic acetylcholine receptor induced tau phosphorylation, which is one of the pathways simufilam is supposed to interrupt.



Because of the contemporaneous examples of western blot manipulation, we undertook an evaluation the author's highest profile publication, a 2006 publication in *Nature Medicine* 12:824-828. Dr. Wang is the co-first author of this work. There are numerous suspicious appearing blots in this publication, as well. Again, blots are suspiciously over-exposed. In the supplementary material accompanying that published manuscript, we encounter the blot shown below. The background has more-or-less been obliterated, except for a small area circled in the red oval. Linear termination of the background signal is suspicious for the original blot having been cut and reassembled. Because of the low quality of this image, we evaluated the images in the main manuscript (which are higher quality), to assess for evidence of tampering.

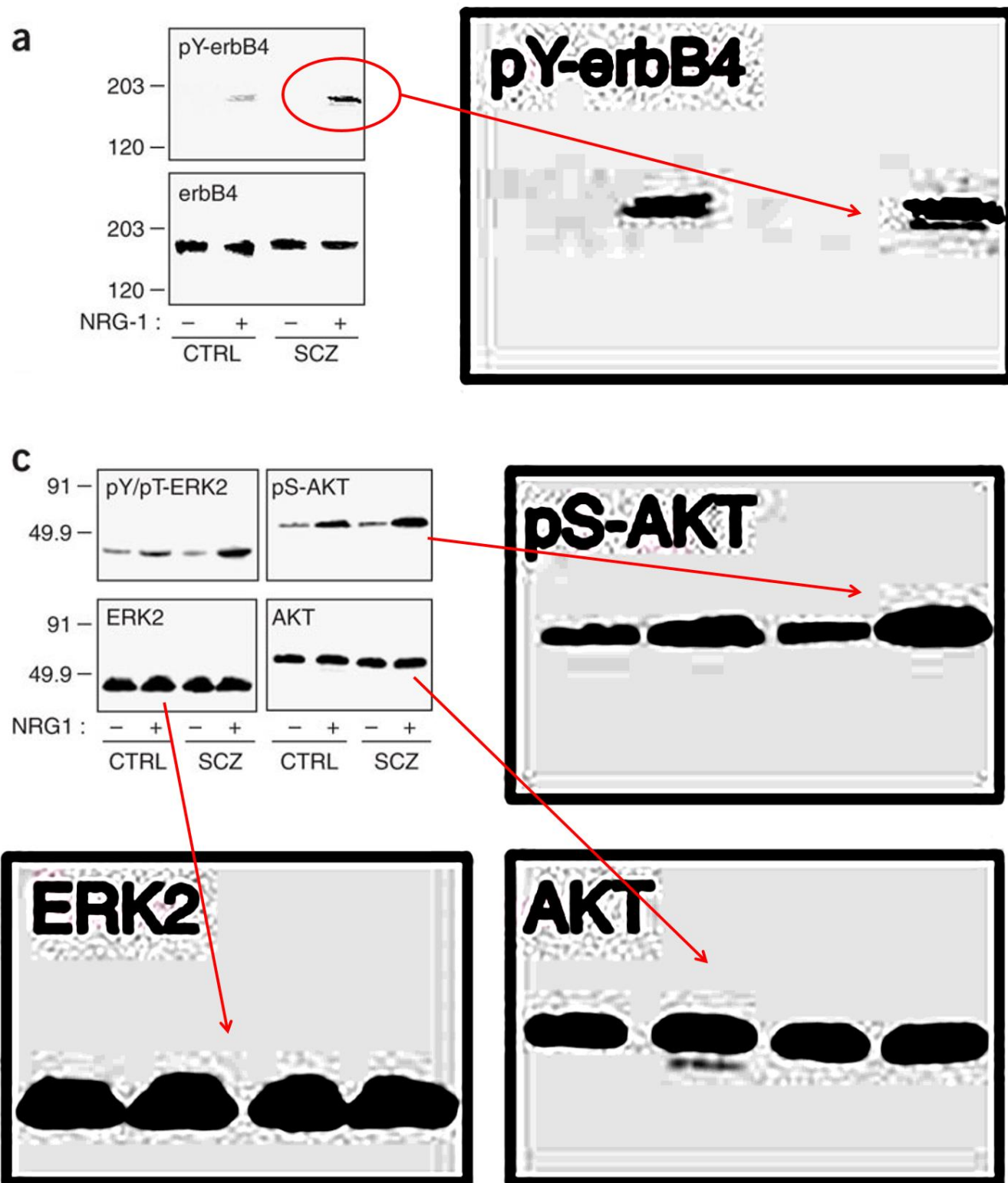
Importantly, this manuscript purports to establish the validity of the functional characterization of NMDA receptor signaling in post-mortem, frozen human brain material which is called into question in section C.3.1. Evidence of tampering with this evidence further calls into question the validity of this unusual technique.

Nature Med. 2006;12:824-828. Supplementary Figure 2



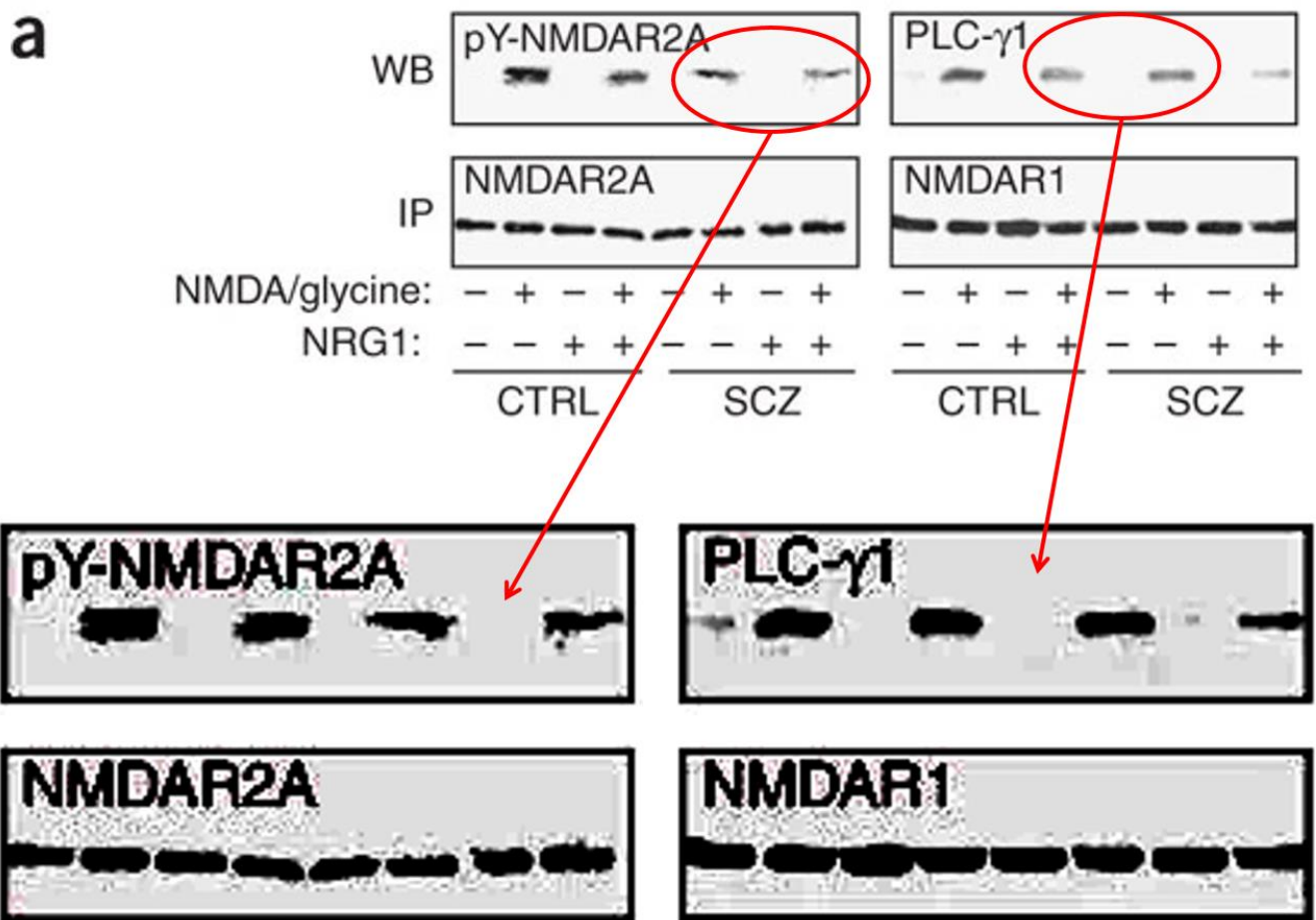
The images in the main text are of higher quality, enabling clearer evaluation. Increasing

Nature Med. 2006;12:824-828. Figure 2.



the contrast in the images published as Figure 4 (below) clearly reveals evidence of linear cuts in the blots. Importantly, there is clearly a smooth background between the two darker bands and a textured background only behind the dark bands. This was not likely done for cosmetic reasons, it strongly suggests a manufactured/fraudulent result. There is no legitimate explanation for this pattern of findings. This high-profile manuscript should be reviewed by the publisher and retracted. All subsequent manuscripts built on this technique should likewise be reviewed.

Nature Med. 2006;12:824-828. Figure 4.



From: Feuerstein, Adam <adam.feuerstein@statnews.com>
Sent time: 08/31/2021 08:04:25 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Reporter query re: Cassava Sciences
Attachments: b2081ad1-0cc5-4e38-a546-1083b91f0843.pdf

Professor Wang --

I'm a reporter with STAT, a digital publication that covers health, medicine and the life sciences. I'm contacting you to see if you're willing to answer some questions about the research you conducted and published on the experimental Alzheimer's drug simufilam, in collaboration with Cassava Sciences.

As you're aware, questions have been raised about the scientific integrity and credibility of papers that you co-authored, along with Cassava's Lindsay Burns.

In particular, I'd like to better understand the specific role that you played in analyzing CSF samples taken from patients in Cassava's phase 2b study. When the "re-analysis" of those CSF samples were announced in September 2020, Cassava said the work was done by an "academic lab" without offering any further details.

Did you perform the biomarker analysis on those CSF samples in your lab at CUNY Medical School?

I've attached a copy of a research paper describing the results of the phase 2b study that was submitted to a preprint server in February 2021. You are the lead author on the paper. Inside the Oversight and Settings section of the paper, it says, "CSF samples were analyzed at CUNY School of Medicine."

Can you confirm that your lab performed the CSF biomarker analysis?

Thank you --

Adam Feuerstein

--

Adam Feuerstein

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Effects of simufilam on cerebrospinal fluid biomarkers in Alzheimer's disease: A randomized clinical trial

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Research

Keywords: filamin A, tau hyperphosphorylation, neuroinflammation, blood-brain barrier

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Abstract

BACKGROUND

Simufilam is a first-in-class drug candidate targeting altered filamin A, a proteopathy in Alzheimer's disease. The primary objective of this Phase 2 clinical trial was to evaluate the effects of simufilam on cerebrospinal fluid (CSF) biomarkers in Alzheimer's disease patients. A secondary objective was to assess cognitive enhancement.

METHODS

In a randomized, placebo-controlled trial conducted across 9 clinical sites in the US, 64 mild-to-moderate Alzheimer's disease patients were randomized to simufilam 50 or 100 mg b.i.d. or placebo for 28 days. Clinical diagnosis was confirmed by CSF total tau/amyloid-beta₁₋₄₂ ($A\beta_{42}$) > 0.28. Co-primary endpoints were changes in CSF $A\beta_{42}$, total tau, phospho-tau (P-tau181), neurogranin, neurofilament light chain, and YKL-40. Secondary endpoints included additional CSF biomarkers assessing neuroinflammation and blood brain barrier integrity, and tests of episodic and spatial working memory.

RESULTS

Adjusting for multiplicity of the six co-primary endpoints ($p < 0.008$ versus placebo required for significance), simufilam 50 and 100 mg significantly reduced CSF levels of total tau, hyperphosphorylated tau (P-tau181), neurogranin, neurofilament light chain and YKL-40. Simufilam 50 mg significantly increased CSF levels of $A\beta_{42}$. On secondary CSF biomarker endpoints, both doses of simufilam significantly reduced IL-6, soluble TREM2 (triggering receptor expressed on myeloid cells-2), HMGB1 (high mobility group box-1), albumin and immunoglobulin G. All but one patient improved from baseline across biomarkers. Simufilam 50 and 100 mg showed effect sizes versus placebo (0.23–0.46) in change from baseline in episodic memory and spatial working memory. Episodic memory improvements correlated most strongly with decreases in P-tau181 ($R^2 = 0.48$). Simufilam was safe and well tolerated. Target engagement was demonstrated by filamin A linkages to nicotinic acetylcholine receptor subtype $\alpha 7$ ($\alpha 7nAChR$) and toll-like receptor 4 (TLR4) in lymphocytes.

CONCLUSIONS

Simufilam was safe and well tolerated and significantly improved eleven CSF biomarkers in patients with Alzheimer's disease, implying biological evidence of disease modification. Simufilam will be further evaluated in large, definitive clinical trials.

TRIAL REGISTRATION:

ClinicalTrials.gov Identifier NCT04079803.

Background

There are no approved treatments to slow the progression of Alzheimer's disease, expected to affect 13.8 million in the U.S. by 2050.¹ Biomarkers may facilitate drug development in Alzheimer's disease by quantifying disease stage, demonstrating target engagement, and supporting disease modification.²

Core CSF biomarkers of Alzheimer's disease are amyloid-beta1-42 ($A\beta_{42}$), total tau and phospho-tau181 (P-tau181).^{3,4} $A\beta_{42}$ decreases while tau and phosphorylated tau, including P-tau181, increase as disease progresses and cognition declines. Neurogranin and neurofilament light chain, indicating damage to dendrites and axons respectively, are used to track disease progression.⁵⁻⁷ Interestingly, neurogranin appears specific to Alzheimer's disease.⁷ The current clinical trial measured CSF biomarkers in Alzheimer's disease dementia patients to evaluate drug candidate simufilam.

Simufilam represents a novel approach to combat amyloid toxicity and resulting neurodegeneration in Alzheimer's disease. Soluble $A\beta_{42}$ initiates a predominant pathogenic pathway by binding $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7nAChR$), the only known sub-nanomolar-affinity binding site of soluble $A\beta_{42}$.⁸⁻¹⁰ This femtomolar interaction poses enormous competition for any agent aiming to reduce soluble $A\beta_{42}$ interactions. $A\beta_{42}$ binds and signals through this receptor to activate kinases that hyperphosphorylate the protein tau,¹⁰⁻¹³ impairing tau's ability to stabilize microtubules. This loss of functional tau is a primary driver of the neuronal degeneration and cognitive impairment in Alzheimer's disease.¹⁴

Without directly competing with the femtomolar binding of $A\beta_{42}$ to $\alpha 7nAChR$, simufilam disrupts this ultra-high-affinity interaction by binding a critical accomplice to $A\beta_{42}$: an altered conformation of filamin A. Filamin A is an intracellular scaffolding protein that is highly expressed in brain and interacts with over 90 proteins to coordinate signaling processes.¹⁵ $A\beta_{42}$ initiates toxic signaling by binding $\alpha 7nAChR$ to recruit filamin A.^{16,17} Without directly contacting filamin A, and likely working through $\alpha 7nAChR$ and other receptors that link to or recruit filamin A, $A\beta_{42}$ induces the altered conformation of the filamin A protein.¹⁷ Simufilam binds altered filamin A, restores its normal shape and disrupts the aberrant filamin A – $\alpha 7nAChR$ linkage, $A\beta_{42}$'s femtomolar binding to $\alpha 7nAChR$ and the ensuing toxic signaling that hyperphosphorylates tau.^{17,18}

$A\beta_{42}$ also binds the toll-like receptor 4 (TLR4) co-receptor cluster-of-differentiation14 (CD14)¹⁹ to recruit and alter filamin A.¹⁷ The filamin A – TLR4 linkage enables persistent TLR4 activation by $A\beta_{42}$, causing inflammatory cytokine release and neuroinflammation. Simufilam's reversal of the filamin A proteopathy also blocks this $A\beta_{42}$ -induced neuroinflammation.^{17,18}

In a previous open-label, 28-day trial in patients with mild-to-moderate Alzheimer's disease dementia (NCT03748706), simufilam significantly reduced CSF total tau, P-tau181 and biomarkers of neurodegeneration and neuroinflammation in all patients, with no safety issues.²⁰ Biomarker reductions implied reduced disease pathophysiology and neurodegeneration, consistent with simufilam's mechanism of action and preclinical data. Based on encouraging prior clinical trial results, we evaluated simufilam in a randomized, double-blind, placebo-controlled Phase 2 trial. We hypothesized simufilam treatment would impact CSF biomarkers and may enhance cognition.

Methods

Patient Population

Patients were 50–85 years old, diagnosed with probable Alzheimer's disease dementia according to National Institute on Aging (NIA)/Alzheimer's Association (AA) criteria and a Mini-Mental State Exam (MMSE) score ≥ 16 and ≤ 26 . Diagnosis was confirmed by CSF total tau/ $A\beta_{42} \geq 0.28$, a ratio selected to exclude dementia due to other causes (0.28 is intermediate between early and late mild cognitive impairment in amyloid-confirmed patients from the Alzheimer's Disease Neuroimaging Initiative²¹). Patients could be receiving acetylcholinesterase inhibitors, memantine and other medications if stable. Chronic opioids, tricyclic antidepressants, monoamine oxidase inhibitors, nicotine therapy (or smokers) were exclusions, as were uncontrolled medical illnesses, other neurodegenerative diseases, or clinically significant laboratory results.

Trial Design

This double-blind, placebo-controlled, trial randomized 64 patients 1:1:1 to placebo or simufilam 50 or 100 mg oral tablets b.i.d. for 28 days. Patients, caregivers, clinic staff, the study sponsor and the laboratory analyzing biomarkers were blind to treatment. A randomization algorithm was generated by an outside vendor using Interactive Response Technology. Doses were selected by body surface area conversion of effective daily doses in mouse efficacy models and prior clinical experience. Sample sizes of 20 per arm were selected based on highly significant changes from baseline in many of the same CSF biomarkers by paired t-test in a prior open-label trial in mild-to-moderate Alzheimer's disease dementia patients.²²

After initial screening, a second screening visit included a CSF draw and practice cognitive test. Cognitive tests were conducted Days 1 and 28. Blood samples were collected Days 1, 7, 14 and 28, with the Day 28 blood sample following the second CSF draw for CSF/plasma ratios of simufilam. Electrocardiograms and physical examinations were conducted on Days 1 and 28.

Oversight and Settings

This trial was conducted between September 2019 and March 2020 at nine U.S. sites. An independent Data and Safety Monitoring Board approved the protocol and assessed safety mid-study. CSF samples

were analyzed at City University School of Medicine. Plasma was analyzed with a qualified assay at Worldwide Clinical Trials Bioanalytical Sciences. Data were analyzed by a data management and statistics contractor. Data was 100% monitored by independent clinical research associates. No protocol changes were made.

Assessments

Levels of eleven CSF biomarkers in the screening and Day 28 samples were measured. Six CSF biomarkers were designated primary: biomarkers of Alzheimer's disease pathology ($A\beta_{42}$, total tau and P-tau181), neurodegeneration (neurofilament light chain and neurogranin) and neuroinflammation (YKL-40). Also assessed were interleukin-6, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), and high mobility group box 1 (HMGB1). These nine biomarkers were measured using commercial enzyme-linked immunosorbent assay plates and an automated plate reader, with samples assayed in triplicate. CSF albumin and immunoglobulin G assessed blood-brain barrier integrity and were measured by immunoblot with densitometric quantitation. Target engagement was evaluated by measuring filamin A linkages to $\alpha 7nAChR$ and TLR4 in patient lymphocytes by co-immunoprecipitation as described.¹⁷

Cognition was assessed on Day 1 and Day 28 by the Paired Associates Learning (an episodic memory test) and Spatial Working Memory tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Both tests increase progressively in difficulty, with errors imputed for levels not reached. Reductions in the total error scores indicate improvement. The CANTAB Reaction Time test assessed psychomotor speed in milliseconds.

Safety was assessed by adverse event monitoring, clinical laboratory tests, electrocardiography, physical examinations and the Columbia-Suicide Severity Rating Scale.

Outcomes

The six co-primary outcome measures were changes in CSF $A\beta_{42}$, total tau, P-tau181, neurogranin, neurofilament light chain, and YKL-40 levels from screening to Day 28. These six biomarkers were prospectively listed in the trial registration. $A\beta_{42}$, total tau and P-tau181 are considered core biomarkers of Alzheimer's disease pathology. Neurogranin and neurofilament light chain are intracellular proteins in dendrites and axons, respectively, that indicate neurodegeneration when found in CSF. YKL-40 is a glycoprotein involved in tissue remodeling after inflammation. Secondary biomarker outcomes included changes in CSF interleukin-6, sTREM2, HMGB1, albumin and immunoglobulin G. Interleukin-6 is an inflammatory cytokine. A marker of microglial-induced inflammation, sTREM2 is the ectodomain of the transmembrane receptor TREM2 that is cleaved and shed by microglia when activated during inflammation.²³ HMGB1 is a damage-associated molecular pattern protein released by necrotic cells and actively secreted by immune cells to further neuroinflammation and neurite damage.²⁴ Finally, albumin and immunoglobulin G are blood proteins that indicate blood-brain barrier compromise when found in CSF.²⁵

Secondary cognitive outcome measures were drug-placebo differences in change from Day 1 to Day 28 in total errors on Paired Associates Learning and Spatial Working Memory tests. The Reaction Time test exploratory outcome was median response time in milliseconds.

The target engagement assay measured changes in filamin A linkages to $\alpha 7$ nAChR and TLR4 in patient lymphocytes from Day 1 to Day 28.

Statistical Analysis

The pre-specified analysis for biomarkers was drug-placebo differences in change from baseline, analyzed by the General Linear Model for the analysis of covariance (ANCOVA) with a two-sided 95% confidence interval and baseline CSF measurement as the covariate. Multiplicity of the six co-primary endpoints was addressed by the significance requirement: $p < 0.008$ (i.e., $p < 0.05/6$).

The Full Analysis Set included all subjects with two CSF samples. Although plasma samples were collected at all visits to confirm compliance, the primary analyses were conducted on all patients. The secondary analyses excluded three subjects with no detectable levels of simufilam in plasma at any visit. Percent change from baseline of compliers in active treatment compared to placebo-treated participants was analyzed by the General Linear Model for the ANCOVA.

Lymphocyte biomarkers were analyzed by ANOVA: comparing to each patient's own baseline was considered more appropriate than adjusting for baseline value by ANCOVA, given the range of baseline values. The FLNA – $\alpha 7$ nAChR linkage for the 100 mg dose arm versus placebo was the only comparison significantly different by ANOVA but not by ANCOVA.

Tests of cognition were not powered for statistical significance and were therefore evaluated by effect size, a standardized measure of relative size of treatment effect. Effect sizes of 20–25% are considered noteworthy, and a 25% effect size is typically considered clinically meaningful if significance is achieved in later, appropriately powered trials. For cognitive tests, effect sizes for each simufilam dose versus placebo were calculated by Hedge's g , appropriate for groups of 20, and these were identical or nearly identical to those calculated by Cohen's d . For the Paired Associates Learning test, the most and least impaired subjects were excluded by baseline score (≤ 11 or ≥ 54 of 70 total possible errors) prior to calculation of effect size. These cutoffs were employed to remove subjects with very few errors (ceiling effects), as well as subjects who performed so poorly that they may not have understood the task. Effect sizes for spatial working memory included all subjects with detectable plasma simufilam. Reaction time was measured in milliseconds between stimulus onset and response.

Results

Trial Population

Of 115 patients screened, 64 patients enrolled. Twenty-two were randomized to placebo and 21 each to simufilam 50 mg and 100 mg. One participant discontinued for non-medical reasons (Fig. 1). One

completer was excluded from the primary analyses due to a missing Day 28 sample. One patient in the 50 mg arm and two in the 100 mg arm were excluded from the secondary analyses due to no detectable plasma levels of simuflam at return visits. Baseline demographics, MMSE, cognitive assessment scores, concomitant cholinesterase inhibitor or memantine use, and baseline biomarker levels were well balanced between groups (Table 1). CSF/plasma simuflam levels in simuflam arms were 0.29 ± 0.21 .

Table 1
Baseline Demographics and Assessments

Demographics and Characteristics	Placebo (N = 22)	Simufilam 50 mg (N = 21)	Simufilam 100 mg (N = 21)
Age, mean (SD)	71.3 (6.68)	69.3 (5.47)	67.1 (8.76)
Female sex, No. (%)	11 (50.0)	12 (57.1)	12 (57.1)
Not white race, No. (%)	3 (13.6)	4 (19.0)	2 (9.5)
Hispanic or Latino ethnicity, No. (%)	9 (40.9)	11 (52.4)	11 (52.4)
CSF total tau/A β ₄₂ ratio (SD)	1.20 (0.55)	1.17 (0.58)	1.08 (0.50)
MMSE, mean (SD)	23.1 (2.78)	22.7 (2.67)	23.0 (2.66)
APOE4 homozygous	1	1	3
APOE4 heterozygous	12	14	10
Taking cholinesterase inhibitor or memantine, No. (%)	8 (36.4)	5 (23.8)	7 (33.3)
Paired Associates Learning total errors, mean (SD)	35.5 (19.65)	36.1 (18.76)	31.0 (20.74)
Spatial Working Memory total errors, mean (SD)	19.0 (7.49)	22.3 (6.64)	22.1 (5.88)
CSF A β ₄₂ pg/mL, mean (SD)	125 (152)	108 (54.8)	117 (51.4)
CSF total tau pg/mL, mean (SD)	104 (32)	101 (17.6)	106 (27.9)
CSF P-tau181 pg/mL, mean (SD)	28.5 (0.73)	29.0 (1.0)	29.7 (1.5)
CSF neurogranin pg/mL, mean (SD)	1200 (365)	1352 (614)	1551 (751)
CSF NfL pg/mL, mean (SD)	161 (42.8)	181 (64.4)	219 (95.3)
CSF YKL-40 pg/mL, mean (SD)	206 (29.5)	194 (26.0)	203 (22.7)
CSF IL-6 pg/mL, mean (SD)	32.5 (1.2)	33.6 (1.7)	33.6 (1.8)
CSF sTREM2, pg/mL, mean (SD)	878 (435)	882 (476)	861 (421)

Demographics and Characteristics	Placebo (N = 22)	Simufilam 50 mg (N = 21)	Simufilam 100 mg (N = 21)
CSF HMGB1, pg/mL, mean (SD)	424 (48.0)	454 (70.6)	446 (67.3)
CSF/plasma albumin ratio, mean (SD)	0.24 (0.03)	0.25 (0.05)	0.25 (0.08)
CSF/plasma IgG ratio, mean (SD)	0.200 (0.07)	0.227 (0.07)	0.217 (0.11)
Lymphocyte filamin A – α 7nAChR, Ratio to total filamin A, mean (SD)	0.59 (0.10)	0.66 (0.12)	0.69 (0.11)
Lymphocyte filamin A – TLR4, Ratio to total filamin A, mean (SD)	0.55 (0.10)	0.58 (0.11)	0.60 (0.07)

CSF Biomarker Change from Baseline

The pre-specified primary analysis was change from baseline to Day 28 on six CSF biomarkers ($A\beta_{42}$, total tau, P-tau181, neurogranin, neurofilament light chain and YKL-40) in the drug arms versus the placebo arm. Significance levels were adjusted for multiplicity ($p < 0.05/6$ or $p < 0.008$). Both dose arms showed significant changes from baseline on five of the six primary biomarkers, with the increase in $A\beta_{42}$ in the 100 mg dose arm not significant, likely due to the range of baseline values (Table 2). The secondary analysis of change from baseline with three non-compliers excluded produced similar results to the primary analysis of the full analysis set. Individual patients' Screening and Day 28 values (pg/mL) are shown by spaghetti plots for each treatment arm (Fig. 2).

Table 2
Biomarkers Change from Baseline in pg/mL (SD)

Biomarker	Placebo (N = 22)	Simufilam 50 mg		Simufilam 100 mg	
		All Patients	Compliers	All Patients	Compliers
		N = 19	N = 18	N = 21	N = 19
CSF A β ₄₂	4.8 (30.9)	16.2 (21.1) p = 0.01	16.9 (21.5) p = 0.006	12.5 (11.9) p = 0.087	13.4 (11.2) p = 0.088
CSF total tau	-3.2 (14.8)	-14.6 (9.6) p = 0.0012	-14.9 (9.8) p = 0.0014	-18.7 (10.4) p = 0.0000	-19.8 (10.3) p = 0.0000
Total tau/A β ₄₂	-0.029 (0.327)	-0.28 (0.27) p = 0.0006	-0.30 (0.27) p = 0.0008	-0.30 (0.22) p = 0.0001	-0.31 (0.22) p = 0.0001
CSF P-tau181	-0.63 (1.8)	-2.4 (1.6) p = 0.002	2.5 (1.6) p = 0.003	-3.1 (1.7) p = 0.005	-3.2 (1.7) p = 0.003
CSF neurogranin	-50.5 (434.0)	-527 (361) p = 0.0005	-531 (371) p = 0.0006	-648 (491) p = 0.0002	-681 (505) p = 0.0002
CSF Neurofilament Light Chain	-10.0 (45.0)	-49.7 (35.5) p = 0.0058	-51.0 (36.1) p = 0.0008	-76.3 (50.6) p = 0.0003	-78.5 (52.9) p = 0.0002
CSF YKL-40	-0.96 (24.2)	-20.4 (17.4) p = 0.0001	-20.9 (17.7) p = 0.002	-22.3 (11.7) p = 0.0001	-23.7 (11.4) p = 0.0001
CSF Interleukin-6	-1.1 (2.0)	-3.3 (1.8) p = 0.011	-3.3 (1.9) p = 0.019	-3.5 (1.8) p = 0.003	-3.7 (1.8) p = 0.0078
CSF sTREM2	-77.3 (510)	-418 (376) p = 0.0005	-424 (386) p = 0.0007	-404 (269) p = 0.0001	-426 (274) p = 0.0002

^a Units are optical density units of immunoblot bands.

^b Densitometric quantities of α 7nAChR or TLR4 in anti-filamin A precipitates as a ratio to total filamin A.

N.B.: p values are compared to placebo for each biomarker.

Biomarker	Placebo (N = 22)	Simufilam 50 mg		Simufilam 100 mg	
		All Patients	Compliers	All Patients	Compliers
		N = 19	N = 18	N = 21	N = 19
CSF	19.4 (172.3)	-149 (50.3)	-152 (50.1)	-140 (51.3)	143 (51.3)
HMGB1		p = 0.0001	p = 0.0001	p = 0.0001	p = 0.0001
CSF albumin ^a	-240 (1620)	-1184 (1707)	-1245 (1735)	-2103 (1774)	-2292 (1760)
		p = 0.054	p = 0.046	p = 0.0001	p = 0.0001
CSF IgG ^a	-574.8 (2518.32)	-2269 (2176)	-2444 (2097)	-2253 (2414)	-2350 (2517)
		p = 0.018	p = 0.014	p = 0.007	p = 0.012
Lymphocyte	-0.07 (0.19)	-0.22 (0.13)	-0.23 (0.13)	-0.22 (0.16)	-0.24 (0.16)
filamin A – α7nAChR ^b		p = 0.014	p = 0.009	P = 0.008	p = 0.005
Lymphocyte	-0.05 (0.18)	-0.19 (0.11)	-0.19 (0.11)	-0.18 (0.13)	-0.19 (0.14)
filamin A – TLR4 ^b		P = 0.011	p = 0.010	p = 0.012	p = 0.010
^a Units are optical density units of immunoblot bands.					
^b Densitometric quantities of α7nAChR or TLR4 in anti-filamin A precipitates as a ratio to total filamin A.					
N.B.: p values are compared to placebo for each biomarker.					

CSF Biomarker Percent Change from Baseline

The secondary analysis of percent change from baseline showed significant differences for both dose arms versus placebo on all eleven CSF biomarkers, adjusted for multiplicity for the six primary biomarkers (Fig. 3). P values for change and percent change from baseline were similar, with Aβ₄₂ in the 100 mg dose arm the sole comparison that was significant by percent change but not by change, due to the range in baseline values.

Biomarkers of AD Pathology and Neurodegeneration

Low in Alzheimer's disease, CSF Aβ₄₂ significantly increased 17% and 14% in the 50 and 100 mg arms, respectively (p = 0.0004 and p = 0.004). CSF total tau decreased 16% and 18% (p = 0.0002 and p = 0.00001) and CSF P-tau181 decreased 8% and 11% (p = 0.002 and p = 0.003) in 50 and 100 mg dose arms compared to placebo, respectively. CSF neurofilament light chain, reflecting axonal damage, decreased 28% and 34% in respective dose arms (p = 0.002 and p = 0.0003). Neurogranin, indicating post-

synaptic damage, significantly decreased 36% and 43% in respective dose arms ($p = 0.0004$ and $p = 0.0001$).

Biomarkers of Neuroinflammation

Simufilam treatment significantly decreased four CSF biomarkers of neuroinflammation compared to placebo. YKL-40 decreased 10% and 11% in the 50 and 100 mg arms, respectively ($p = 0.0003$ and $p = 0.0002$). Inflammatory cytokine interleukin-6 decreased 10% and 11% in the 50 and 100 mg arms ($p = 0.017$ and $p = 0.007$). Indicating reduced microglial activation, sTREM2 decreased 43% and 46% in the 50 and 100 mg arms ($p = 0.0009$ and $p = 0.0003$). Finally, the damage-associated molecular pattern protein HMGB1 decreased 33% and 32% in the 50 and 100 mg arms ($p = 0.0002$ and $p = 0.0001$).

Biomarkers of Blood-Brain Barrier Integrity

Simufilam improved blood-brain barrier integrity, evidenced by lower levels of albumin and immunoglobulin G in CSF. Simufilam 50 and 100 mg significantly decreased CSF albumin by 15% and 29%, respectively ($p = 0.04$ and $p = 0.0001$). CSF immunoglobulin G decreased 30% in both drug arms (both $p = 0.02$).

Validation of Biomarker Analyses

The statistical validation of biomarker data is supported by the placebo dataset: modest changes (-2%, on average) and robust correlations (mean $R^2 = 0.96$) between all pair combinations among total tau, P-tau181, neurogranin, neurofilament light chain, YKL-40 and IL-6 in change from baseline. Because $A\beta_{42}$ decreases in CSF in Alzheimer's disease as other markers increase, $A\beta_{42}$ movement negatively correlated with changes in those six biomarkers (mean $R^2 = -0.82$ in placebo). Biomarker changes also correlated in simufilam arms (mean $R^2 = 0.77$, excluding $A\beta_{42}$), indicating that the magnitude of change in individual patients was generally consistent across biomarkers.

Target Engagement

Both $\alpha 7nAChR$ and TLR4 receptors and filamin A are present in lymphocytes, allowing assessment of target engagement in patients' lymphocytes. Filamin A linkages to $\alpha 7nAChR$ and TLR4 in lymphocytes were significantly reduced 31–34% from baseline in both drug arms ($p \leq 0.01$).

Cognition

On the Paired Associate Learning test assessing episodic memory, patients in the 50 mg arm made on average 5.7 fewer errors on Day 28, patients in the 100 mg arm made 4.5 fewer errors, and placebo patients made 1.5 fewer errors (Fig. 4). These differences represent 0.37 and 0.23 effect sizes for 50 and 100 mg arms, respectively, versus placebo. The most and least impaired subjects were removed by baseline score (≥ 54 and ≤ 11 of 70 possible total errors) to eliminate ceiling effects (those with very few errors) and subjects who performed so poorly that they may not have understood the task. Standard deviations for change from baseline in PAL total errors were 8.5, 13.6, 17.7 for placebo, 50 and 100 mg, respectively.

In Spatial Working Memory, patients in 50 and 100 mg arms made 2.3 and 3.3 fewer errors, respectively, compared to 0.4 in placebo, representing 0.25 and 0.46 effect sizes. Standard deviations for change from baseline in Spatial Working Memory total errors were 7.5, 7.5, 4.7 for placebo, 50 and 100 mg, respectively.

Improvements in episodic memory, correlated most strongly with decreases in P-tau181 ($R^2 = 0.48$). Interleukin-6, total tau, albumin, neurofilament light chain and YKL-40 also correlated (R^2 values 0.41, 0.37, 0.37, 0.36 and 0.30, respectively).

In reaction time, placebo, 50 and 100 mg arms showed mean (SD) changes from baseline in median reaction time of -11 (57), -19 (38) and 11 (66) milliseconds, respectively.

Safety

Simufilam was safe and well-tolerated. There were no serious adverse events. Adverse events were mostly mild; none caused discontinuation; none were noted likely to be drug related. Total adverse events were 20, 9 and 15 in placebo, 50 and 100 mg arms, respectively. Adverse events that occurred in 3 or more patients were headache (3, 1 and 2), fatigue (2, 1 and 0), nausea (2, 0 and 1), and upper respiratory infection (1, 2 and 2) for placebo, 50 and 100 mg, respectively.

Discussion

In a randomized clinical trial of 64 patients with Alzheimer's disease dementia, simufilam 50 or 100 mg significantly improved multiple biomarkers of Alzheimer's disease, neurodegeneration, neuroinflammation and blood-brain barrier integrity, with no safety issues. Collectively, results of this randomized controlled trial are consistent with the drug's mechanism of action and replicate a prior, open-label study.²⁰

Increases in $A\beta_{42}$ and reductions in total tau and p-Tau181 imply reduced Alzheimer's disease pathophysiology. Reduced levels of neurofilament light chain and neurogranin suggest a slower rate of neurodegeneration. The 36% and 43% reductions in neurogranin, considered specific to Alzheimer's disease,²⁴ additionally suggest reduced disease pathology. Reductions in neuroinflammatory markers YKL-40, interleukin-6, sTREM2 and HMGB1 indicate suppressed neuroinflammation. Because HMGB1 also damages neurites and furthers neuroinflammation,²⁴ the more than 30% reductions in HMGB1 imply reduced pathogenic drive. Finally, lower CSF albumin and immunoglobulin G indicate improved blood-brain barrier integrity, possibly related to simufilam's suppression of neuroinflammation, as blood-brain barrier breakdown correlates with neuroinflammation and cognitive decline.^{25,26} Restoring $\alpha 7nAChR$ function by displacing $A\beta_{42}$ from this receptor may also improve blood-brain barrier integrity.^{27,28}

Robust statistical correlations between biomarkers in changes from baseline within the placebo arm illustrate the interdependency of biomarkers in Alzheimer's disease and validate the study's biomarker assessments. Strong correlations between biomarkers in changes from baseline within simufilam arms suggest that the filamin A proteopathy is a critical, upstream pathogenic event in Alzheimer's disease.

Reductions in filamin A linkages to $\alpha 7$ nAChR and TLR4 in patient lymphocytes, demonstrating target engagement, likely mirror the target engagement of simufilam in brain. Reductions in these filamin A linkages were previously demonstrated in both brain and lymphocytes of simufilam-treated Alzheimer's disease transgenic mice (lymphocytes unpublished), and in postmortem human Alzheimer's disease brain tissue incubated with simufilam.¹⁷

The small dose-response in this study suggests near saturation of the target protein, anticipated because simufilam, a small molecule, binds the altered conformation of filamin A with ultra-high (580 femtomolar) affinity.¹⁷ Clean safety, a mild dose-response, high (98%) response rate and clear evidence of target engagement collectively suggest 50–100 mg b.i.d. is an optimal dose range.

Effect sizes on tests of episodic and spatial working memory suggest a drug response. Episodic memory improvements correlated best with decreases in levels of CSF P-tau181. Because cognitive decline is not expected over 28 days in mild-to-moderate Alzheimer's disease patients, the biomarker changes that imply slowed disease progression may also reflect suppressed disease mechanisms and improved neuronal function. Certainly, any benefit to cognition over this trial's duration implies cognitive enhancement.

FDA Guidance requires clinical trials in Alzheimer's disease to show a clinical benefit on cognitive and functional co-primary endpoints. Meaningful benefits are unlikely to occur without concurrent improvements in a broad panel of disease biomarkers. There are few reports of drug effects on CSF biomarkers, and these effects on one to three markers have not always shown concurrent effects on cognition or function.²⁹ Drug effects on biomarkers that are compellingly related to the neurobiology of Alzheimer's disease in the pathway(s) affected by a drug candidate can support a regulatory claim for disease modification.³⁰

Simufilam's potential to modify the disease and enhance cognition is supported by preclinical data. In a triple transgenic mouse model of Alzheimer's disease, simufilam improved cognitive behavior and reduced amyloid deposits, tau hyperphosphorylation, neurofibrillary lesions and inflammatory cytokine release.¹⁷ Additionally, in brains of these transgenic mice, and in postmortem human brain tissue, simufilam restored function of $\alpha 7$ nAChR, N-methyl-D-aspartate (NMDA) receptors and insulin receptors and improved synaptic plasticity (indicated by NMDA-induced activity-dependent expression of the master synaptic plasticity regulator Arc).¹⁷ Improvements in receptor function and synaptic plasticity could underlie the apparent cognitive enhancement in this trial.

Limitations

There are several limitations to this study. The sample size is small. The directional changes and statistical significance are encouraging; however, the magnitude of observed biomarker changes is of uncertain significance. The relationships of changes in biomarkers to cognitive and functional measures have not been established, and multiple studies assessing a similar panel of biomarkers are required to

determine these correlations and mechanistic relationships. Studies of simuflam large enough to detect treatment effects on clinical measures are warranted. Despite an interpretation of slowed disease processes, this study was not long enough to allow conclusions regarding disease modification. Longer studies are needed to measure effects on the trajectory of clinical decline.

Conclusions

Simuflam is the first of a new class of drug candidates to target altered filamin A, a proteopathy in Alzheimer's disease. This clinical dataset of CSF biomarker changes offers new insights into the pathophysiology of Alzheimer's disease and a potential new therapeutic strategy. Effect sizes on memory assessments indicate potential for cognitive enhancement. Simuflam's ability to slow disease progression in patients will need to be evaluated in large, definitive clinical trials.

Abbreviations

Amyloid-beta1-42 (A β 42), phospho-tau181 (P-tau181), α 7 nicotinic acetylcholine receptor (α 7nAChR), toll-like receptor 4 (TLR4), cluster-of-differentiation14 (CD14), National Institute on Aging (NIA), Alzheimer's Association (AA), Mini-Mental State Exam (MMSE), soluble triggering receptor expressed on myeloid cells 2 (sTREM2), high mobility group box 1 (HMGB1), Cambridge Neuropsychological Test Automated Battery (CANTAB)

Declarations

Ethics Approval and Consent to Participate:

This study was reviewed and approved by Advarra, Inc., a central institutional review board. Written informed consent was obtained from all participants.

Consent for Publication:

As patient data is presented only in aggregate, no consent for publication was required.

Availability of Data:

Cassava Sciences has not established a data sharing repository for the data from this trial.

Competing Interests:

Simuflam is the chemical name for a compound owned by Cassava Sciences, Inc. CC, GBT, RB, NF and LHB are Cassava Sciences employees. H-YW and JC are consultants and scientific advisory board members for Cassava Sciences.

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This trial was supported by NIA grant AG050878. NIA personnel approved the clinical trial protocol. NIA personnel also approved the selection of Data and Safety Monitoring Board members and participate in these meetings.

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Author Contributions

RB, NF and LHB designed the clinical trial with guidance from JC. Biomarker analyses were conducted blind to treatment and time point by H-YW, ZP and K-CL. K-CL and H-YW conducted APOE genotyping. CC oversaw clinical operations and trial monitors. YGR, TAD, JP, BB, PS, ELB and BN were clinical investigators. GBT analyzed lymphocyte assays. LHB wrote the manuscript with help from HYW, RB and JC. All authors have access to the data via an electronic data capture system, except H-YW, ZP and K-CL who remain blinded to treatment.

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Figures



Figure 1

Patient Flow Diagram

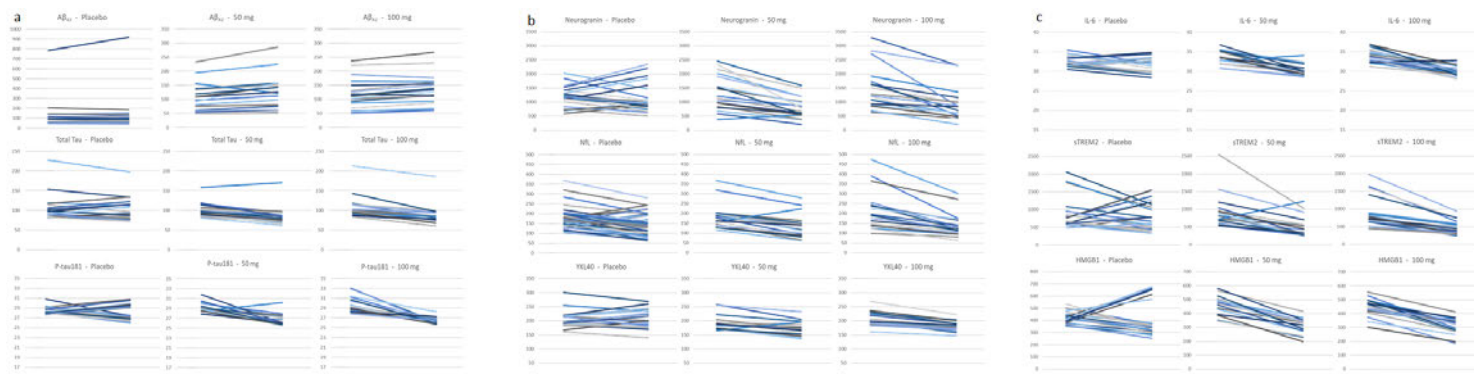


Figure 2

Simufilam improved biomarkers of AD pathology, neurodegeneration, neuroinflammation and BBB integrity. Percent change from baseline of CSF biomarkers (A) and lymphocyte target engagement markers (B). Reductions in filamin A linkages to α7nAChR or TLR4 in lymphocytes indicate target engagement. These secondary analyses of percent change from baseline on all biomarkers excluded the 3 patients with no detectable simufilam in plasma at return visits. Data are means ± SEM. * $p \leq 0.0001$, # $p < 0.001$, † $p < 0.01$ and + $p < 0.05$ versus placebo. N=22, 20, 19 for placebo, 50 and 100 mg, respectively.

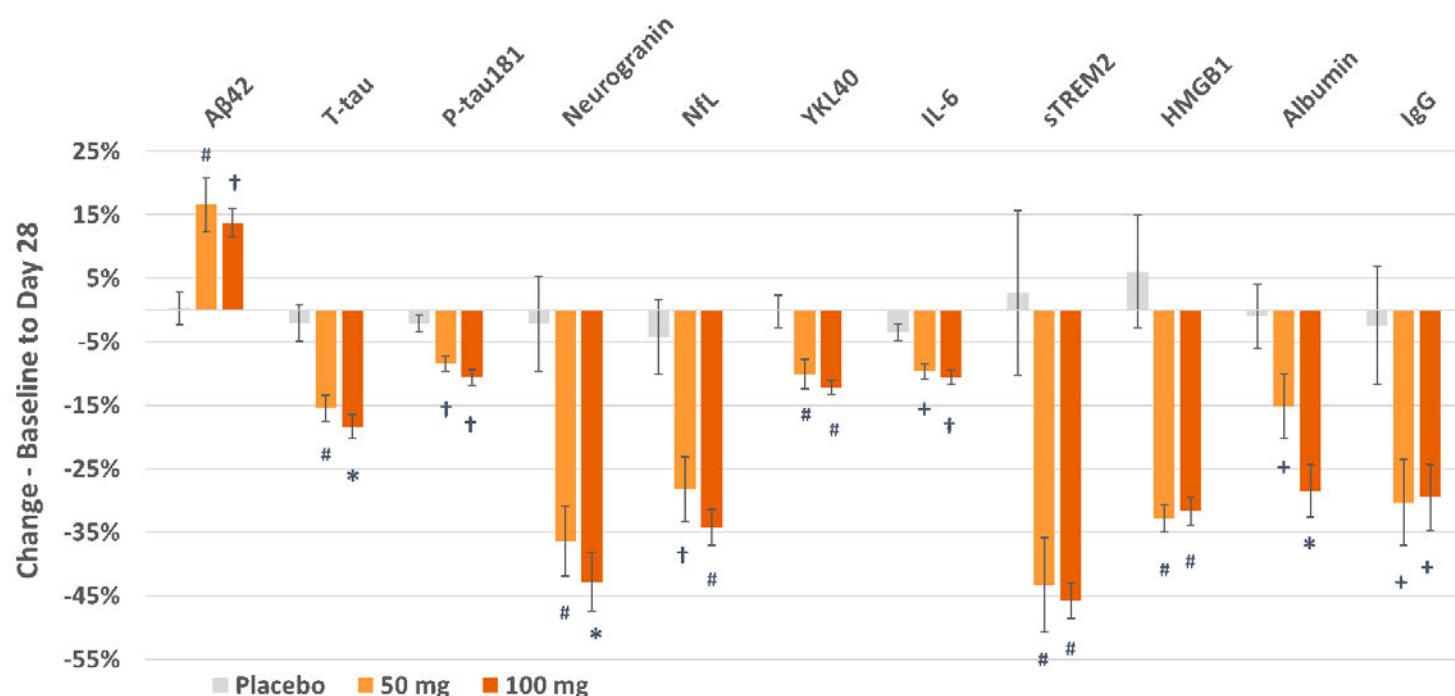


Figure 3

Spaghetti plots by group for biomarkers measured by ELISA. Plots show individual patient levels (pg/mL) at screening (left) and at Day 28 (right). All patients in simufilam groups show decreases in all biomarkers except one individual in the 50 mg group. By contrast, placebo patients show movement in

both directions for each biomarker. A: Core AD pathology biomarkers. B: Neurogranin, neurofilament light chain (NfL), and YKL-40. C: Secondary biomarkers IL-6, sTREM2 and HMGB1.

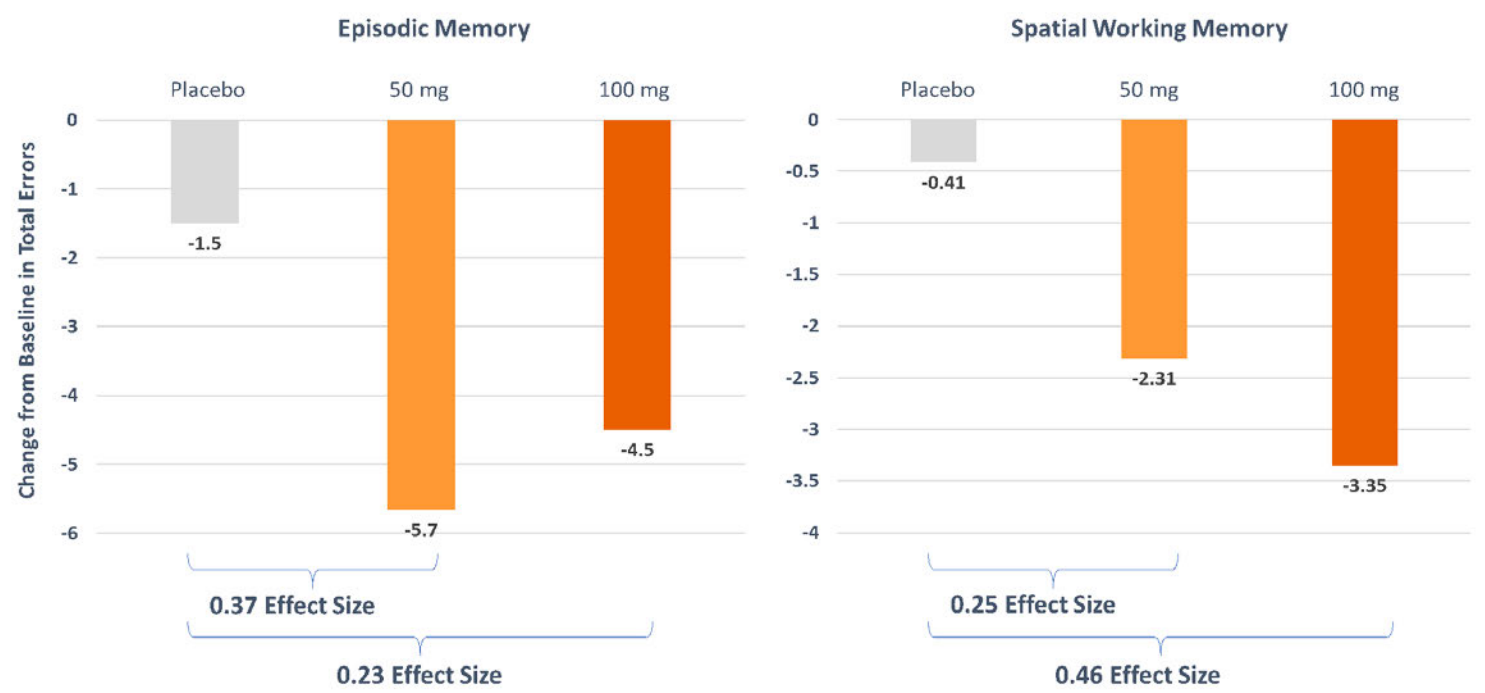


Figure 4

Simufilam appeared to improve both episodic memory and spatial working memory. Effect sizes were calculated by Hedge's g. For the episodic memory test (Paired Associates Learning), the least impaired patients (11 or fewer errors, representing a ceiling effect) and patients with 54 or more errors (very poor performance suggesting not understanding the task) were removed from the analysis. Both datasets removed the 3 patients with no detectable drug in plasma, 2 patients with $\geq 25\%$ non-compliance by pill counts, one patient with no baseline test and one who did not understand instructions per rater notes. N=14, 13, 10 for PAL, and N=22, 17, 18 for spatial working memory for placebo, 50 and 100 mg, respectively.

From: Hoau-yan Wang
Sent time: 08/31/2021 10:53:53 AM
To: Lindsay Burns <lburns@cassavasciences.com>
Subject: Fw: [EXTERNAL] Reporter query re: Cassava Sciences
Attachments: b2081ad1-0cc5-4e38-a546-1083b91f0843.pdf

I am NOT responding to this.

From: Feuerstein, Adam <adam.feuerstein@statnews.com>
Sent: Tuesday, August 31, 2021 8:04 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Reporter query re: Cassava Sciences

Professor Wang --

I'm a reporter with STAT, a digital publication that covers health, medicine and the life sciences. I'm contacting you to see if you're willing to answer some questions about the research you conducted and published on the experimental Alzheimer's drug simufilam, in collaboration with Cassava Sciences.

As you're aware, questions have been raised about the scientific integrity and credibility of papers that you co-authored, along with Cassava's Lindsay Burns.

In particular, I'd like to better understand the specific role that you played in analyzing CSF samples taken from patients in Cassava's phase 2b study. When the "re-analysis" of those CSF samples were announced in September 2020, Cassava said the work was done by an "academic lab" without offering any further details.

Did you perform the biomarker analysis on those CSF samples in your lab at CUNY Medical School?

I've attached a copy of a research paper describing the results of the phase 2b study that was submitted to a preprint server in February 2021. You are the lead author on the paper. Inside the Oversight and Settings section of the paper, it says, "CSF samples were analyzed at CUNY School of Medicine."

Can you confirm that your lab performed the CSF biomarker analysis?

Thank you --

Adam Feuerstein

--

Adam Feuerstein

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Effects of simufilam on cerebrospinal fluid biomarkers in Alzheimer's disease: A randomized clinical trial

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Research

Keywords: filamin A, tau hyperphosphorylation, neuroinflammation, blood-brain barrier

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Abstract

BACKGROUND

Simufilam is a first-in-class drug candidate targeting altered filamin A, a proteopathy in Alzheimer's disease. The primary objective of this Phase 2 clinical trial was to evaluate the effects of simufilam on cerebrospinal fluid (CSF) biomarkers in Alzheimer's disease patients. A secondary objective was to assess cognitive enhancement.

METHODS

In a randomized, placebo-controlled trial conducted across 9 clinical sites in the US, 64 mild-to-moderate Alzheimer's disease patients were randomized to simufilam 50 or 100 mg b.i.d. or placebo for 28 days. Clinical diagnosis was confirmed by CSF total tau/amyloid-beta₁₋₄₂ ($A\beta_{42}$) > 0.28. Co-primary endpoints were changes in CSF $A\beta_{42}$, total tau, phospho-tau (P-tau181), neurogranin, neurofilament light chain, and YKL-40. Secondary endpoints included additional CSF biomarkers assessing neuroinflammation and blood brain barrier integrity, and tests of episodic and spatial working memory.

RESULTS

Adjusting for multiplicity of the six co-primary endpoints ($p < 0.008$ versus placebo required for significance), simufilam 50 and 100 mg significantly reduced CSF levels of total tau, hyperphosphorylated tau (P-tau181), neurogranin, neurofilament light chain and YKL-40. Simufilam 50 mg significantly increased CSF levels of $A\beta_{42}$. On secondary CSF biomarker endpoints, both doses of simufilam significantly reduced IL-6, soluble TREM2 (triggering receptor expressed on myeloid cells-2), HMGB1 (high mobility group box-1), albumin and immunoglobulin G. All but one patient improved from baseline across biomarkers. Simufilam 50 and 100 mg showed effect sizes versus placebo (0.23–0.46) in change from baseline in episodic memory and spatial working memory. Episodic memory improvements correlated most strongly with decreases in P-tau181 ($R^2 = 0.48$). Simufilam was safe and well tolerated. Target engagement was demonstrated by filamin A linkages to nicotinic acetylcholine receptor subtype $\alpha 7$ ($\alpha 7nAChR$) and toll-like receptor 4 (TLR4) in lymphocytes.

CONCLUSIONS

Simufilam was safe and well tolerated and significantly improved eleven CSF biomarkers in patients with Alzheimer's disease, implying biological evidence of disease modification. Simufilam will be further evaluated in large, definitive clinical trials.

TRIAL REGISTRATION:

ClinicalTrials.gov Identifier NCT04079803.

Background

There are no approved treatments to slow the progression of Alzheimer's disease, expected to affect 13.8 million in the U.S. by 2050.¹ Biomarkers may facilitate drug development in Alzheimer's disease by quantifying disease stage, demonstrating target engagement, and supporting disease modification.²

Core CSF biomarkers of Alzheimer's disease are amyloid-beta1-42 ($A\beta_{42}$), total tau and phospho-tau181 (P-tau181).^{3,4} $A\beta_{42}$ decreases while tau and phosphorylated tau, including P-tau181, increase as disease progresses and cognition declines. Neurogranin and neurofilament light chain, indicating damage to dendrites and axons respectively, are used to track disease progression.⁵⁻⁷ Interestingly, neurogranin appears specific to Alzheimer's disease.⁷ The current clinical trial measured CSF biomarkers in Alzheimer's disease dementia patients to evaluate drug candidate simufilam.

Simufilam represents a novel approach to combat amyloid toxicity and resulting neurodegeneration in Alzheimer's disease. Soluble $A\beta_{42}$ initiates a predominant pathogenic pathway by binding $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7nAChR$), the only known sub-nanomolar-affinity binding site of soluble $A\beta_{42}$.⁸⁻¹⁰ This femtomolar interaction poses enormous competition for any agent aiming to reduce soluble $A\beta_{42}$ interactions. $A\beta_{42}$ binds and signals through this receptor to activate kinases that hyperphosphorylate the protein tau,¹⁰⁻¹³ impairing tau's ability to stabilize microtubules. This loss of functional tau is a primary driver of the neuronal degeneration and cognitive impairment in Alzheimer's disease.¹⁴

Without directly competing with the femtomolar binding of $A\beta_{42}$ to $\alpha 7nAChR$, simufilam disrupts this ultra-high-affinity interaction by binding a critical accomplice to $A\beta_{42}$: an altered conformation of filamin A. Filamin A is an intracellular scaffolding protein that is highly expressed in brain and interacts with over 90 proteins to coordinate signaling processes.¹⁵ $A\beta_{42}$ initiates toxic signaling by binding $\alpha 7nAChR$ to recruit filamin A.^{16,17} Without directly contacting filamin A, and likely working through $\alpha 7nAChR$ and other receptors that link to or recruit filamin A, $A\beta_{42}$ induces the altered conformation of the filamin A protein.¹⁷ Simufilam binds altered filamin A, restores its normal shape and disrupts the aberrant filamin A – $\alpha 7nAChR$ linkage, $A\beta_{42}$'s femtomolar binding to $\alpha 7nAChR$ and the ensuing toxic signaling that hyperphosphorylates tau.^{17,18}

$A\beta_{42}$ also binds the toll-like receptor 4 (TLR4) co-receptor cluster-of-differentiation14 (CD14)¹⁹ to recruit and alter filamin A.¹⁷ The filamin A – TLR4 linkage enables persistent TLR4 activation by $A\beta_{42}$, causing inflammatory cytokine release and neuroinflammation. Simufilam's reversal of the filamin A proteopathy also blocks this $A\beta_{42}$ -induced neuroinflammation.^{17,18}

In a previous open-label, 28-day trial in patients with mild-to-moderate Alzheimer's disease dementia (NCT03748706), simufilam significantly reduced CSF total tau, P-tau181 and biomarkers of neurodegeneration and neuroinflammation in all patients, with no safety issues.²⁰ Biomarker reductions implied reduced disease pathophysiology and neurodegeneration, consistent with simufilam's mechanism of action and preclinical data. Based on encouraging prior clinical trial results, we evaluated simufilam in a randomized, double-blind, placebo-controlled Phase 2 trial. We hypothesized simufilam treatment would impact CSF biomarkers and may enhance cognition.

Methods

Patient Population

Patients were 50–85 years old, diagnosed with probable Alzheimer's disease dementia according to National Institute on Aging (NIA)/Alzheimer's Association (AA) criteria and a Mini-Mental State Exam (MMSE) score ≥ 16 and ≤ 26 . Diagnosis was confirmed by CSF total tau/ $A\beta_{42} \geq 0.28$, a ratio selected to exclude dementia due to other causes (0.28 is intermediate between early and late mild cognitive impairment in amyloid-confirmed patients from the Alzheimer's Disease Neuroimaging Initiative²¹). Patients could be receiving acetylcholinesterase inhibitors, memantine and other medications if stable. Chronic opioids, tricyclic antidepressants, monoamine oxidase inhibitors, nicotine therapy (or smokers) were exclusions, as were uncontrolled medical illnesses, other neurodegenerative diseases, or clinically significant laboratory results.

Trial Design

This double-blind, placebo-controlled, trial randomized 64 patients 1:1:1 to placebo or simufilam 50 or 100 mg oral tablets b.i.d. for 28 days. Patients, caregivers, clinic staff, the study sponsor and the laboratory analyzing biomarkers were blind to treatment. A randomization algorithm was generated by an outside vendor using Interactive Response Technology. Doses were selected by body surface area conversion of effective daily doses in mouse efficacy models and prior clinical experience. Sample sizes of 20 per arm were selected based on highly significant changes from baseline in many of the same CSF biomarkers by paired t-test in a prior open-label trial in mild-to-moderate Alzheimer's disease dementia patients.²²

After initial screening, a second screening visit included a CSF draw and practice cognitive test. Cognitive tests were conducted Days 1 and 28. Blood samples were collected Days 1, 7, 14 and 28, with the Day 28 blood sample following the second CSF draw for CSF/plasma ratios of simufilam. Electrocardiograms and physical examinations were conducted on Days 1 and 28.

Oversight and Settings

This trial was conducted between September 2019 and March 2020 at nine U.S. sites. An independent Data and Safety Monitoring Board approved the protocol and assessed safety mid-study. CSF samples

were analyzed at City University School of Medicine. Plasma was analyzed with a qualified assay at Worldwide Clinical Trials Bioanalytical Sciences. Data were analyzed by a data management and statistics contractor. Data was 100% monitored by independent clinical research associates. No protocol changes were made.

Assessments

Levels of eleven CSF biomarkers in the screening and Day 28 samples were measured. Six CSF biomarkers were designated primary: biomarkers of Alzheimer's disease pathology ($A\beta_{42}$, total tau and P-tau181), neurodegeneration (neurofilament light chain and neurogranin) and neuroinflammation (YKL-40). Also assessed were interleukin-6, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), and high mobility group box 1 (HMGB1). These nine biomarkers were measured using commercial enzyme-linked immunosorbent assay plates and an automated plate reader, with samples assayed in triplicate. CSF albumin and immunoglobulin G assessed blood-brain barrier integrity and were measured by immunoblot with densitometric quantitation. Target engagement was evaluated by measuring filamin A linkages to $\alpha 7nAChR$ and TLR4 in patient lymphocytes by co-immunoprecipitation as described.¹⁷

Cognition was assessed on Day 1 and Day 28 by the Paired Associates Learning (an episodic memory test) and Spatial Working Memory tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Both tests increase progressively in difficulty, with errors imputed for levels not reached. Reductions in the total error scores indicate improvement. The CANTAB Reaction Time test assessed psychomotor speed in milliseconds.

Safety was assessed by adverse event monitoring, clinical laboratory tests, electrocardiography, physical examinations and the Columbia-Suicide Severity Rating Scale.

Outcomes

The six co-primary outcome measures were changes in CSF $A\beta_{42}$, total tau, P-tau181, neurogranin, neurofilament light chain, and YKL-40 levels from screening to Day 28. These six biomarkers were prospectively listed in the trial registration. $A\beta_{42}$, total tau and P-tau181 are considered core biomarkers of Alzheimer's disease pathology. Neurogranin and neurofilament light chain are intracellular proteins in dendrites and axons, respectively, that indicate neurodegeneration when found in CSF. YKL-40 is a glycoprotein involved in tissue remodeling after inflammation. Secondary biomarker outcomes included changes in CSF interleukin-6, sTREM2, HMGB1, albumin and immunoglobulin G. Interleukin-6 is an inflammatory cytokine. A marker of microglial-induced inflammation, sTREM2 is the ectodomain of the transmembrane receptor TREM2 that is cleaved and shed by microglia when activated during inflammation.²³ HMGB1 is a damage-associated molecular pattern protein released by necrotic cells and actively secreted by immune cells to further neuroinflammation and neurite damage.²⁴ Finally, albumin and immunoglobulin G are blood proteins that indicate blood-brain barrier compromise when found in CSF.²⁵

Secondary cognitive outcome measures were drug-placebo differences in change from Day 1 to Day 28 in total errors on Paired Associates Learning and Spatial Working Memory tests. The Reaction Time test exploratory outcome was median response time in milliseconds.

The target engagement assay measured changes in filamin A linkages to $\alpha 7$ nAChR and TLR4 in patient lymphocytes from Day 1 to Day 28.

Statistical Analysis

The pre-specified analysis for biomarkers was drug-placebo differences in change from baseline, analyzed by the General Linear Model for the analysis of covariance (ANCOVA) with a two-sided 95% confidence interval and baseline CSF measurement as the covariate. Multiplicity of the six co-primary endpoints was addressed by the significance requirement: $p < 0.008$ (i.e., $p < 0.05/6$).

The Full Analysis Set included all subjects with two CSF samples. Although plasma samples were collected at all visits to confirm compliance, the primary analyses were conducted on all patients. The secondary analyses excluded three subjects with no detectable levels of simufilam in plasma at any visit. Percent change from baseline of compliers in active treatment compared to placebo-treated participants was analyzed by the General Linear Model for the ANCOVA.

Lymphocyte biomarkers were analyzed by ANOVA: comparing to each patient's own baseline was considered more appropriate than adjusting for baseline value by ANCOVA, given the range of baseline values. The FLNA – $\alpha 7$ nAChR linkage for the 100 mg dose arm versus placebo was the only comparison significantly different by ANOVA but not by ANCOVA.

Tests of cognition were not powered for statistical significance and were therefore evaluated by effect size, a standardized measure of relative size of treatment effect. Effect sizes of 20–25% are considered noteworthy, and a 25% effect size is typically considered clinically meaningful if significance is achieved in later, appropriately powered trials. For cognitive tests, effect sizes for each simufilam dose versus placebo were calculated by Hedge's g , appropriate for groups of 20, and these were identical or nearly identical to those calculated by Cohen's d . For the Paired Associates Learning test, the most and least impaired subjects were excluded by baseline score (≤ 11 or ≥ 54 of 70 total possible errors) prior to calculation of effect size. These cutoffs were employed to remove subjects with very few errors (ceiling effects), as well as subjects who performed so poorly that they may not have understood the task. Effect sizes for spatial working memory included all subjects with detectable plasma simufilam. Reaction time was measured in milliseconds between stimulus onset and response.

Results

Trial Population

Of 115 patients screened, 64 patients enrolled. Twenty-two were randomized to placebo and 21 each to simufilam 50 mg and 100 mg. One participant discontinued for non-medical reasons (Fig. 1). One

completer was excluded from the primary analyses due to a missing Day 28 sample. One patient in the 50 mg arm and two in the 100 mg arm were excluded from the secondary analyses due to no detectable plasma levels of simuflam at return visits. Baseline demographics, MMSE, cognitive assessment scores, concomitant cholinesterase inhibitor or memantine use, and baseline biomarker levels were well balanced between groups (Table 1). CSF/plasma simuflam levels in simuflam arms were 0.29 ± 0.21 .

Table 1
Baseline Demographics and Assessments

Demographics and Characteristics	Placebo (N = 22)	Simufilam 50 mg (N = 21)	Simufilam 100 mg (N = 21)
Age, mean (SD)	71.3 (6.68)	69.3 (5.47)	67.1 (8.76)
Female sex, No. (%)	11 (50.0)	12 (57.1)	12 (57.1)
Not white race, No. (%)	3 (13.6)	4 (19.0)	2 (9.5)
Hispanic or Latino ethnicity, No. (%)	9 (40.9)	11 (52.4)	11 (52.4)
CSF total tau/A β ₄₂ ratio (SD)	1.20 (0.55)	1.17 (0.58)	1.08 (0.50)
MMSE, mean (SD)	23.1 (2.78)	22.7 (2.67)	23.0 (2.66)
APOE4 homozygous	1	1	3
APOE4 heterozygous	12	14	10
Taking cholinesterase inhibitor or memantine, No. (%)	8 (36.4)	5 (23.8)	7 (33.3)
Paired Associates Learning total errors, mean (SD)	35.5 (19.65)	36.1 (18.76)	31.0 (20.74)
Spatial Working Memory total errors, mean (SD)	19.0 (7.49)	22.3 (6.64)	22.1 (5.88)
CSF A β ₄₂ pg/mL, mean (SD)	125 (152)	108 (54.8)	117 (51.4)
CSF total tau pg/mL, mean (SD)	104 (32)	101 (17.6)	106 (27.9)
CSF P-tau181 pg/mL, mean (SD)	28.5 (0.73)	29.0 (1.0)	29.7 (1.5)
CSF neurogranin pg/mL, mean (SD)	1200 (365)	1352 (614)	1551 (751)
CSF NfL pg/mL, mean (SD)	161 (42.8)	181 (64.4)	219 (95.3)
CSF YKL-40 pg/mL, mean (SD)	206 (29.5)	194 (26.0)	203 (22.7)
CSF IL-6 pg/mL, mean (SD)	32.5 (1.2)	33.6 (1.7)	33.6 (1.8)
CSF sTREM2, pg/mL, mean (SD)	878 (435)	882 (476)	861 (421)

Demographics and Characteristics	Placebo (N = 22)	Simufilam 50 mg (N = 21)	Simufilam 100 mg (N = 21)
CSF HMGB1, pg/mL, mean (SD)	424 (48.0)	454 (70.6)	446 (67.3)
CSF/plasma albumin ratio, mean (SD)	0.24 (0.03)	0.25 (0.05)	0.25 (0.08)
CSF/plasma IgG ratio, mean (SD)	0.200 (0.07)	0.227 (0.07)	0.217 (0.11)
Lymphocyte filamin A – α 7nAChR, Ratio to total filamin A, mean (SD)	0.59 (0.10)	0.66 (0.12)	0.69 (0.11)
Lymphocyte filamin A – TLR4, Ratio to total filamin A, mean (SD)	0.55 (0.10)	0.58 (0.11)	0.60 (0.07)

CSF Biomarker Change from Baseline

The pre-specified primary analysis was change from baseline to Day 28 on six CSF biomarkers ($A\beta_{42}$, total tau, P-tau181, neurogranin, neurofilament light chain and YKL-40) in the drug arms versus the placebo arm. Significance levels were adjusted for multiplicity ($p < 0.05/6$ or $p < 0.008$). Both dose arms showed significant changes from baseline on five of the six primary biomarkers, with the increase in $A\beta_{42}$ in the 100 mg dose arm not significant, likely due to the range of baseline values (Table 2). The secondary analysis of change from baseline with three non-compliers excluded produced similar results to the primary analysis of the full analysis set. Individual patients' Screening and Day 28 values (pg/mL) are shown by spaghetti plots for each treatment arm (Fig. 2).

Table 2
Biomarkers Change from Baseline in pg/mL (SD)

Biomarker	Placebo (N = 22)	Simufilam 50 mg		Simufilam 100 mg	
		All Patients	Compliers	All Patients	Compliers
		N = 19	N = 18	N = 21	N = 19
CSF A β ₄₂	4.8 (30.9)	16.2 (21.1) p = 0.01	16.9 (21.5) p = 0.006	12.5 (11.9) p = 0.087	13.4 (11.2) p = 0.088
CSF total tau	-3.2 (14.8)	-14.6 (9.6) p = 0.0012	-14.9 (9.8) p = 0.0014	-18.7 (10.4) p = 0.0000	-19.8 (10.3) p = 0.0000
Total tau/A β ₄₂	-0.029 (0.327)	-0.28 (0.27) p = 0.0006	-0.30 (0.27) p = 0.0008	-0.30 (0.22) p = 0.0001	-0.31 (0.22) p = 0.0001
CSF P-tau181	-0.63 (1.8)	-2.4 (1.6) p = 0.002	2.5 (1.6) p = 0.003	-3.1 (1.7) p = 0.005	-3.2 (1.7) p = 0.003
CSF neurogranin	-50.5 (434.0)	-527 (361) p = 0.0005	-531 (371) p = 0.0006	-648 (491) p = 0.0002	-681 (505) p = 0.0002
CSF Neurofilament Light Chain	-10.0 (45.0)	-49.7 (35.5) p = 0.0058	-51.0 (36.1) p = 0.0008	-76.3 (50.6) p = 0.0003	-78.5 (52.9) p = 0.0002
CSF YKL-40	-0.96 (24.2)	-20.4 (17.4) p = 0.0001	-20.9 (17.7) p = 0.002	-22.3 (11.7) p = 0.0001	-23.7 (11.4) p = 0.0001
CSF Interleukin-6	-1.1 (2.0)	-3.3 (1.8) p = 0.011	-3.3 (1.9) p = 0.019	-3.5 (1.8) p = 0.003	-3.7 (1.8) p = 0.0078
CSF sTREM2	-77.3 (510)	-418 (376) p = 0.0005	-424 (386) p = 0.0007	-404 (269) p = 0.0001	-426 (274) p = 0.0002

^a Units are optical density units of immunoblot bands.

^b Densitometric quantities of α 7nAChR or TLR4 in anti-filamin A precipitates as a ratio to total filamin A.

N.B.: p values are compared to placebo for each biomarker.

Biomarker	Placebo (N = 22)	Simufilam 50 mg		Simufilam 100 mg	
		All Patients	Compliers	All Patients	Compliers
		N = 19	N = 18	N = 21	N = 19
CSF	19.4 (172.3)	-149 (50.3)	-152 (50.1)	-140 (51.3)	143 (51.3)
HMGB1		p = 0.0001	p = 0.0001	p = 0.0001	p = 0.0001
CSF albumin ^a	-240 (1620)	-1184 (1707)	-1245 (1735)	-2103 (1774)	-2292 (1760)
		p = 0.054	p = 0.046	p = 0.0001	p = 0.0001
CSF IgG ^a	-574.8 (2518.32)	-2269 (2176)	-2444 (2097)	-2253 (2414)	-2350 (2517)
		p = 0.018	p = 0.014	p = 0.007	p = 0.012
Lymphocyte	-0.07 (0.19)	-0.22 (0.13)	-0.23 (0.13)	-0.22 (0.16)	-0.24 (0.16)
filamin A – α7nAChR ^b		p = 0.014	p = 0.009	P = 0.008	p = 0.005
Lymphocyte	-0.05 (0.18)	-0.19 (0.11)	-0.19 (0.11)	-0.18 (0.13)	-0.19 (0.14)
filamin A – TLR4 ^b		P = 0.011	p = 0.010	p = 0.012	p = 0.010
^a Units are optical density units of immunoblot bands.					
^b Densitometric quantities of α7nAChR or TLR4 in anti-filamin A precipitates as a ratio to total filamin A.					
N.B.: p values are compared to placebo for each biomarker.					

CSF Biomarker Percent Change from Baseline

The secondary analysis of percent change from baseline showed significant differences for both dose arms versus placebo on all eleven CSF biomarkers, adjusted for multiplicity for the six primary biomarkers (Fig. 3). P values for change and percent change from baseline were similar, with Aβ₄₂ in the 100 mg dose arm the sole comparison that was significant by percent change but not by change, due to the range in baseline values.

Biomarkers of AD Pathology and Neurodegeneration

Low in Alzheimer's disease, CSF Aβ₄₂ significantly increased 17% and 14% in the 50 and 100 mg arms, respectively (p = 0.0004 and p = 0.004). CSF total tau decreased 16% and 18% (p = 0.0002 and p = 0.00001) and CSF P-tau181 decreased 8% and 11% (p = 0.002 and p = 0.003) in 50 and 100 mg dose arms compared to placebo, respectively. CSF neurofilament light chain, reflecting axonal damage, decreased 28% and 34% in respective dose arms (p = 0.002 and p = 0.0003). Neurogranin, indicating post-

synaptic damage, significantly decreased 36% and 43% in respective dose arms ($p = 0.0004$ and $p = 0.0001$).

Biomarkers of Neuroinflammation

Simufilam treatment significantly decreased four CSF biomarkers of neuroinflammation compared to placebo. YKL-40 decreased 10% and 11% in the 50 and 100 mg arms, respectively ($p = 0.0003$ and $p = 0.0002$). Inflammatory cytokine interleukin-6 decreased 10% and 11% in the 50 and 100 mg arms ($p = 0.017$ and $p = 0.007$). Indicating reduced microglial activation, sTREM2 decreased 43% and 46% in the 50 and 100 mg arms ($p = 0.0009$ and $p = 0.0003$). Finally, the damage-associated molecular pattern protein HMGB1 decreased 33% and 32% in the 50 and 100 mg arms ($p = 0.0002$ and $p = 0.0001$).

Biomarkers of Blood-Brain Barrier Integrity

Simufilam improved blood-brain barrier integrity, evidenced by lower levels of albumin and immunoglobulin G in CSF. Simufilam 50 and 100 mg significantly decreased CSF albumin by 15% and 29%, respectively ($p = 0.04$ and $p = 0.0001$). CSF immunoglobulin G decreased 30% in both drug arms (both $p = 0.02$).

Validation of Biomarker Analyses

The statistical validation of biomarker data is supported by the placebo dataset: modest changes (-2%, on average) and robust correlations (mean $R^2 = 0.96$) between all pair combinations among total tau, P-tau181, neurogranin, neurofilament light chain, YKL-40 and IL-6 in change from baseline. Because $A\beta_{42}$ decreases in CSF in Alzheimer's disease as other markers increase, $A\beta_{42}$ movement negatively correlated with changes in those six biomarkers (mean $R^2 = -0.82$ in placebo). Biomarker changes also correlated in simufilam arms (mean $R^2 = 0.77$, excluding $A\beta_{42}$), indicating that the magnitude of change in individual patients was generally consistent across biomarkers.

Target Engagement

Both $\alpha 7nAChR$ and TLR4 receptors and filamin A are present in lymphocytes, allowing assessment of target engagement in patients' lymphocytes. Filamin A linkages to $\alpha 7nAChR$ and TLR4 in lymphocytes were significantly reduced 31–34% from baseline in both drug arms ($p \leq 0.01$).

Cognition

On the Paired Associate Learning test assessing episodic memory, patients in the 50 mg arm made on average 5.7 fewer errors on Day 28, patients in the 100 mg arm made 4.5 fewer errors, and placebo patients made 1.5 fewer errors (Fig. 4). These differences represent 0.37 and 0.23 effect sizes for 50 and 100 mg arms, respectively, versus placebo. The most and least impaired subjects were removed by baseline score (≥ 54 and ≤ 11 of 70 possible total errors) to eliminate ceiling effects (those with very few errors) and subjects who performed so poorly that they may not have understood the task. Standard deviations for change from baseline in PAL total errors were 8.5, 13.6, 17.7 for placebo, 50 and 100 mg, respectively.

In Spatial Working Memory, patients in 50 and 100 mg arms made 2.3 and 3.3 fewer errors, respectively, compared to 0.4 in placebo, representing 0.25 and 0.46 effect sizes. Standard deviations for change from baseline in Spatial Working Memory total errors were 7.5, 7.5, 4.7 for placebo, 50 and 100 mg, respectively.

Improvements in episodic memory, correlated most strongly with decreases in P-tau181 ($R^2 = 0.48$). Interleukin-6, total tau, albumin, neurofilament light chain and YKL-40 also correlated (R^2 values 0.41, 0.37, 0.37, 0.36 and 0.30, respectively).

In reaction time, placebo, 50 and 100 mg arms showed mean (SD) changes from baseline in median reaction time of -11 (57), -19 (38) and 11 (66) milliseconds, respectively.

Safety

Simufilam was safe and well-tolerated. There were no serious adverse events. Adverse events were mostly mild; none caused discontinuation; none were noted likely to be drug related. Total adverse events were 20, 9 and 15 in placebo, 50 and 100 mg arms, respectively. Adverse events that occurred in 3 or more patients were headache (3, 1 and 2), fatigue (2, 1 and 0), nausea (2, 0 and 1), and upper respiratory infection (1, 2 and 2) for placebo, 50 and 100 mg, respectively.

Discussion

In a randomized clinical trial of 64 patients with Alzheimer's disease dementia, simufilam 50 or 100 mg significantly improved multiple biomarkers of Alzheimer's disease, neurodegeneration, neuroinflammation and blood-brain barrier integrity, with no safety issues. Collectively, results of this randomized controlled trial are consistent with the drug's mechanism of action and replicate a prior, open-label study.²⁰

Increases in $A\beta_{42}$ and reductions in total tau and p-Tau181 imply reduced Alzheimer's disease pathophysiology. Reduced levels of neurofilament light chain and neurogranin suggest a slower rate of neurodegeneration. The 36% and 43% reductions in neurogranin, considered specific to Alzheimer's disease,²⁴ additionally suggest reduced disease pathology. Reductions in neuroinflammatory markers YKL-40, interleukin-6, sTREM2 and HMGB1 indicate suppressed neuroinflammation. Because HMGB1 also damages neurites and furthers neuroinflammation,²⁴ the more than 30% reductions in HMGB1 imply reduced pathogenic drive. Finally, lower CSF albumin and immunoglobulin G indicate improved blood-brain barrier integrity, possibly related to simufilam's suppression of neuroinflammation, as blood-brain barrier breakdown correlates with neuroinflammation and cognitive decline.^{25,26} Restoring $\alpha 7nAChR$ function by displacing $A\beta_{42}$ from this receptor may also improve blood-brain barrier integrity.^{27,28}

Robust statistical correlations between biomarkers in changes from baseline within the placebo arm illustrate the interdependency of biomarkers in Alzheimer's disease and validate the study's biomarker assessments. Strong correlations between biomarkers in changes from baseline within simufilam arms suggest that the filamin A proteopathy is a critical, upstream pathogenic event in Alzheimer's disease.

Reductions in filamin A linkages to $\alpha 7$ nAChR and TLR4 in patient lymphocytes, demonstrating target engagement, likely mirror the target engagement of simufilam in brain. Reductions in these filamin A linkages were previously demonstrated in both brain and lymphocytes of simufilam-treated Alzheimer's disease transgenic mice (lymphocytes unpublished), and in postmortem human Alzheimer's disease brain tissue incubated with simufilam.¹⁷

The small dose-response in this study suggests near saturation of the target protein, anticipated because simufilam, a small molecule, binds the altered conformation of filamin A with ultra-high (580 femtomolar) affinity.¹⁷ Clean safety, a mild dose-response, high (98%) response rate and clear evidence of target engagement collectively suggest 50–100 mg b.i.d. is an optimal dose range.

Effect sizes on tests of episodic and spatial working memory suggest a drug response. Episodic memory improvements correlated best with decreases in levels of CSF P-tau181. Because cognitive decline is not expected over 28 days in mild-to-moderate Alzheimer's disease patients, the biomarker changes that imply slowed disease progression may also reflect suppressed disease mechanisms and improved neuronal function. Certainly, any benefit to cognition over this trial's duration implies cognitive enhancement.

FDA Guidance requires clinical trials in Alzheimer's disease to show a clinical benefit on cognitive and functional co-primary endpoints. Meaningful benefits are unlikely to occur without concurrent improvements in a broad panel of disease biomarkers. There are few reports of drug effects on CSF biomarkers, and these effects on one to three markers have not always shown concurrent effects on cognition or function.²⁹ Drug effects on biomarkers that are compellingly related to the neurobiology of Alzheimer's disease in the pathway(s) affected by a drug candidate can support a regulatory claim for disease modification.³⁰

Simufilam's potential to modify the disease and enhance cognition is supported by preclinical data. In a triple transgenic mouse model of Alzheimer's disease, simufilam improved cognitive behavior and reduced amyloid deposits, tau hyperphosphorylation, neurofibrillary lesions and inflammatory cytokine release.¹⁷ Additionally, in brains of these transgenic mice, and in postmortem human brain tissue, simufilam restored function of $\alpha 7$ nAChR, N-methyl-D-aspartate (NMDA) receptors and insulin receptors and improved synaptic plasticity (indicated by NMDA-induced activity-dependent expression of the master synaptic plasticity regulator Arc).¹⁷ Improvements in receptor function and synaptic plasticity could underlie the apparent cognitive enhancement in this trial.

Limitations

There are several limitations to this study. The sample size is small. The directional changes and statistical significance are encouraging; however, the magnitude of observed biomarker changes is of uncertain significance. The relationships of changes in biomarkers to cognitive and functional measures have not been established, and multiple studies assessing a similar panel of biomarkers are required to

determine these correlations and mechanistic relationships. Studies of simuflam large enough to detect treatment effects on clinical measures are warranted. Despite an interpretation of slowed disease processes, this study was not long enough to allow conclusions regarding disease modification. Longer studies are needed to measure effects on the trajectory of clinical decline.

Conclusions

Simuflam is the first of a new class of drug candidates to target altered filamin A, a proteopathy in Alzheimer's disease. This clinical dataset of CSF biomarker changes offers new insights into the pathophysiology of Alzheimer's disease and a potential new therapeutic strategy. Effect sizes on memory assessments indicate potential for cognitive enhancement. Simuflam's ability to slow disease progression in patients will need to be evaluated in large, definitive clinical trials.

Abbreviations

Amyloid-beta1-42 (A β 42), phospho-tau181 (P-tau181), α 7 nicotinic acetylcholine receptor (α 7nAChR), toll-like receptor 4 (TLR4), cluster-of-differentiation14 (CD14), National Institute on Aging (NIA), Alzheimer's Association (AA), Mini-Mental State Exam (MMSE), soluble triggering receptor expressed on myeloid cells 2 (sTREM2), high mobility group box 1 (HMGB1), Cambridge Neuropsychological Test Automated Battery (CANTAB)

Declarations

Ethics Approval and Consent to Participate:

This study was reviewed and approved by Advarra, Inc., a central institutional review board. Written informed consent was obtained from all participants.

Consent for Publication:

As patient data is presented only in aggregate, no consent for publication was required.

Availability of Data:

Cassava Sciences has not established a data sharing repository for the data from this trial.

Competing Interests:

Simuflam is the chemical name for a compound owned by Cassava Sciences, Inc. CC, GBT, RB, NF and LHB are Cassava Sciences employees. H-YW and JC are consultants and scientific advisory board members for Cassava Sciences.

Funding:

This trial was supported by NIA grant AG050878. NIA personnel approved the clinical trial protocol. NIA personnel also approved the selection of Data and Safety Monitoring Board members and participate in these meetings.

Acknowledgements

We thank the patients and caregivers, clinical investigators, site staff and monitors involved in this trial. We are grateful for advice of our advisors and the scientific and financial support of the National Institute on Aging (NIA).

Author Contributions

RB, NF and LHB designed the clinical trial with guidance from JC. Biomarker analyses were conducted blind to treatment and time point by H-YW, ZP and K-CL. K-CL and H-YW conducted APOE genotyping. CC oversaw clinical operations and trial monitors. YGR, TAD, JP, BB, PS, ELB and BN were clinical investigators. GBT analyzed lymphocyte assays. LHB wrote the manuscript with help from HYW, RB and JC. All authors have access to the data via an electronic data capture system, except H-YW, ZP and K-CL who remain blinded to treatment.

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Figures



Figure 1

Patient Flow Diagram

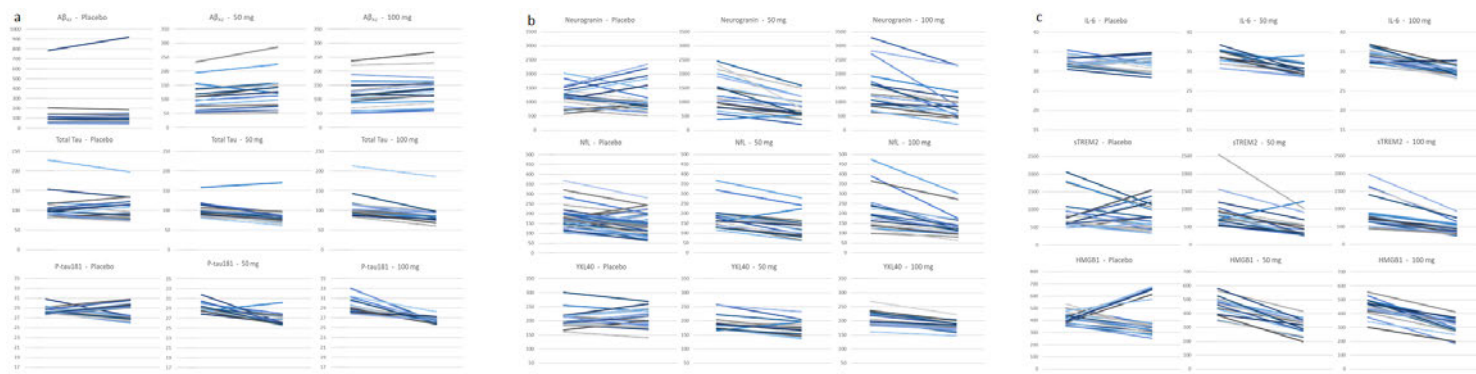


Figure 2

Simufilam improved biomarkers of AD pathology, neurodegeneration, neuroinflammation and BBB integrity. Percent change from baseline of CSF biomarkers (A) and lymphocyte target engagement markers (B). Reductions in filamin A linkages to α7nAChR or TLR4 in lymphocytes indicate target engagement. These secondary analyses of percent change from baseline on all biomarkers excluded the 3 patients with no detectable simufilam in plasma at return visits. Data are means ± SEM. * $p \leq 0.0001$, # $p < 0.001$, † $p < 0.01$ and + $p < 0.05$ versus placebo. N=22, 20, 19 for placebo, 50 and 100 mg, respectively.

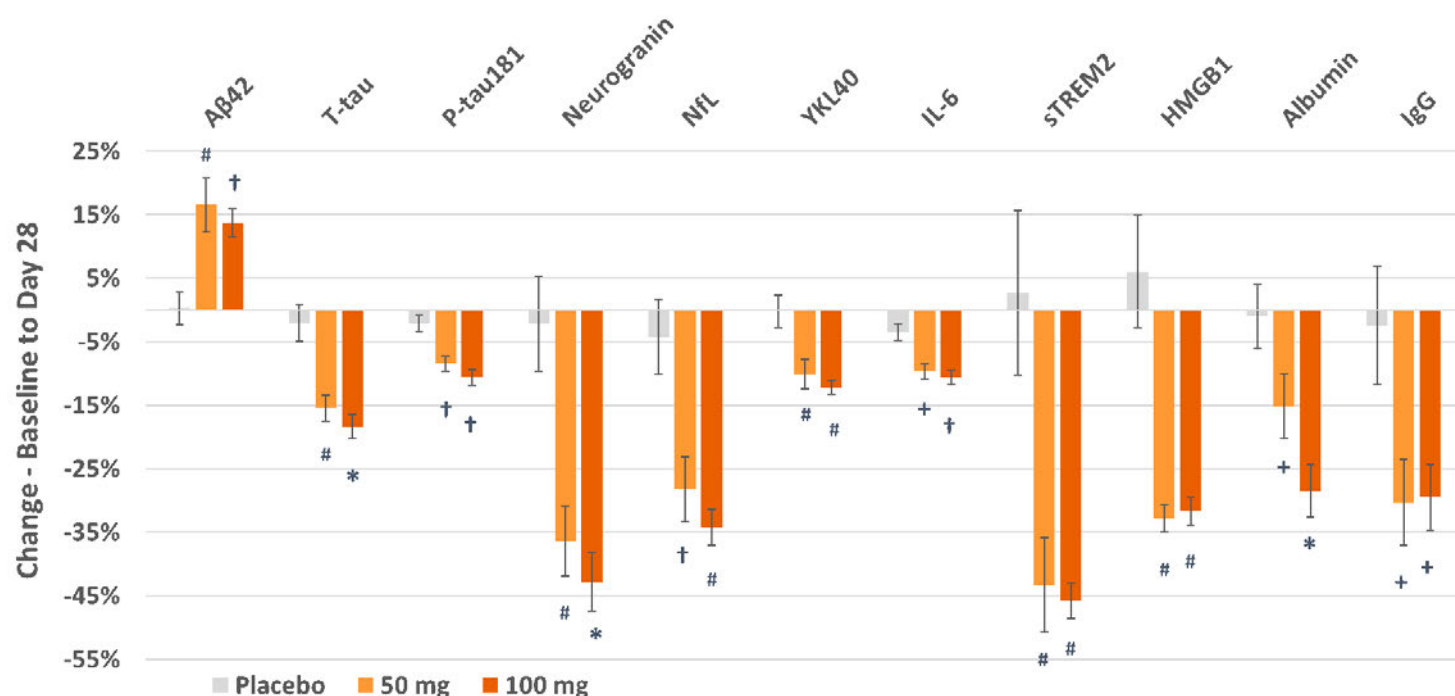


Figure 3

Spaghetti plots by group for biomarkers measured by ELISA. Plots show individual patient levels (pg/mL) at screening (left) and at Day 28 (right). All patients in simufilam groups show decreases in all biomarkers except one individual in the 50 mg group. By contrast, placebo patients show movement in

both directions for each biomarker. A: Core AD pathology biomarkers. B: Neurogranin, neurofilament light chain (NfL), and YKL-40. C: Secondary biomarkers IL-6, sTREM2 and HMGB1.

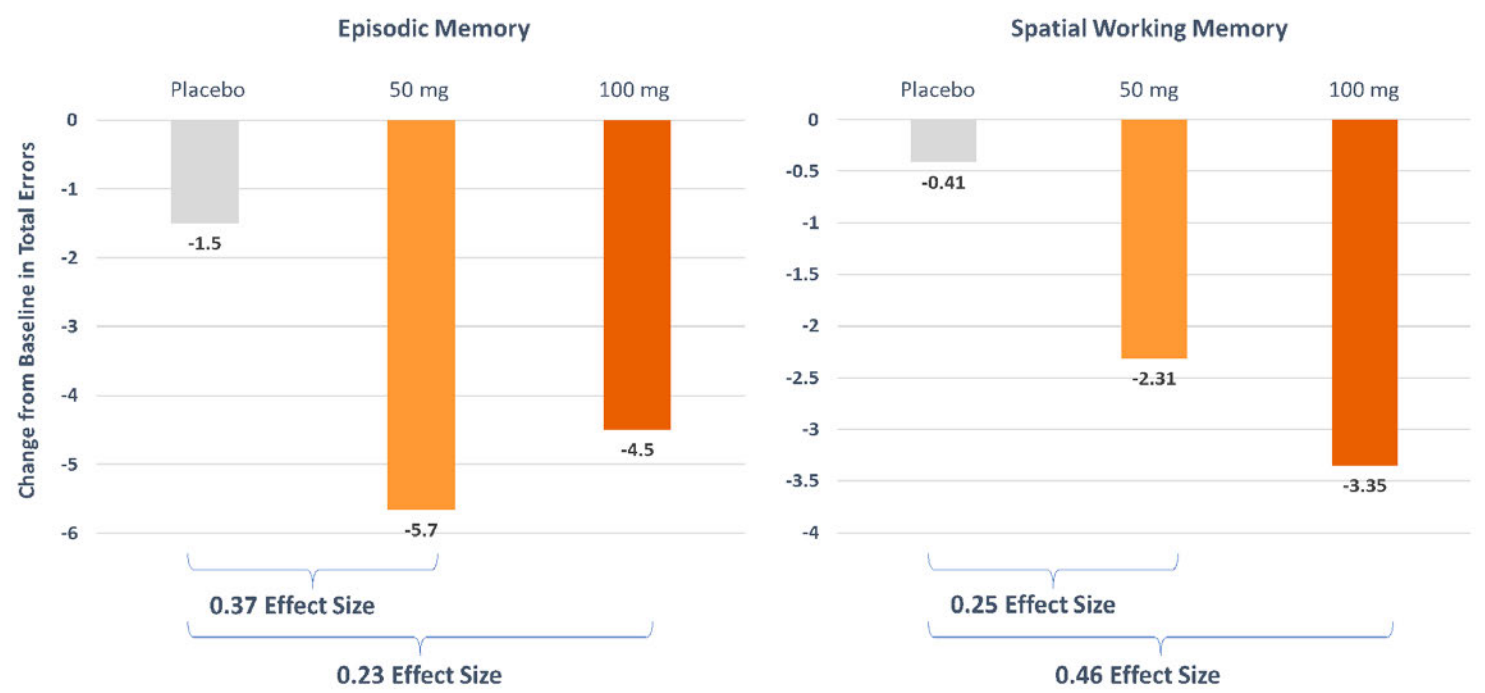


Figure 4

Simufilam appeared to improve both episodic memory and spatial working memory. Effect sizes were calculated by Hedge's g. For the episodic memory test (Paired Associates Learning), the least impaired patients (11 or fewer errors, representing a ceiling effect) and patients with 54 or more errors (very poor performance suggesting not understanding the task) were removed from the analysis. Both datasets removed the 3 patients with no detectable drug in plasma, 2 patients with $\geq 25\%$ non-compliance by pill counts, one patient with no baseline test and one who did not understand instructions per rater notes. N=14, 13, 10 for PAL, and N=22, 17, 18 for spatial working memory for placebo, 50 and 100 mg, respectively.

From: AD Science <adscienceblog21@gmail.com>
Sent time: 09/14/2021 06:18:24 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Hello from ad-science blog

Dear Dr. Wang,

Hope you are doing well.

We are a group of scientists and investors in Cassava Sciences and our blog <https://ad-science.org>, aims to provide scientific facts in support of the company and distinguished scientists like yourself. For example, our [recent article](#), counters the claims made in the newest citizen petition supplement. Your scientific contributions are greatly appreciated by us and our readers.

As part of research on a new blog post on PTI-125 and its relationship to altered Filamin A, we had some questions. Note that we recognize that you may be unable to answer questions considering the current circumstances. Do let us know if you cannot do so. Please also feel free to correct any inaccurate assumptions we may have made.

Question: On PTI-125's ability to bind with FLNA Ig24.

PTI-125 was developed against a short peptide located on the first beta strand of FLNA Ig24 domain. It binds an "altered" conformation of filamin A (FLNA) and restores its shape. We discuss what the altered FLNA could mean with questions/comments below:

Altered FLNA monomer: A monomer of filamin A (FLNA) is a large, rod-like protein containing an actin binding domain at the N-terminal, followed by 24 Ig domains. These domains are covalently connected, so a FLNA monomer cannot be broken unless it is cleaved by some enzymes called proteases. **Thus in this conformation, PTI-125 may be unable to restore it?**

Altered FLNA dimer: The functional form of FLNA is a dimer, and this dimer is mediated by Ig24 via a non-covalent Ig24-Ig24 interaction. A dimerized FLNA may be broken into two monomers by some molecules that block the dimerization interface. PTI-125 binds to Ig24, so it is well possible that it may affect the Ig24 mediated dimerization. NLX, which is claimed to bind to the same site of Ig24, does not affect the dimerization. **Could PTI-125 affect this dimerization?**

Altered FLNA-receptor association: As a dimer, FLNA can crosslink actin filaments. In addition, several domains such as Ig19 and Ig21 in FLNA are known to bind membrane receptors including GPCRS. If PTI-125 can inhibit the association of FLNA dimer to the membrane receptors, it may be able to reduce FLNA-dependent dysfunction of $\alpha 7$ nAChRs, which in turn could decrease the hyperphosphorylation of the tau protein and A-beta aggregations (Wang and Burns, J. Neurosci., July 18, 2012 32: 9773–9784). **However, since PTI-125 binds to Ig24, instead of Ig21 or Ig19, it may be unable to perturb the membrane receptor association of FLNA?**

Altered FLNA-actin association: The N-terminus of FLNA bind actin filament. Therefore, FLNA can link the actin cytoskeleton network to membrane receptors including GPCRs and can crosslink actin filaments since each FLNA dimer contains to actin binding sites. The FLNA-actin binding is non-covalent, so it is possible to be inhibited or suppressed with some interfering drug molecules. **But since PTI-125 binds Ig24 which is located at the other end of FLNA, it may be unable to do it?**

There is also a question on **how well PTI-125 binds Ig24**, since the previously published competition assays were based on a pentapeptide from the first strand of Ig24. An isolated peptide is flexible and assumes a randomly coiled conformation - thus it may not present the same conformation as the peptide bound in the folded Ig24.

Question on paper PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis

doi: 10.1016/j.neurobiolaging.2017.03.016

One of the experiments on the post-mortem human brain specified that PTI-125 dose-dependently restored NMDA receptor signaling that is impaired in postmortem AD. Would you be able to elaborate on this experiment? Some concerns were raised on what this signaling might refer to and if it can be triggered in a post mortem human brain.

We greatly appreciate you taking the time to address our questions. We are genuinely trying to learn this complex material and pass what we learn on to our readers. Wishing you the best.

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From your work [here](#),

This altered form of FLNA was evidenced by a shift in isoelectric focusing point (pI) from 5.9 in the native state to 5.3 in postmortem human AD brain or brains of mouse models[13]. An altered pI can indicate an altered conformation, reflecting changes in hydrogen bonding, charge-charge interactions or accessibility of ionizable residues within the molecule[48-50]. In this case, the shifted pI is resistant to complete dephosphorylation by alkaline phosphatase. Hence, unlike the proteopathies of tau and alpha-synuclein, the altered conformation of FLNA is not due to changes in phosphorylation state. Further studies are needed to reveal the details of FLNA's conformational change and whether altered FLNA is unique to AD.

Are there other possible experiments beyond isoelectric focusing that may point to altered FLNA?

The previously published experiments were based on a pentapeptide from the first strand of Ig24 and since it is flexible and assumes a randomly coiled conformation - is it possible that it may not present the same conformation for PTI-125 to target?

However If it did, this can be strong evidence of the effectiveness of PTI-125. It binds to an altered Ig24 site that should not be interacting with receptors - but the alterations make it happen. By changing conformation, PTI-125 thus can restore normal FLNA function (i.e. Ig24 site no longer interacts with receptors).

Another way to perhaps frame an interpretation of our earlier question is, just because the Ig24 site in normal FLNA does not interact with receptors, does not preclude it from interacting with receptors in the altered state. Is this a valid representation to make?

We also are encouraged by the results independently demonstrated in [Filamin A inhibition reduces seizure activity in a mouse model of focal cortical malformations](#)

Is it possible for you to share more independent research with us and your observations if any?

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+Dr.Burns cassavasciences email id

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Subject: [EXTERNAL] Re: Questions from ad-science blog team

Dear AD Science team,

Dr. Wang was the first person to publish that soluble Abeta42 binds ultra-tightly to the alpha7 nicotinic acetylcholine receptor (<https://pubmed.ncbi.nlm.nih.gov/10936198/>) and that this interaction results in activation of kinases that hyperphosphorylate tau (<https://pubmed.ncbi.nlm.nih.gov/12801934/>). These seminal publications resulted in several pharma co's working on alpha7 programs as a potential treatment for Alzheimer's. This target was eventually deemed too difficult to develop: partial agonists and allosteric modulators either didn't work or were toxic. I will see what I can answer below.

1. What does the altered shape mean, especially in relation to the simufilam binding site: The altered shape of FLNA is found in AD brain and AD mouse models but can also be induced by exogenous Abeta42 either in postmortem human control brain tissue or rat brain slices, or by infusing Abeta42 into the ventricles of mice (see NBA 2017). We don't really know what causes Abeta42 to bind tightly and signal through alpha7, but we do know that the linkage of FLNA from the inside of the cell to the receptor enables the femtomolar binding of Abeta42 for the receptor and the signaling that hyperphosphorylates tau. We have shown that the drug reduces this binding affinity (of Abeta42 for alpha7) by 1000- to 10,000-fold. So altered FLNA is kind of the back-door approach to the alpha7 target. Simufilam binds altered FLNA 100x more tightly than native FLNA, probably because the binding site is more exposed in the altered conformation. Of course, the evidence we have right now of altered shape is the shift in isoelectric focusing point and this differential binding affinity.
2. We do not know exactly where on FLNA it is that FLNA interacts with the alpha7 and TLR4 receptors (and whether this is the same as the simufilam binding site VAKGL, but it is all fairly close to the membrane-bound region. Keep in mind that native FLNA constitutively interacts with MOR and IR, just not with alpha7 or TLR4.
3. As far as other work (in addition to the epilepsy model from the Bordey lab at Yale), we have demonstrated other potential therapeutic effects in one or more patent filings. We know of other academics who may be interested in testing the drug in different disease models.
4. The NMDAR activation in the postmortem tissue is recruitment or activation of different signaling molecules in the pathway after stimulating with NMDA and glycine. Enzymes are not destroyed in flash frozen tissue; otherwise embryos would never be viable after freezing at -70 (just one example). I don't know if enzymes are needed for NMDA receptor activation. The synaptic plasticity marker arc is expressed after NMDAR activation via the immediate early gene ARC -- this activity-dependent expression we were able to show is impaired in postmortem human control brain incubated with Abeta42 and improved in the presence of simufilam.

To your point, this is a very complex area of science.

Hope this helps for now.

Thanks again,
Lindsay

From: AD Science <adscienceblog21@gmail.com>
Sent: Wednesday, September 15, 2021 2:42 PM
To: hywang@med.cuny.edu <hywang@med.cuny.edu>; lindsayhb@yahoo.com <lindsayhb@yahoo.com>; Lindsay Burns <lburns@cassavasciences.com>
Subject: Re: Questions from ad-science blog team

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+Dr.Burns cassavasciences email id

On Wed, Sep 15, 2021 at 12:34 PM AD Science <adscienceblog21@gmail.com> wrote:

Dear Dr. Wang and Dr. Burns,

Hope
you are doing well.

We

are a group of scientists and investors in Cassava Sciences and our blog

<https://ad-science.org>

aims to provide scientific facts in support of the company and distinguished scientists like yourselves. For example, our [recent article](#),

counters the claims made in the newest citizen petition supplement. Your scientific contributions are greatly appreciated by us and our readers.

As

part of research on a new blog post on PTI-125 and its relationship to altered Filamin A, we have some questions. Note that we recognize that you may be unable to answer questions considering the current circumstances. Do let us know if you cannot do so. Please

also feel free to correct any inaccurate assumptions we may have made.

Question:

On PTI-125's ability to bind to FLNA Ig24.

PTI-125

was developed against a short peptide located on the first beta strand of FLNA Ig24 domain. It binds an altered conformation of filamin A (FLNA) and restores its shape and function. As part of our blog post, we plan to discuss what altered FLNA may mean. Is

it possible for you to explain what these alterations could represent and how they impact the binding sites?

From

your work [here](#),

This

altered form of FLNA was evidenced by a shift in isoelectric focusing point (pI) from 5.9 in the native state to 5.3 in postmortem human AD brain or brains of mouse models[13]. An altered pI can indicate an altered conformation, reflecting changes in hydrogen

bonding, charge-charge interactions or accessibility of ionizable residues within the molecule[48-50]. In this case, the shifted pI is resistant to complete dephosphorylation by alkaline phosphatase. Hence, unlike the proteopathies of tau and alpha-synuclein,

the altered conformation of FLNA is not due to changes in phosphorylation state. Further studies are needed to reveal the details of FLNA's conformational change and whether altered FLNA is unique to AD.

Are

there other possible experiments beyond isoelectric focusing that may point to altered FLNA?

The

previously published experiments were based on a pentapeptide from the first strand of Ig24 and since it is flexible and assumes a randomly coiled conformation - is it possible that it may not present the same conformation for PTI-125 to target?

However

If it did, this can be strong evidence of the effectiveness of PTI-125. It binds to an altered Ig24 site that should not be interacting with receptors - but the alterations make it happen. By changing conformation, PTI-125 thus can restore normal FLNA function

(i.e. Ig24 site no longer interacts with receptors).

Another

way to perhaps frame an interpretation of our earlier question is, just because the Ig24 site in normal FLNA does not interact with receptors, does not preclude it from interacting with receptors in the altered state. Is this a valid representation to make?

We

also are encouraged by the results independently demonstrated in [Filamin](#)
[A inhibition reduces seizure activity in a mouse model of focal cortical malformations](#)

Is it possible for you to share
more independent research with us and your observations if any?

Question

on paper *PTI-125 binds and
reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis*
doi:

10.1016/j.neurobiolaging.2017.03.016

One

of the experiments on the post-mortem human brain specified that PTI-125 dose-dependently restored NMDA receptor signaling that is impaired in postmortem AD. Would you be able to elaborate on this experiment? Some concerns were raised on what this signaling

might refer to and if it can be triggered in a post mortem human brain. Our take is this represents an enzymatic response from the receptor. Please share with us your thoughts.

We

greatly appreciate you taking the time to address our questions. We are genuinely trying to learn this complex material and pass what we learn on to our readers. Wishing you the best.

Sincerely,

the

ad-science blog team

<https://ad-science.org/>

From: AD Science <adscienceblog21@gmail.com>
Sent time: 09/16/2021 12:50:34 PM
To: Lindsay Burns <lburns@cassavasciences.com>
Cc: Hoau-yan Wang
Subject: [EXTERNAL] Re: Questions from ad-science blog team

Thank you so much Dr. Burns and Dr. Wang. This is very useful information. All our volunteers are crowdsourced at this point. We have in our team a neuroscientist who is doing the basic research to write this article. We are also in the process of getting an FLNA research scientist who at the moment is a bit of a sceptic. As we get further, we hope you may be able to continue helping us understand the underlying science published in the papers.

Thank you again!

Sincerely,
the ad-science blog team
<https://ad-science.org/>

On Wed, Sep 15, 2021 at 8:28 PM Lindsay Burns <lburns@cassavasciences.com> wrote:

Dear AD Science team,

Dr. Wang was the first person to publish that soluble Abeta42 binds ultra-tightly to the alpha7 nicotinic acetylcholine receptor (<https://pubmed.ncbi.nlm.nih.gov/10936198/>) and that this interaction results in activation of kinases that hyperphosphorylate tau (<https://pubmed.ncbi.nlm.nih.gov/12801934/>). These seminal publications resulted in several pharma co's working on alpha7 programs as a potential treatment for Alzheimer's. This target was eventually deemed too difficult to develop: partial agonists and allosteric modulators either didn't work or were toxic. I will see what I can answer below.

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To your point, this is a very complex area of science.

Hope this helps for now.

Thanks again,
Lindsay

From: AD Science <adscienceblog21@gmail.com>
Sent: Wednesday, September 15, 2021 2:42 PM
To: hywang@med.cuny.edu <hywang@med.cuny.edu>; lindsayhb@yahoo.com <lindsayhb@yahoo.com>; Lindsay Burns <lburns@cassavasciences.com>

Subject: Re: Questions from ad-science blog team

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+Dr.Burns cassavasciences email id

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Dear Dr. Wang and Dr. Burns,

Hope
you are doing well.

We
are a group of scientists and investors in Cassava Sciences and our blog
<https://ad-science.org>
aims to provide scientific facts in support of the company and distinguished scientists like yourselves. For example,
our
[recent article](#),
counters the claims made in the newest citizen petition supplement. Your scientific contributions are greatly
appreciated by us and our readers.

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part of research on a new blog post on PTI-125 and its relationship to altered Filamin A, we have some questions.
Note that we recognize that you may be unable to answer questions considering the current circumstances. Do let us
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*altered form of FLNA was evidenced by a shift in isoelectric focusing point (pI) from 5.9 in the native state to 5.3 in
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shifted pI is resistant to complete dephosphorylation by alkaline phosphatase. Hence, unlike the proteopathies of tau
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doi:

10.1016/j.neurobiolaging.2017.03.016

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greatly appreciate you taking the time to address our questions. We are genuinely trying to learn this complex material and pass what we learn on to our readers. Wishing you the best.

Sincerely,

the

ad-science blog team

<https://ad-science.org/>

From: Holli-Anne S Tai
Sent time: 09/21/2021 10:45:43 AM
To: Legal Affairs <LegalAffairs@rfcuny.org>
Cc: Awards; Marc Scullin; Hoau-yan Wang
Subject: FW: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)
Attachments: CIF 7xxxx-0001 Hoau-Yan Wang (Cassava Sciences)_2021 0921_fx.pdf NoA 1_ Investigational Research Contract CUNY 17 June 2021.docx
21-4073_Wang_Cassava Sciences xls COI Determination Memo Wang.pdf

Dear Legal,

Please see attached CIF for Professor Hoau-Yan Wang's new project with Cassava Sciences.

Please let me know if anything is needed.

Best,

Holli-Anne Tai
Grants Associate
Grants and Sponsored Programs
The City College of New York
160 Convent Avenue | SH – Room 16
New York, NY 10031
Ph: 212-650-5418 | F: 212-650-7906
GSP - <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <http://www.ccny.cuny.edu/research/pars.cfm>

From: Holli-Anne S Tai
Sent: Wednesday, June 30, 2021 9:43 AM
To: Lindsay Burns <lburns@cassavasciences.com>; Sharki Ahmed <sahmed9@ccny.cuny.edu>; Awards <awards@ccny.cuny.edu>
Cc: Marc Scullin <mscullin@med.cuny.edu>; Hoau-yan Wang <hywang@med.cuny.edu>
Subject: RE: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Lindsay,

Thank you for the clarification, and duly noted. We will keep you updated on the status of the contract review.

Best,

Holli-Anne Tai
Grants Associate
Grants and Sponsored Programs
The City College of New York
160 Convent Avenue | SH – Room 16
New York, NY 10031
Ph: 212-650-5418 | F: 212-650-7906
GSP - <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <http://www.ccny.cuny.edu/research/pars.cfm>

From: Lindsay Burns lburns@cassavasciences.com
Sent: Tuesday, June 29, 2021 4:35 PM
To: Holli-Anne S Tai htai@ccny.cuny.edu; Sharki Ahmed sahmed9@ccny.cuny.edu; Awards <awards@ccny.cuny.edu>
Cc: Marc Scullin <mscullin@med.cuny.edu>; Hoau-yan Wang <hywang@med.cuny.edu>
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

All,

I am sending the contract again with the payment schedule section complete (in Attachment A). The detailed budget was always there in the Attachment B. If your contracts people would like the contract amount listed elsewhere, please ask them to insert it in the appropriate place.

Thanks,
Lindsay

From: Holli-Anne S Tai <htai@ccny.cuny.edu>
Sent: Tuesday, June 29, 2021 3:15 PM

To: Sharki Ahmed <sahmed9@ccny.cuny.edu>; Lindsay Burns <lburns@cassavasciences.com>; Awards <awards@ccny.cuny.edu>
Cc: Marc Scullin <mscullin@med.cuny.edu>; Hoau-yan Wang <hywang@med.cuny.edu>
Subject: RE: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

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Thank you Sharki,

Dr. Burns, we have received the contract, but before we can route it to our Legal team for review, we required a line item budget to be completed.

Professor Wang: Per CUNY policy, Your FCOI supplement form will also need to be sent to the College Conflicts Office for further review and determination. I will copy you on the email.

Best,

Holli-Anne Tai
Grants Associate
Grants and Sponsored Programs
The City College of New York
160 Convent Avenue | SH – Room 16
New York, NY 10031
Ph: 212-650-5418 | F: 212-650-7906
GSP - <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <http://www.ccny.cuny.edu/research/pars.cfm>

From: Sharki Ahmed <sahmed9@ccny.cuny.edu>
Sent: Tuesday, June 29, 2021 3:38 PM
To: Lindsay Burns <lburns@cassavasciences.com>; Awards <awards@ccny.cuny.edu>
Cc: Marc Scullin <mscullin@med.cuny.edu>; Hoau-yan Wang <hywang@med.cuny.edu>
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Dr. Burns,

I am looping in the awards team for information on that.

Awards Team- Do you have the contract? And has it been reviewed as per Dr. Burns' email? (We have finished on the Pre-award side).

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
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From: Lindsay Burns <lburns@cassavasciences.com>
Sent: Tuesday, June 29, 2021 3:35 PM

To: Sharki Ahmed
Cc: Marc Scullin; Hoau-yan Wang
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Sharki,

Has the contract been reviewed? Is it ready to sign? Did you pass it on or are you asking me to do that? I thought it would have been there when I sent it over. I'm just confused.

Thanks,
Lindsay

From: Sharki Ahmed <sahmed9@ccny.cuny.edu>
Sent: Tuesday, June 29, 2021 2:15 PM
To: Lindsay Burns <lburns@cassavasciences.com>
Cc: Marc Scullin <msscullin@med.cuny.edu>; Hoau-yan Wang <hywang@med.cuny.edu>
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

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Hi Dr. Burns,

Below is the email address for our post-award team.

awards@ccny.cuny.edu

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Tuesday, June 29, 2021 3:13 PM
To: Lindsay Burns
Cc: Marc Scullin; Grants Preaward; Hoau-yan Wang
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Dr. Burns,

Please find attached the documents for Prof. Wang.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
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GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
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From: Sharki Ahmed
Sent: Tuesday, June 29, 2021 10:59 AM
To: Lindsay Burns; Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Dr. Burns,

Noted. So I will provide you with the budget, budget justification and a letter. The agreements on the contract terms would be a post-award function, I will send you the appropriate email once I send you the above mentioned documents.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
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GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
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From: Lindsay Burns <lburns@cassavasciences.com>
Sent: Tuesday, June 29, 2021 10:50 AM
To: Sharki Ahmed; Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Sharki,

What we really need is agreement on the contract terms. The budget is fine from our perspective. We have seen the justification.

Thank you!
Lindsay

From: Sharki Ahmed <sahmed9@ccny.cuny.edu>

Sent: Tuesday, June 29, 2021 9:48 AM

To: Hoau-yan Wang <hywang@med.cuny.edu>

Cc: Marc Scullin <mscullin@med.cuny.edu>; Lindsay Burns <lburns@cassavasciences.com>

Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Hi Prof. Wang,

Just wanted to touch base on this proposal. I have listed a deadline for tomorrow. Since we have finalized the budget, please provide us with a budget justification (in Word format).

Dr. Burns- What is needed for this submission? A letter of commitment? CV? Budget? Budget justification?

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Wednesday, June 9, 2021 3:06 PM
To: Lindsay Burns; Hoau-yan Wang
Cc: Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Hi Lindsay,

Noted. Thank you for the explanation and clarification.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
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GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>

PARS - <https://www.ccny.cuny.edu/research/pars>

From: Lindsay Burns <lburns@cassavasciences.com>

Sent: Wednesday, June 9, 2021 11:03 AM

To: Sharki Ahmed; Hoau-yan Wang

Cc: Marc Scullin

Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Sharki,

We were planning to submit to an RFA from the Michael J Fox Foundation, but it won't be released now until August 9. So instead, we are suggesting that Cassava Sciences fund this work so that it can start this summer. Dr. Wang and I have worked on many projects together, and he has been a sub-awardee on multiple Cassava Sciences NIH grants, where the 57% has been used. Because we are proposing that Cassava Sciences fund this work directly, I proposed a lower overhead rate that is in line with what we used in earlier agreements for research conducted by Dr. Wang several years ago.

Kind regards,
Lindsay

From: Sharki Ahmed <sahmed9@ccny.cuny.edu>

Sent: Wednesday, June 9, 2021 8:51 AM

To: Hoau-yan Wang <hywang@med.cuny.edu>

Cc: Marc Scullin <mscullin@med.cuny.edu>; Lindsay Burns <lburns@cassavasciences.com>

Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

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Hi Prof. Wang,

Is there a specific solicitation(RFP) to which you are applying to? If in that solicitation the IDC rate stated is 25%, then that is fine.

Best,

Sharki Ahmed
Grants Associate

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GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>

PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-yan Wang

Sent: Monday, June 7, 2021 4:06 PM

To: Sharki Ahmed

Cc: Marc Scullin; Afrodita Feratovic; Lindsay Burns

Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Sharki,

Thanks for the budget, I don't see anything in need to be modified.

Regarding the 25% indirect cost, this is from the sponsor, Cassava Sciences (Dr. Lindsay Burns copied here) set the indirect cost rate of 25%. This is a 10% increase from our original plan to submit the grant to Michael J Fox foundation (15% indirect). Since I think it is advantageous to Research foundation (I get the same budget from either sources). If this is not agreeable, we can then in turn submit via Michael J. Fox Foundation. Any question regarding indirect, please communicate with Dr. Burns.

Thanks again.

Best,

Hoau-Yan Wang

Hoau-Yan Wang, Ph.D.

Medical Professor

CUNY SOM

From: Sharki Ahmed
Sent: Monday, June 7, 2021 10:46 AM
To: Hoau-yan Wang
Cc: Marc Scullin; Afrodita Feratovic
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Prof. Wang,

As Afrodita mentioned, I will be assisting you on this proposal. Please find attached the draft budget and let me know if there are any changes needed.

Please provide us the solicitation/guidelines for this proposal. Also, you indicated the 25% IDC rate. I have included it as is, but please provide me with the appropriate source for the reduced rate (must be stated in the solicitation). Otherwise, the 57% IDC rate must be used.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <http://www.ccny.cuny.edu/research/gsp.cfm>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Afrodita Feratovic
Sent: Monday, June 7, 2021 9:45 AM
To: Hoau-yan Wang
Cc: Sharki Ahmed; Marc Scullin
Subject: Re: [EXTERNAL] New Proposal Assistance Request for Hoau-Yan Wang. (Submission Due Date: 06-30-2021)

Dear Prof. Wang,

Sharki Ahmed is assigned to work with you on this proposal and will follow up with you directly concerning the preparation for this proposal.

IMPORTANT NOTE:

The CUNY Financial Conflict of Interest Form is required. Please complete and return the attached FCOI form by the date indicated below. This form **MUST be completed by all CUNY investigators identified** on the project. While this disclosure form is not required at this application stage for investigators who have not yet been named in this proposal, please keep in mind that once the project is funded and such investigators are identified to be involved in your project activities, **You should notify them that they are required to submit the CUNY Financial Conflict of Interest at that time.**

Please log into **Cayuse SP** now to complete these required sections:

- **Regulatory Compliance** - regarding human and animal subjects
- **Export Control**
- **Intellectual Property**
- **Proposal Abstract** - a draft version is fine

Your SP number is 21-0505

Please finalize your submission according to this timeline:

- **Cayuse SP:** Complete required sections (see above) as soon as possible, no later than **9 am on Monday, June 21st.**
- **Budget:** Finalize with GA by **9 am on Wednesday, June 23rd.**
- **CUNY Conflict of Interest Forms:** Complete and return by **12 pm on Wednesday, June 23rd.**
- **Departmental Approval:** GA initiates approval routing by **3 pm on Wednesday, June 23rd.**
- **Final proposal review:** Provide all proposal documents for GA review by **5 pm on Monday, June 28th.**


Please note that any requests for proposal assistance (PARS) received within 10 business days of scheduled submission, will not be reviewed for full compliance of the sponsor's guidelines. In such cases, the proposal will be submitted as is.

Logging into Cayuse SP: for tutorial and links, visit CCNY's Cayuse website at: <https://www.ccny.cuny.edu/research/cayuse>

RF APPS Peer Review: The RF APPS team has established a proposal peer review system to provide constructive feedback from colleagues to improve the competitiveness of your proposal. For more details, please contact apps@rfccny.org

Best,

Afrodita Feratovic
Grants Associate | Pre-Award

Grants and Sponsored Programs 
The City College of New York
160 Convent Avenue | SH – Room 16

New York, NY 10031-9101

(E): aferatovic@ccny.cuny.edu

GSP - <https://www.ccny.cuny.edu/research/gsp>

PARS - <https://www.ccny.cuny.edu/research/pars>

CCNY - Grants and Sponsored Programs

Proposal Assistance Request Summary

Budget Request Number	# 4073
Proposal Title	Effects of simufilam on pathogenesis associated with Parkinson's disease dementia using postmortem brain tissue
PI Name	Hoau-Yan Wang
Department	Physiology & Pharmacology
E-mail	hywang@med.cuny.edu
Phone Number	(212) 6508813
	-
Co-PIs	-
	-
Is CCNY the lead?	Yes
Grant Announcement Number	
Agency	AGENCY NOT LISTED
	CASSAVA Sciences
Submission Due Date	06-30-2021
Project Start Date	08-01-2021
# of years for the budget?	1
Mandatory Cost Sharing	No
Subcontract Information	N/A
Budget Limitations	Yes
	Salary & fringe benefit:
	Principal Investigator:
	\$11,041 (\$7,312 + \$3,729)
	Professor Hoau-Yan Wang, Ph.D. requests 5% effort (1.10 Academic months per year). He will design and execute the assays using postmortem brain. He will oversee the data collection and analysis.
	Post-doctoral research associate:
	Zhe Pei, Ph.D. (1 Calendar months per year) will assist PI in running Immunoprecipitation and Western blotting.
	\$ 7,747 (\$ 5,600 + \$ 2,147)
	Technician:

Kuo-Chieh Lee, M.S. (2.4 Calendar months per year) will assist PI in tissue processing, cell isolation and myriad of experimental procedures and reagent preparation.

\$ 14,388 (\$ 10,400 + \$ 3,988)

Fringe Benefit

RFCUNY maintains its own fringe benefits program for employees (comparable to those of other academic and non-profit institutions). The cost of providing benefits to employees is included in grants as a direct charge.

To simplify both pre-award budget preparation and post-award accounting procedures, RFCUNY developed a system of Multiple Fringe Benefits Pools. Each grant is charged a flat percentage of each employee's gross annual wages, based on their classification. The percentages represent the best estimate of the actual costs of providing benefits to each employee.

Released Time Faculty:

CUNY Faculty released to work on a grant or contract a rate of 51% is applied to the requested salary support.

A rate of 38% is applied to Full Time/Part Time A employees with an additional .34% of MTA tax.

Specific Budget Needs

Expendable Supplies:

Antibodies and immunoprecipitation agents

Primary antibodies \$350 x 14 \$ 4,900

protein A/G-conjugated agarose beads x2 \$ 3,224

HRP-secondary antibodies-\$156 x 3 \$ 468

\$ 8,592

Drugs and Chemicals

Phosphatase inhibitor tablets @ \$245 x 2 \$ 490

Protease inhibitor tablets@ \$225 x 2 \$ 450

Digitonin @ \$186/ 500 mg x 2 \$ 372

NP-40 @ \$64/250 ml \$ 64

Bradford reagent \$ 156

\$ 1,532

Electrophoresis and Western blotting equipment and supplies, ECL reagents, Film and Immunohistochemistry

ECL reagent \$490 \$ 490

Methanol \$ 120

Buffer reagents \$ 350

\$ 960

Supplies

Ependoff tubes \$ 250

Pipette tips \$ 200

Cuvettes \$ 100

Gloves \$ 190

\$ 740

Research materials & supplies \$ 11,824

Direct cost \$ 45,000.00

Indirect Costs (25%) \$ 11,250.00

Total \$ 56,250.00

Additional
Comments

Draft Budget
Upload

Grant
Announcement
Upload

RCR Certificate citiCompletionReport713185 (1)-RCR certificate.pdf

CONTRACT INTAKE FORM

 If this is an **INTERAGENCY AGREEMENT** send to OGC@cuny.edu

 If this is a **MATERIAL TRANSFER AGREEMENT (MTA)** send to Info.TCO@cuny.edu
This request is for review and execution of the following (Please Select Only One):
☐ **New Agreement**
☐ **Amendment to Log Number** _____

College _____ Principal Investigator (PI) _____

Title of Project: _____ PI Email _____

Date Contract Received _____ Date Submitted to RF _____

 Increase/Decrease Amount (Amend) _____ New Total Amount _____ OR ☐ Budget Mod. ☐ No Cost Mod.

Sponsor Name _____ Sponsor Contact _____

Sponsor Contact Phone Number: _____ Sponsor Contact Email _____

Is the Research Foundation named as a party to the agreement?

☐ Yes ☐ No

Does the contract contain the Research Foundation's address?

☐ N/A ☐ Yes ☐ No

**If No, the
contract will
be returned to
you**

 Is the person named on the signature line authorized to sign on behalf of the Research Foundation? ☐ Yes ☐ No

Has the sponsor set a deadline for signature by the Research Foundation? If so, attach communication from sponsor.

What is the deadline? _____

*If the deadline is 10 business days or less from the date of your submission, **request an extension from the sponsor** and attach communication from the sponsor showing the result of your request.*
*If the deadline is 5 business days or less from your submission, **email LegalAffairs@rfcuny.org immediately.***

 Has each Investigator filed a Conflict of Interest disclosure form for this contract as required by [CUNY Policy and CUNY Procedures](#)?

Note that amendments also require disclosure. ☐ Yes ☐ No (If No - the contract will be returned to you)

If Yes, what was the determination of the College Conflicts Officer:

☐ No Financial Conflict of Interest exists

☐ A Financial Conflict of Interest exists

 If there is a Conflict of Interest, you must attach the Conflict of Interest Management Plan issued by the CUNY Conflicts Committee for this contract or amendment. **If the Management Plan is not attached, this contract will be returned to you.**
IRB / IACUC - Please check the applicable statement below regarding IRB and/or IACUC approval:

☐ IRB/IACUC approval is not applicable. The research does not involve the use of human or animal subjects.

☐ The research involves human and/or animal subjects. An IRB and/or IACUC letter is/are included.

☐ The research involves human and/or animal subjects, and IRB/IACUC approval is pending. The IRB/IACUC determination will be submitted once received. ****

****Submission of this form constitutes a certification that no human or animal subjects research will be commenced until an IRB/IACUC determination is in place.

Note: If proceeding under another institution's IRB approval, in accordance with CUNY Policy an IRB authorization agreement executed by CUNY must be attached.

Where indicated, the following documents must be attached for this agreement to be processed:
☐ Scope of Work (SOW should not include proprietary or confidential information.)

 (For amendments, attach a new Scope if there is one. If Scope is unchanged, check here ☐)

 Budget (for amendments, attach a new Budget if there is one. If Budget is unchanged, check here ☐)

☐ Proposal (if the agreement references or incorporates the proposal)

☐ Completed Attachment 3B (for Federal FDP awards)

College Authorization – By signing below, the College acknowledges that:

1. If this is not a New York Sponsor, the RF cannot advise on, interpret or apply non-New York law. In the event of a dispute, there may be costly legal or litigation expenses, or both, for which the College will be responsible. The College understands and accepts those risks and wants the RF to administer the project.
2. The Research Foundation Administrative Fees will be charged to the College and the College authorizes the Research Foundation to execute the attached Agreement on behalf of:

Name _____ Signed _____ Date _____

Title _____ Phone No. _____



Office of Research
205 East 42nd Street
New York, NY 10017
646-664-8910

TO: Hoau-Yan Wang, PhD, MS, Molecular, Cellular and Biomedical Sciences, City College of New York

FROM: Tamera Schneider, Associate Vice Chancellor, Vice Provost for Research & Chair, CUNY Conflicts Committee

CC: Vincent Boudreau, PhD, President, City College of New York
Maria Lima, PhD, College Conflicts Officer
Holli-Anne Tai, Grants Associate, Grants and Sponsored Programs
Rosemarie Wesson, PhD, Research Integrity Officer
Jeffrey Slonim, Chief Counsel, the Research Foundation of CUNY

DATE: 9/20/2021

RE: CUNY Conflict Committee Determination

PROJECT: Preclinical assessing the effectiveness of Simufilam on cognitively impaired Parkinson's Disease Cases Using Postmortem Brains

FUNDING: Cassava Sciences

The CUNY Conflicts Committee met on 09/15/2021 to review your disclosure of Significant Financial Interest related to the above-referenced project.

Summary of the Conflict

The PI receives a salary for consultancy of \$24,000. The PI also holds stocks as an equity interest of undisclosed percentage in the company at a value of \$125,000. The project is currently a preclinical study to develop diagnostic biomarkers for future patients and clinical trials. The PI's role as a consultant and PI to determine effectiveness of this drug is a potential conflict. The College Conflicts Officer recommends Dr. Gonzalo Torres, chairperson of the PI's Academic Department (Molecular, Cellular and Biomedical Sciences) to serve as the Conflicts Overseer.

- **Salary:** Dr. Wang receives \$24,000 in consultancy fees from Cassava Sciences.
- **Equity Interest:** Dr. Wang holds % equity interest in Cassava Sciences valued at \$125,000.

Conflict Determination

The Committee determined that a conflict exists and it is manageable.

Conflict Management Plan

The Committee issued the following management plan:

1. The Supplemental Form – Question #5 must be revised to reflect that the PI is supervising a post-doc for this project.
2. The Conflicts Committee determined that the post-doc should be made aware of all contract stipulations.
3. The Conflicts Committee determined that a Conflicts Overseer is required for this project. Since the work will be conducted at The City College of New York, the Conflicts Committee agrees with the College Conflicts Officer to appoint Dr. Gonzalo Torres as the Conflicts Overseer. Dr. Gonzalo Torres may also serve as the Student Overseer as his position is the Academic Department Chairperson. The Conflicts Overseer must review in advance, with the Principal Investigator, the hiring of all individuals working on the research project and their work assignments in order to determine whether or not the hiring of any such individual represents an actual or potential conflict.
4. All students and post-doctoral researchers expected to work on this project must meet with the PI, the Student Overseer, the College Conflicts Officer and the Research Integrity Officer prior to their involvement in this project and once per semester thereafter. The Student Overseer was selected by the CUNY Conflicts Committee to call the above-referenced meeting to ensure that the students/post-doctoral researchers understand the conflict of interest, the management plan, and whom to contact in case of any concerns related to compliance with CUNY policies and/or this management plan.

During the meeting(s), the Student Overseer and the PI shall review the *Information for Students Regarding Conflicts of Interest, Compliance, and Grievance Reporting* form (attached to this correspondence) with the students/post-doctoral researchers, and answer any questions they may have regarding the conflict and/or the form. This student information form must be signed by each CUNY student/postdoctoral researcher working on this project, the PI, Student Overseer, the College Conflicts Officer and the Research Integrity Officer. Once all parties have signed the form, copies of the form must be retained by the PI and the Student Overseer, and must be available for audit at any time.

- a) Please report back to the committee any publication restrictions for students and post-docs that you plan to implement.
 - b) The Student Overseer must keep the College Conflicts Officer informed of his or her oversight activities on a regular basis.
5. Please note that you are required to disclose this conflict of interest in all dissemination of research results.

Additional Requirements

1. Please also be advised that new disclosures must be submitted for each new grant or contract at the time of submission/application.
2. Promptly report any substantial modifications to the contract to your College Conflicts Officer.
3. Per section 4.3.5 of the CUNY Conflict of Interest Policy, all Investigators must disclose to the College Conflicts Officer any material change in a previously disclosed Significant Financial Interest within thirty (30) days after the change.

The **Conflict and Student Overseers** must provide regular updates to the College Conflicts Officer, retain documentation of compliance with this management plan, and make it available for auditing purposes.

If you have any objections to the proposed management plan, please notify the Committee within ten (10) days of the date of this memo. Alternately, please confirm your agreement to comply with this management plan via email to travis.mccarthy@cuny.edu.

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INVESTIGATIONAL RESEARCH AGREEMENT

This Investigational Research Agreement ("Agreement"), effective as of **June 15, 2021**, is entered into by and between Cassava Sciences, Inc. ("Cassava"), a Delaware CUNY whose principal business address is 7801 N. Capital of Texas Highway, Suite 260, Austin, TX 78731 ("Cassava"), and **Hoau-Yan Wang, Ph.D.** located at the **Research Foundation of CUNY (RFCUNY)** of the City College of New York, each a "Party" or collectively, the "Parties."

WHEREAS, Cassava has developed proprietary technology and desires to fund the investigational research of Hoau-Yan Wang, Ph.D., Medical Professor, Physiology & Pharmacology, RFCUNY Medical School ("Researcher") under this Agreement ("Research") in the evaluation of the Cassava's proprietary molecule 'simufilam' ("Research Drug") in accordance with the research entitled: **Effects of simufilam on pathogenesis associated with Parkinson's disease dementia using postmortem brain tissue** ("Protocol"), which is incorporated herein by reference as Attachment A.

WHEREAS, Cassava desires to have such Research conducted by RFCUNY and Researcher in accordance with the terms and conditions of this Agreement; and

NOW, THEREFORE, in consideration of the mutual covenants contained herein, and intending to be legally bound hereby, the Parties hereto agree as follows:

ARTICLE 1: DEFINITIONS

1.1 Confidential Information means and includes all technical information, inventions, software, know-how, methods, techniques, patient records, data and other legally protected or proprietary ideas or materials, whether or not patentable or copyrightable, involving Research Drug or Research that is identified as confidential or proprietary at the time it is delivered or communicated or where Confidential Information is not designated as confidential or confirmed in writing to be confidential, it will still be deemed to be Confidential Information if a person, familiar with the industry, would reasonably believe the information to be confidential in nature based on the circumstances. Any obligation to maintain the confidentiality of Confidential Information will not apply to information that: (a) was known to the receiving Party before receipt from the disclosing Party as evidenced by the receiving Party's written records; (b) is or becomes available to the public through no fault of the receiving Party; (c) is received in good faith by the receiving Party from a third party and is not subject to an obligation of confidentiality owed by the third party to the disclosing Party, or (d) is required to be disclosed by order of governmental authority or a court of

competent jurisdiction, provided that the receiving Party shall use its best efforts to obtain confidential treatment of such information by the agency or court.

1.2 Intellectual Property means and includes all technical information, inventions, discoveries, software, know-how, methods, techniques, formulae, data, processes and other proprietary ideas, whether or not patentable or copyrightable, that are conceived, discovered, developed or reduced to practice in the conduct of Research.

ARTICLE 2: PERFORMANCE

2.1 RFCUNY and Researcher will perform all the services described herein, or incidental to those described herein, in accordance with the highest standards of clinical research practice. The Research will be conducted in full compliance with this Agreement and in accordance with the Protocol, any Protocol amendments mutually agreed to by the Parties, and all applicable laws and regulations. For clarity it is agreed that RFCUNY and Researcher will only use Cassava's test compounds for the work set forth in the Protocol, unless specifically agreed in writing by Cassava, and Researcher and RFCUNY will return any unused test compounds to the Cassava at the conclusion of the Protocol.

2.2 Performance of the Research under this Agreement shall commence no later than **August 1st, 2021** and Research activities shall be completed on or before **January 31st, 2022**. In case of delayed performance, this Agreement may, at Cassava's option, be extended for subsequent one-month periods until the Research is completed. Cassava shall, in any case, have the option to terminate this Agreement by giving written notice of termination in accordance with Article 7.

The Parties acknowledge that the Researcher will utilize RFCUNY's facilities for this Research.

ARTICLE 3: PAYMENT

3.1 Cassava shall make payments to RFCUNY in accordance with the payment schedule and to the payee as set forth in Attachment B.

3.2 Cassava shall reimburse RFCUNY for all direct and indirect costs incurred by CUNY in connection with the Research up to the amount in Attachment B. Cassava will not be liable for any payment in excess of the amount set forth in Attachment B except upon Cassava's written agreement.

ARTICLE 4: RECORDS AND REPORTS AND CONFIDENTIAL INFORMATION

4.1 All data generated in the Research, including all information required in the Protocol, records, reports, and other work product generated by or on behalf of Researcher in the course of performance of the Research ("Data") shall be the sole and exclusive property of Cassava. The RFCUNY and Researcher may use such Data for their own non-commercial research, publication (subject to article 6) and education purposes in accordance with this Agreement, but will not disclose or transfer any such Data collected under the Protocol to any third party, without the prior written permission of Cassava. All Data collected under the Protocol shall be delivered to Cassava

by Investigator in a timely manner throughout the performance of this Research, as provided in the Protocol, and in no event later than ten (10) working days after the date of termination of this Agreement or on which Cassava otherwise requests delivery of the Data. Cassava shall have the right to review, publish, disclose and use, any Data developed during the course of this Research as Cassava, in its sole discretion, deems appropriate, including, without limitation, in submission to FDA and other regulatory authorities.

4.2 RFCUNY and Researcher shall not disclose to any other party or use for any purpose other than performance of Research, Cassava's Confidential Information.

ARTICLE 5: INTELLECTUAL PROPERTY

5.1 Title to any Intellectual Property generated in the Research by RFCUNY or Researcher, including but not limited to Intellectual Property relating to Research or use of the Research Drug, or variants thereof, whether or not contemplated by the written description or Protocol of Research ("Research Drug Use"), shall vest exclusively in Cassava. Title to any Intellectual Property developed solely by Cassava shall vest exclusively in Cassava. All rights, title and interests to Intellectual Property developed in the performance of Research shall at all times be owned exclusively and throughout the world by Cassava without demand for further payment by RFCUNY or Researcher. RFCUNY and Researcher agrees that whenever requested to do so by Cassava, it shall, at Cassava's sole cost and expense: give testimony; execute all registrations, applications, assignments, renewals, extensions or other instruments; or take other steps that Cassava shall deem necessary to secure, maintain and protect the intellectual property rights in the services in the United States or any foreign country or to otherwise protect Cassava's interests therein.

The Parties intend and consider the services and intellectual property provided by RFCUNY and Researcher under this Agreement to be works made for hire for Cassava. If for any reason the services are not considered works made for hire under applicable law, RFCUNY and Researcher hereby sells, assigns and transfers exclusively to Cassava and its successors and assigns all rights, title and interest, including goodwill, in and to the intellectual property, including registrations and applications, in all services, and all works based upon, derived from or incorporating all or part of services, and all rights corresponding to the forgoing throughout the world.

5.2 RFCUNY shall promptly report to Cassava in writing any Intellectual Property developed in the performance of Research.

Researcher and all other study personnel are bound or shall have agreed: (a) to comply with the terms of this Agreement; and (b) not to enter into agreements with third parties which would impair their ability to perform Research.

5.3 Nothing in this Agreement shall be interpreted as giving RFCUNY any rights under any intellectual property rights now, or hereafter, owned by Cassava prior to the effective date of this Agreement. Nothing in this Agreement shall be interpreted as giving Cassava any rights under any intellectual property rights now, or hereafter, owned by RFCUNY prior to the effective date of this Agreement.

ARTICLE 6: PUBLICATION

6. It is understood and mutually agreed upon that the study design and Research proposed herein are a collaborative effort by Cassava and RFCUNY and, if appropriate, that both Parties will share in Publication authorship commensurate with intellectual contribution. RFCUNY and Researcher shall be free to publish, present or use any results arising out of the performance of this Agreement ("Publication") for their own instructional, research or publication objectives, provided that such Publication does not disclose any Confidential Information. At least forty-five (45) days prior to submission for publication, presentation or use, RFCUNY and Researcher shall submit to Cassava for review and comment any proposed oral, written, or electronic Publication, which period may be extended for an additional thirty (30) days if requested in writing by Cassava in the event that Cassava provides reasonable need for such extension. Expedited reviews for abstracts or poster presentations may be arranged if mutually agreeable to Cassava, RFCUNY and Researcher. In the event that any proposed Publication contains Confidential Information of Cassava, at the request of Cassava, such information shall be removed. Upon notice to RFCUNY that Cassava reasonably believes that one or more patent applications relating to an Invention (as defined in Article 1.2 hereof) should be filed prior to any Publication, then such Publication will be delayed until such patent application(s) have been filed, provided that RFCUNY and Researcher and Cassava shall cooperate in expeditiously filing any such patent application(s).

ARTICLE 7: TERMINATION

7.1 In addition to termination upon the conclusion of Research as provided in Article 2, either Party may terminate this Agreement effective upon written notice to the other Party, if the other Party breaches any of the terms or conditions of this Agreement and fails to cure such breach within thirty (30) days after receiving written notice thereof. In the event of an incurable breach, the non-breaching Party may terminate this Agreement effective immediately upon written notice to the breaching Party.

7.2 In addition, either Party may terminate this Agreement for any reason upon thirty (30) days prior written notice to the other Party. In such event, RFCUNY and Researcher shall immediately take proper steps to terminate activities in a cost-effective manner.

7.3 In the event of termination of this Agreement prior to its stated term whether for breach or for any other reason whatsoever, RFCUNY shall be entitled to retain from the payments made by Cassava prior to termination RFCUNY's reasonable costs of concluding the work in progress. Allowable costs include, without limitation, all costs or non-cancelable commitments incurred prior to the receipt or issuance, by RFCUNY, of the notice of termination. In the event of termination, RFCUNY and Researcher shall submit a final report of all costs incurred and all funds received under this Agreement within thirty (30) days after the effective termination date. The report shall be accompanied by a check in the amount of any excess of funds advanced over costs and allowable commitments incurred.

7.4 Termination of this Agreement shall not affect the rights and obligations of the Parties accrued prior to the date of termination. The provisions of Article 5, entitled Intellectual Property, Article 6, entitled Publication, Article 8, entitled Disclaimer of Warranties, Indemnification and Article

11 entitled Miscellaneous, shall survive such termination. Section 4.1 shall survive termination for a period of five (5) years.

ARTICLE 8: REPRESENTATIONS AND WARRANTIES, INDEMNIFICATION

8.1 RFCUNY and Researcher each represent and warrant that:

- (i) they have the legal authority and right to enter into this Agreement;
- (ii) they have no obligations to any other Party which is in conflict with their obligations under this Agreement;
- (iii) they will conduct the Research in accordance with the Protocol in full compliance with all applicable laws and regulations;
- (iv) The Research will be conducted solely at RFCUNY's facilities;
- (v) All representations made, directly or indirectly, by RFCUNY and Researcher to Cassava related to RFCUNY and Researcher qualifications, ability and competence to perform the Services or as set forth in any document or as a part of any other understanding by Cassava in relation thereto, are true and correct to the best of RFCUNY and Researcher knowledge at the time of RFCUNY's execution of this Agreement;
- (vi) they acknowledge that (i) Cassava's Confidential Information may represent material, non-public information of the Cassava, (ii) federal securities laws prohibit anyone who is in possession of material, non-public information of Cassava from purchasing or selling Cassava's securities on the basis of material, non-public information of Cassava and (iii) neither it, its affiliates nor its representatives in possession of material, non-public information of Cassava shall purchase or sell securities of Cassava on the basis of material, non-public information of Cassava during the Agreement Term and for one (1) year thereafter;

8.2 Cassava represents and warrants that: (i) Cassava has the legal authority and right to enter into this Agreement; and (ii) Cassava has no obligation to any other Party which is in conflict with Cassava's obligation under this Agreement.

8.3 Cassava agrees to indemnify RFCUNY and Researcher from any and all liability, loss, or damage they might suffer as a result of claims, demands, costs or judgment against them arising out of or relating to a breach by Cassava of any of its representations, warranties or obligations under this Agreement except to the extent that the RFCUNY's or Researcher's negligent actions or gross omissions contributed to the liability, loss or damage.

8.4 RFCUNY and Researcher agree to indemnify and hold Cassava harmless from any and all liability, loss, or damage it might suffer as a result of claims, demands, costs or judgment which are or alleged to be arising solely out of:

Gross negligence or willful misconduct on the part of RFCUNY or Researcher; or

A breach of its representations, warranties or obligations under this Agreement; or

Services and any other materials or information provided by RFCUNY and Researcher to Cassava, arising from the actual or alleged infringement by the services or software products used by RFCUNY and Researcher in connection with the services of any third-

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party's intellectual property rights including, but not limited to, copyrights, trademarks, trade names, service marks or patent rights.

8.5 Each Party's agreement to indemnify and hold the other harmless is conditioned on the indemnified Party:

Providing written notice to the indemnifying Party of any claim, demand or action arising out of the Indemnified activities within thirty (30) days after the indemnified Party has knowledge of such claim, demand or action;

Permitting the indemnifying Party to assume full responsibility to investigate, prepare for and defend against any such claim or demand;

Assisting the indemnifying Party, at the indemnifying Party's reasonable expense, in the investigation of preparation for and defense of any such claim or demand;

Not compromising or settling such claim or demand without the indemnifying Party's written consent.

ARTICLE 9: NOTICES

9.1 Notices under this Agreement shall be in writing and sent only by prepaid, recognized public courier and addressed as follows:

If to RFCUNY:

<**CONTACT INFORMATION**>

If to Cassava:

Cassava Sciences, Inc.
Attention President and CEO
7801 N. Capital of Texas Highway, Suite 260
Austin, TX 78731
512-501-2480

ARTICLE 10: PUBLICITY

10.1 Neither Party will issue a press release or make any other public statement that references this Agreement or identify the other in any promotional advertising or other promotional materials to be disseminated to the public or use the name of Researcher, employee of RFCUNY, or any trademark, service mark, trade name, or symbol of the other without the other's prior written consent, except to the extent required by law or federal agencies.

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ARTICLE 11: MISCELLANEOUS

11.1 This Agreement shall in all respects be governed by and construed in accordance with the laws in force in the State of New York.

11.2 Neither RFCUNY nor Researcher may assign this Agreement without the prior written consent of Cassava. Cassava may assign this Agreement with written notice to the RFCUNY.

11.3 If any provision of this Agreement becomes or is declared illegal, invalid, or unenforceable, such provision will be divisible from this Agreement and will be deemed to be deleted from this Agreement. If such deletion substantially alters the basis of this Agreement the Parties will negotiate in good faith to amend the provisions of this Agreement to give effect to the original intent of the Parties.

11.4 RFCUNY and Cassava are independent contractors and neither is an agent, joint venturer, or partner of the other.

11.5 In the event of any inconsistencies between the terms of this Agreement and the documents referenced or incorporated herein, the terms of this Agreement will prevail.

11.6 This Agreement represents the entire agreement and understanding between the Parties with respect to its subject matter and supersedes any prior and/or contemporaneous discussions, representations, or agreements, whether written or oral, of the Parties regarding this subject matter.

11.7 Amendments or changes to this Agreement must be in writing and signed by duly authorized representatives of the Parties.

11.8 Cassava and its designated representatives shall have the right, upon reasonable notice, to audit all applicable records of RFCUNY for the purpose of determining RFCUNY's compliance with the obligations set forth in this Section. This right to audit shall extend throughout the Agreement Term and for one (1) year after the (i) expiration or termination of this Agreement or (ii) resolution of any dispute between Cassava and RFCUNY hereunder.

11.9 Each Party may sign this Agreement via electronic signature or deliver a signed copy by electronic mail. Signatures obtained in this manner shall be legally binding.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be signed as of the dates entered below.

[SIGNATURE PAGE FOLLOWS]

CONFIDENTIAL

RFCUNY:

Signature:

Date:

Name:

Title:

RESEARCHER:

Signature:

Date:

Name: Hoau-Yan Wang, Ph.D.,
Title: Medical Professor, CUNY

CASSAVA SCIENCES, Inc:

Signature:

Date:

Remi Barbier
President & CEO, Cassava Sciences, Inc.

ATTACHMENTS:

Attachment A – Protocol

Study Title: **Effects of simufilam on pathogenesis associated with Parkinson's disease dementia using postmortem brain tissue**

1. Executive Summary

Dementia and mild cognitive impairment are prevalent in advanced stages of Parkinson disease (PD). Similar to Alzheimer's disease (AD) dementia, there is no effective treatment for dementia associated with PD. In addition to Lewy pathology in the limbic and cortical regions, the molecular mechanisms contributing to cognitive decline in PD remain elusive. Despite with overlapping symptoms, AD and PD appear to differentially affect cognitive domains, although, as in AD, low CSF amyloid- β 42 (A β 42) also predicts future cognitive decline and dementia in PD. We propose to test a novel therapeutic agent, simufilam that binds pathological form of filamin A (FLNA) to reduce A β 42 toxic signaling to hyper-phosphorylation of tau via α 7nAChR, neuroinflammation by TLR4 and brain insulin resistance. Specifically, we aim to use an established ex vivo stimulation method in postmortem brains from PD without and with dementia as well as neurologically normal controls to assess the effects of simufilam on (1) A β 42-induced FLNA association with α 7nAChRs and TLR4, (2) A β 42- α 7nAChR linkage, (3) insulin signaling, (4) A β 42-associated α -synuclein levels, (5) phosphorylated tau, and (6) inflammatory cytokine levels (TNF α , IL-6 and IL-1 β). Improvements in these measures by simufilam in vitro treatment would add support to the rationale for testing simufilam in patients with Parkinson's disease dementia.

2. Plan of Work

This study will use 8 sets of posterior parietal cortices (PPCs) from matched control, Parkinson's disease, Parkinson's disease with mild cognitive impairment (MCI), and Parkinson's disease with dementia cases. Approximately 20 mg of postmortem brain tissues will be prepared to 100 μ m x 100 μ m x 3 mm prisms using a chilled McIlwain tissue chopper. PPC prisms will be washed with oxygenated 0.3 mM Mg²⁺-containing Krebs' Ringer (LMKB) 3 times and incubated with 1 nM Simufilam containing LMKB for 1 hour and oxygenated with 95% O₂/5% CO₂ for 1 min every 15 min as described previously (Wang et al., 2017). The treated PPC tissues will be used to assess: (1) **FLNA- α 7nAChR/TLR4 and A β 42 - α -synuclein complex levels.** The α 7nAChR and TLR4 levels in the anti-FLNA immunoprecipitates will be measured by immunoblotting with specific antibodies, and the levels of α -synuclein in the anti-A β 42 immunoprecipitates will be measured with an α -synuclein specific antibody. Each will be quantified by densitometric quantitation.

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Equally divided tissue will be incubated with 10 μ M NMDA/ 1 μ M glycine to assess
(2) **NMDAR signaling**: The levels of pY⁴¹⁶Src, pY⁴⁰²PyK2, nNOS, PLC- γ , and PKC γ in the anti-NR1 immunoprecipitate by immunoblotting with specific antibodies. The levels of pY¹²⁴⁶-NR2A will also be determined.

The other portions of divided tissue will be incubated with 1 nM insulin to examine
(3) **Insulin signaling**: The levels of pY^{1150/1151}IR β and IRS-1 will be measured by coimmunoprecipitation and detection with specific antibodies.

3. Quality Statement

It is understood that this work is not subject to GLP requirements, but will be performed according to sound scientific principles, in compliance with City University of New York Medical School standard operating procedures, and with review by supervisory technical staff.

4. Timing

The project can be started in August 1st, 2021 and is expected to finish before January 31st, 2022.

Summary of Costs and Payment Schedule

A summary of costs and payment schedule is listed in Attachment B.

Wet lab and statistical analyses work will be performed at:

Department of Molecular, Cellular & Biomedical Sciences
Center for Discovery and Innovation
CDI-3370 85 St. Nicholas Terrace,
New York, NY 10031

All accounting activities will be processed at:

Department of Molecular, Cellular & Biomedical Sciences
City University of New York School of Medicine
160 Convent Avenue
New York, NY 10031

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3. Summary of Costs and Payment Schedule

ATTACHMENTS:

Attachment B – Payment and Budget

Detailed Budget:

Salary & fringe benefit:

Principal Investigator:

\$11,041 (\$7,312 + \$3,729)

Professor Hoau-Yan Wang, Ph.D. requests 5% effort (1.10 Academic months per year). He will design and execute the assays using postmortem brain. He will oversee the data collection and analysis.

Post-doctoral research associate:

Zhe Pei, Ph.D. (1 Calendar months per year) will assist PI in running Immunoprecipitation and Western blotting.

\$ 7,747 (\$ 5,600 + \$ 2,147)

Technician:

Kuo-Chieh Lee, M.S. (2.4 Calendar months per year) will assist PI in tissue processing, cell isolation and myriad of experimental procedures and reagent preparation.

\$ 14,388 (\$ 10,400 + \$ 3,988)

Fringe Benefit

RFCUNY maintains its own fringe benefits program for employees (comparable to those of other academic and non-profit institutions). The cost of providing benefits to employees is included in grants as a direct charge.

To simplify both pre-award budget preparation and post-award accounting procedures, RFCUNY developed a system of Multiple Fringe Benefits Pools. Each grant is charged a flat percentage of each employee's gross annual wages, based on their classification. The percentages represent the best estimate of the actual costs of providing benefits to each employee.

Released Time Faculty:

CUNY Faculty released to work on a grant or contract a rate of 51% is applied to the requested salary support.

A rate of 38% is applied to Full Time/Part Time A employees with an additional .34% of MTA tax.

Expendable Supplies:

Antibodies and immunoprecipitation agents

Primary antibodies \$350 x 14	\$ 4,900
protein A/G-conjugated agarose beads x2	\$ 3,224
HRP-secondary antibodies-\$156 x 3	\$ 468

\$ 8,592

Drugs and Chemicals

Phosphatase inhibitor tablets @ \$245 x 2	\$ 490
Protease inhibitor tablets@ \$225 x 2	\$ 450
Digitonin @ \$186/ 500 mg x 2	\$ 372
NP-40 @ \$64/250 ml	\$ 64
Bradford reagent	\$ 156

\$ 1,532

Electrophoresis and Western blotting equipment and supplies, ECL reagents, Film and Immunohistochemistry

ECL reagent \$490	\$ 490
Methanol	\$ 120
Buffer reagents	\$ 350

\$ 960

Supplies

Ependoff tubes	\$ 250
Pipette tips	\$ 200
Cuvettes	\$ 100
Gloves	\$ 190

\$ 740

Research materials & supplies

\$ 11,824

Direct cost

\$ 45,000.00

Indirect Costs (25%)

\$ 11,250.00

Total

\$ 56,250.00

21-4073

THE CITY COLLEGE

6/30/2021

TITLE Preclinical assessing the effectiveness of Simufilam on cognitively impaired Parkinson's disease cases using postmortem brains

P.I.: Professor Hoau-Yan Wang

PERIOD: 8/1/2021 TO 7/31/2022

REQUESTED SUPPORT (A)	COST SHARE COMMITTED (B)	TOTALS
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DIRECT COSTS**SALARIES AND WAGES**

PI: Hoau-Wang- Academic Yr	5.00 % Effort x \$ 146,241	7,312		7,312
----------------------------	----------------------------	-------	--	-------

Post-Doctoral Research Associate	8.33 % Effort x \$ 67,200	5,601		5,601
Technician	20.00 % Effort x \$ 52,000	10,400		10,400

TOTAL SALARIES AND WAGES**FRINGE BENEFITS**

	Rate		FB Base			
Full Time/ Part Time A	38.0%	X	16,001	6,080		6,080
Part Time B	9.0%	X	-	-		-
GRA	9.0%	X	-	-		-
GRA (J1/F1)	2.0%	X	-	-		-
Released Time	51%	X	7,312	3,729	-	3,729
Summer Salary	26.7%	X	-	-		-
Adjunct	13%	X	-	-		-
MTA Tax	0.34%	X	16,001	54		54
				9,863	-	9,863

14% as of 7/1/21

TOTAL PERSONNEL & FRINGES

Permanent Equipment	-		-
Supplies and Materials	11,824		11,824
TRAVEL - Domestic	-		-
TRAVEL - Foreign	-		-

OTHER DIRECT COSTS

Subcontract	-		-
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TOTAL DIRECT COSTS**INDIRECT COSTS**

(A)	25%	X	\$ 45,000	MTDC (*)	11,250	11,250
	0%	X	-	MTDC (*)	-	-
Less Additional Contribution					-	-

(Net Request is \$ 11,250)

TOTAL COSTS	YEAR 1	56,250	-	56,250
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(*)

DHHS Approved Rate, Predetermined 8/26/20

(B)

Committed Cost Share (Mandatory/Voluntary) -Reported to Sponsor

From: Hoau-yan Wang
Sent time: 10/09/2021 06:21:27 PM
To: jennifer.beidel@saul.com
Subject: Fw: Review of Trading in CASSAVA SCIENCES, INC. (SAVA) FINRA Matter No: 20200679449
Attachments: FINRA inquiry response - 20200679449.pdf

FYI

From: Hoau-yan Wang
Sent: Monday, October 26, 2020 11:16 AM
To: Lindsay.Burch@finra.org
Subject: Fw: Review of Trading in CASSAVA SCIENCES, INC. (SAVA) FINRA Matter No: 20200679449

Dear Lindsay,

Thanks for returning my call. I am forwarding the response I sent last Friday.

Thank you.

Best regards,

Hoau-Yan Wang

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY School of Medicine
CDI-3370, 85 St. Nicholas Terrace, New York, NY 10031
p: 212-650-8813 [O], -6682 [Lab]
Email: hywang@med.cuny.edu

From: Hoau-yan Wang
Sent: Friday, October 23, 2020 12:46 PM
To: FINRACHronology@finra.org
Subject: Review of Trading in CASSAVA SCIENCES, INC. (SAVA) FINRA Matter No: 20200679449

Dear Sr/Madam,

In response to your letter requesting information, enclosed please find my response to each of the inquiries.

Thank you.

Best regards,

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY School of Medicine
CDI-3370, 85 St. Nicholas Terrace, New York, NY 10031
p: 212-650-8813 [O], -6682 [Lab]
Email: hywang@med.cuny.edu

October 23rd, 2020

National Cause and Financial Crimes Detection Programs

9509 Key West Ave

Rockville, MD 20850-3329

Re: Review of Trading in CASSAVA SCIENCES, INC. (SAVA)
FINRA Matter No: 20200679449

Dear Sir/Madam,

I here provide the response (information) directly underneath each of the inquiries.

- 1) The date and circumstances of the initial contact between CUNY or its representatives and SAVA or its representatives regarding the corporate disclosure. Please also include the dates that any formal agreements (nondisclosure, exclusivity, etc.) were signed and attach copies of the agreements;

Response:

No direct contact from SAVA regarding corporate disclosure prior to 9/14/2020. CUNY learned of the disclosure on **9/14/2020** morning the same time as the general public.

- 2) The date that CUNY first received samples from the SAVA's Phase 2b study of PTI-125 in Alzheimer's disease and the date and circumstances surrounding SAVA's request that CUNY conduct bioanalysis on the samples;

Response:

CUNY received samples directly from clinical trial sites starting 08/30/2019 till 05/30/2020 with back up CSF samples. All the samples were stored in the -80°C freezer. Formal request to re-evaluate the samples on 06/01/2020 after the approval to entering laboratory had been issued and sufficient amounts of CSF samples to be tested had been confirmed by CUNY.

- 3) The date and time when the clinical trial became unblinded to individuals at CUNY and the names of all individuals present. Include the home and business addresses, if not already provided;

Response:

NEVER unblinded to CUNY.

- 4) The dates that CUNY began conducting bioanalysis and the earliest date preliminary results were internally available;

Response:

CUNY conducted the first of bioanalysis on 6/8/2020 and 6/12/2020 was the earliest date to send the first set of raw data on CSF Aβ42 levels directly to Dr. Lindsay Burns at the SAVA.

5) The names of all individuals who had access to clinical data throughout the trial and/ or tracked the results. Include the home and business addresses of these individuals, if not already provided;

Response:

CUNY **NEVER** has access to demographic (age, gender, etc.) information, clinical protocol and clinical data so that **CUNY can NOT and is unable to track the results.**

6) The name and home and business addresses of any individuals who knew which patients received the placebo and which patients received PTI-125;

Response:

Since there is **NO unblinding** to CUNY (**remain blinded indefinitely**) so that CUNY has **no knowledge** on which patients received placebo and which patients received PTI-125.

7) A description of all contacts and/or correspondences (including dates, individuals involved and a description of what was discussed) between SAVA and CUNY during the period of May 13, 2020 through September 11, 2020 regarding CUNY's bioanalysis;

Response:

5/20/2020 - Discuss with Dr. Lindsay Burns at SAVA on ordering info of neurogranin and Neurofilament light chain (NfL) ELISA plates, re-opening lab status and confirming the residual back up CSF samples from clinical trial sites.

5/29/2020 - Discuss with Dr. Lindsay Burns to confirm shipping address that allows reliable delivery of the ELISA plates.

6/1/2020 - Dr. Lindsay Burns forwarded ordering info of YKL-40 and IL-6 ELISA plates, No discussion

6/9 & 6/11/2020 - Dr. Lindsay Burns forwarded Lifespan shipping confirmation, No discussion

Raw data were delivered to Dr. Lindsay Burns on the following dates **without discussion**. Dr. Burns acknowledged receiving the data.

6/12/2020: A β 42, 6/13/2020: Total Tau, 6/14/2020: pTau-181, 6/19/2020: Neurogranin, 6/20: Neurofilament light chain (NfL), 6/26/2020: YKL-40, 6/27/2020: IL-6, 7/13/2020: CSF albumin, 7/14/2020: CSF IgG, 7/16/2020: sTREM-2, 8/11/2020: α 7nAChR/TLR4-FLNA association in lymphocytes, 8/19/2020: HMGB1,

8/28/2020 Discuss with Dr. Lindsay Burns regarding whether the APOE genotyping in the phase 2b cohort can be conducted timely in light of limited access to CUNY laboratory during pandemic.

9/4/2020 & 9/11/2020 Discuss with Dr. Lindsay Burns on CTAD abstract draft and edition.

and 8) Please provide an overview, of CUNY's relationship with SAVA as it related to PTI-125 and its ongoing development and clinical trials.

Response:

CUNY is an academic collaborator of the SAVA. CUNY runs bioanalysis blinded at the request of SAVA and send the raw data to SAVA. CUNY answers scientific questions and provides relevant literature pertain to disease mechanisms, drug targets and evaluation methods of brain disorders of interest, especially Alzheimer's disease and related neurodegenerative disorders. **CUNY plays NO ROLE in PTI-125's ongoing development and how PTI-125 clinical trials are conducted.**

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Hoau-Yan Wang', with a stylized, flowing script.

Hoau-Yan Wang, PhD

Medical Professor

Department of molecular, cellular & biomedical sciences

CUNY school of Medicine

CDI-3370 [85 St. Nicholas terrace, New York, NY 10027](#)

Phone: 212-640-8813 (office), -6682 (lab)

Email: hywang@med.cuny.edu

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent time: 10/11/2021 03:30:03 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

How's going recently after all these events of speculation ? I felt deeply compassionate for your years of hardships and motives to find reliefs to people in need, Putting these aside, I have read some papers related to astrocyte which is associated with AD as below :

<https://www.nature.com/articles/s41593-020-0624-8>
<https://www.pnas.org/content/118/33/e2102191118>
[https://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914\(18\)30224-7](https://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914(18)30224-7)

Biomarkers such as apoE are mentioned in related literatures. Since many efforts with reactive glia fell short of therapeutic effectiveness, I am not sure if astrocyte is a valid pathology and target to AD. If there is a correlation, is it a possibility to find another bad guy in this complicated cascades of AD events ?

Another issue is my personal matter. My mother was diagnosed with Parkinson's disease and AD by a local clinic with brain scan. Her memory and motor conditions declined and I am very heart-broken to see her with helpless efforts after my mother took care of my father for so many years . She was prescribed to have 3mg Rivastigmine twice a day and I persuade to take 1.5mg each day. Is it possible for my mother to take part in the global study of PTI-125 if this would be helpful ? Thanks a lot for your listening to my personal matters. Your assistances are very much appreciated,

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, August 10, 2021 12:08 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your kind words. Your questions keep me thinking of my answers so that I can be as clear as possible in my answers to most. I am truly impressed with and appreciate your viewpoints. Obviously, we have a lot of unknown factors in Alzheimer's disease that harboring many pathogenic pathways. I am working as hard as I can to find other possible pathogenic triggers - bad guys (aging process is one of them, and I think mental stress may also push the brain into neurodegenerative path). Regardless, we got to find these damaging pathways as soon as we can - early diagnosis that is.

Thanks for the reminder of the COVID delta variants. I am glad that Taiwan is very cautious on this pandemic development. In US, there are people still hesitate to be vaccinated. Unlike Taiwan, the availability of vaccine is less a problem because 4 mainstream vaccines are produced in US. I think Taiwan's domestic vaccines look great and more importantly can solve the supply issues although I do not get there are politicians that constantly trying to discredit these vaccines. In any case, please be very careful still especially in Taipei and New Taipei cities.

Thanks again for your support and keeping me informed of other developments. Please also keep asking questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, August 7, 2021 2:16 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Nice to have your replies especially when you are fully occupied. Your answers to my naïve questions help me to understand more properties of PTI-125 which surely would provide viable solutions to needed patients never before. Especially for meaningful researches, PTI-125 would have more indications and implications as time goes on. If you

could find additional bad guys behind AD, a Nobel prize for you is not too far away.

Stay safe when delta virus poses new threats in US. In Taiwan, we are cautious about recent pandemic developments with protective measures. Looking ahead, I would expect an oral solution with protease inhibitor or some combination therapy would truly alleviate this human dilemma. Thanks again for your insights and sharing with me.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, August 7, 2021 4:29 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

As always, I am completely booked up with research activities. Your questions kept me thinking. I answer your questions directly underneath each of your queries.

Hope all is well,

Thank you.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, July 31, 2021 2:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Thanks for your kindly reply during busy hours as always. Knocking off hard nuts is especially tough especially there was no precedent before. Your persistence and genuine contributions to global AD community is obvious. I am happy that your finding of the bad guy will eventually be a history of AD and even mankind. Your family and friends will be certainly proud of you after so many tough years spent in lab and related researches.

Your answers to my naïve questions are plain and understandable. To my personal curiosity which might be common to most people, I have additional questions as below.

1. Is there any plateau effect after months of oral treatment of PTI-125 since biomarkers of neuroinflammation and neurodegeneration will eventually reach their peaks ? Will responded patients need to take oral treatments of PTI-125 in their lifetime ? *True. neuroinflammation and neurodegeneration will reach a breaking point down the road without treatments. Our hope is that this treatment will delay the neuroinflammation and neurodegeneration so that brain can recover (those not dead yet) some so that brain can function better. My guess is that there is some sort of limitations (not plateau per se). We hope the window is big enough (beyond the nature life span).*
2. When temporal changes of individual patient during the span of treatments will be revealed ? This information might show more consistent and clearer trend of treatment effects. *I am not sure what you are referring to. It would be difficult to gauge patient's response rate since each patient is different in many aspects (other diseases, genetic make up etc). Very difficult to tell.*
3. For neurons already beyond repairs or dead, is there any viable therapeutic or complimentary solution ? *No. Raise from death is NOT any humans can do.*
4. Would mental or physical rehabilitations for patients during or after treatments add more values to their health ? *We have evidence to show exercise and good nutrients (diet) help to elevate the treatment effects.*

There must be lots of works needed to be done after this stage. For all your dedication, I believe that all time spent in search of better treatments will be meaningful and greatly appreciated. Thanks again in advance.

Best Regards,

宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, July 31, 2021 1:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your encouragements always and giving your opinions and questions as I need such reminders to keep my comments plain and understandable.

I will **answer your questions directly underneath each query you posted**. Since I am blind to all patient related info, I can only answer in general terms.

Hope all is well with you and your family.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Thursday, July 29, 2021 10:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Congratulation to your researches going with a gigantic step forward. After reading updated PTI-125 related papers in CCAI 2021, I had a feeling that your lab works have gradually verified the MOA of Filamin A with abnormal conformation. There are thoughts with results of SavaDx and 9-month data as follows :

- 1) Correlation studies of Abnormal Filamin A in phase 2b patients is a positive step. That is a great findings and direction in the framework of diagnosis tool. However, taking Abnormal Filamin A as a biomarker needs more works to establish that which level of Abnormal Filamin A should be detected as an early sign of AD. I am wondering if a totally new or compatible antibody in your earlier works of SavaDx is employed in this study.
- Indeed, this is just the initial steps. The antibodies used obviously required constant verifications using that was used earlier. It is a tedious work but there are no short cuts. We need to define the timeline when the abnormal FLNA can be detected (not an easy task because we don't even know when is early).
- 2) Cognition Improvement of 3.0 Points on ADAS-Cog at 9 Months ($p < 0.001$) is great for patients as a process of Filamin A normalization. However, most people are wondering why NPI score in 9 month improved less than in 6 month by 0.6 points. All tested biomarkers are consistent with improvements which relieved lots of overhangs.
- People forget Alzheimer's disease is a progressive neurodegenerative disease with multiple factors at play. As patients deteriorate cognitively due to brain function declines, there are added factors hence the magnitude of improvements become less comparing the the baseline. The 0.6 points less at 9 month reflects just that (obviously it also depends on the stage of disease when patients first enrolled) but the curve will be stabilize for period of time.
- 3) 22% of patients declined less than reported in the science literature at 9 months. Why these patients are so hard to respond to treatment of simufilam ? Any other upstream catalyst for these patients ?
- Well, we don't actually know but my guess is that these patients have other issues or they were selected at later stage of the disease even though their MMSE or ADAS-Cog when enrolled were not bad. While we like to have 100% responsive rate, it is an unrealistic expectation. This drive home the importance of early diagnosis. I am sure if we treat earlier, we will see a better result.
- 4) As reported earlier, Evonik will supply Cassava Sciences with large-scale, clinical-grade quantities of simufilam. I am wondering if Evonik will produce good qualities of simufilam as in phase 2b study and it should be carefully verified before entering phase 3.
- Clearly, QC will be done carefully.
- 5) Finally, is abnormal filamin A responsible for the symptom or modifying answer to AD ?
- While we all want to find the "bad" guy (abnormal FLNA is a critical but one of the bad guys I am sure there are many others). Fortunately, fixing abnormal FLNA promotes healthier and more resilient brain but unfortunately can't fix anything already beyond repairs or dead. I am a realistic person by showing people what I saw but I don't want to give a wrong impression that fixing abnormal FLNA can bring back what have already

damaged.

I am honored to be with your ongoing researches and contributions to AD patients. Thanks for your hard works.

Best Regards,

宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, June 30, 2021 8:29 PM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Sorry for my late reply. I often just get occupied by too many tasks in hand and consequently delay in my response to you and many.

Yes, lots efforts had been on the multiple fronts and there should be an update in phase 2b study. I will be interest in learning of your comments.

I watch the COVID-19 situation in Taiwan closely. It is most unfortunately some careless acts led to such a spread. Even though it is pale by comparison to US and EU, it is still very concerning especially in Taipei (the worst in transparency) and New Taipei. A solution to this monumental disaster must include understand the pathogen (virus) so that more effective medications together with vaccination can put this pandemic out for good.

Best wishes to you and your family, it is looking better recently so that normalcy is near.

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, June 22, 2021 12:18 AM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After reading a recent news from Cassava Sciences, I realized that there will be a presentation at AAIC during the week of July 26-30th about SavaDx clinical dataset from PTI-125's Phase 2b study of 64 patients. Look forward to seeing more updates of SavaDx developments which you must devote lots of time and energy.

Affected by recent COVID-19 impacts in Taiwan, I have been working from home more than 1 month. Hope that this history-making pandemics will be alleviated or solved by pharmaceutical solutions. The same goes to PTI-125 to help patients in need. Thanks.

Best Regards,

宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Tuesday, February 23, 2021 10:26 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

The MOA for PTI-125 is very different from that of ANVS401. PTI-125 reverses an abnormal filamin A thereby reducing the toxic signaling pathways that drive neurodegeneration and inflammation. ANVS401 functions as a translational blockers that presumably (based on cell and transgenic models) to reduce toxic substances such as amyloid beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. The major problem is that reducing those "toxic" substances do not work in humans. In fact, ANVS401 blocks APP (amyloid precursor protein) to reduce amyloid beta. APP is a known trophic factor whose expression increases when brain is injured. More of the problem, we know reduction in amyloid beta by beta or gamma secretase inhibitors do not stop Alzheimer's disease progression and in some cases actually worsen cognitive impairments. Hence, I don't predict any synergy between PTI-125 and ANVS401.

Postmortem brains are not suitable to study metabolic dysfunction because one can only show there is metabolic disturbance but can not conclusively show the source, when and how the metabolic dysfunction occur. Transgenic animal models are partial models at best and are very different from actual disease, therefore they are inheritably insufficient to any pathogenic pathway questions just about any diseases.

I hope my explanations help answering your questions.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, February 21, 2021 3:05 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

I had some thoughts again regarding to the upstream causes of Alzheimer disease and MOA of PTI-125.

As you mentioned earlier, there were complicated lab works deriving chemical compounds of PTI-125 to restore of Filamin A with abnormal conformation. I am curious to know what is the chemical MOA of PTI-125 which differentiates from other approaches such as ANVS401 of Annovis Bio Inc. to decrease multiple neurotoxic in Cerebrospinal Fluid (CSF) and improve axonal transport of nerve cell. Their therapeutic target also aims for reductions of neuroinflammation and neurodegeneration. Is there any synergetic effect to combine PTI-125 and ANVS401 ?

As in previous email, I am skeptical about causes of metabolic dysfunction related to Alzheimer disease. Is there any direct proof from human postmortem model instead of mouse model ?
Thanks again for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 16, 2021 1:08 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

First, Happy Lunar New Year. Wishing you and your family a happy, healthy and prosperous year of Ox.

Regarding your question, Donepezil's ADAS-cog score you are referring to are raw score. Once taking placebo control into consideration, the improvement achieved by 24 months of 5 mg and 10 mg daily dose of donepezil were around 0.35 and 0.39 (page 16 stat significant). By now we know donepezil's clinical effectiveness eventually diminished as disease progresses. Obviously, we hope the cognitive benefit of PTI-125 continues based on the biomarker data. The improvement in cognition is depending on the baseline state of the patients (how severe the dementia and obviously the accuracy of diagnosis). I can't say too much and frankly nobody is all that certain.

Based on the mechanism of action, we predict the therapeutic effects of PTI-125 are applicable to a broad range of Alzheimer's disease patients. Again, the magnitude of benefits depend on the severity of dementia - the earlier the better. Hence, it is important to have a reliable early diagnosis tool though we still not entirely sure how to define "early".

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, February 15, 2021 10:32 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After some thoughts and review of data during Chinese New Year, I have some questions needed for your comments as

follows :

1. ADAS-Cog Improvement between ARICEPT and PTI-125 : In https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively after 24 weeks of treatment. These differences were statistically significant for 473 patients. Compared with baseline, 5 mg/day and 10 mg/day treatments of donepezil at 24 weeks showed 1.06 and 1.6 benefits in a controlled study. However, the press release of Cassava Sciences on Feb. 2, 2021 mentioned that six months of PTI-125 treatment improved cognition scores by 1.6 points on ADAS-Cog11.

These comparative improvements did not clearly distinguish the therapeutic advantage of PTI-125 compared with ARICEPT in 24 weeks of treatment. Is it true for this simple observation as above ? Is there any indication that PTI-125 will have better effects after prolonged period of time (such as 1 year) by restoring of Filamin A with abnormal conformation ?

2. You mentioned that collective efforts try to bring some solutions for Alzheimer's disease patients. Does it mean that a subset of Alzheimer patients would be appropriate for therapeutic effects of PTI-125 and diagnosis tool of SavaDx ? While other patients are not ideal enough ?

Thanks so much for your insights again.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, February 4, 2021 4:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thank you for your well wishes and positive comments. Your continued interests in finding solutions for Alzheimer's disease research motivate us and I can truly say I am trying my very best . I thank you for keeping me informed and discussions on the findings from other investigators. We will keep moving forward and hope our collective efforts can bring some solutions for Alzheimer's disease patients.

Will keep safe the best I can as the COVID pandemic is still very bad here. Hopefully, with vaccination the situation improves in the coming months.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, February 2, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

Nice to know that the interim result of PTI-125 is positive and brings lights to the Alzheimer community. Congratulation to your continued efforts. There must be lots of persons sending emails to you regarding to this matter. To continue your clinical endeavors, I truly wish you to keep safe in this covid-19 epidemics. Your academic and real-word contributions are very much appreciated.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, January 21, 2021 11:55 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for keeping me informed of the recent development. I am all tied up by my extensive teaching load and research activities (this pandemic has caused tremendous pain with limited access).

Regarding the levels of N-terminal fragment of tau in the blood as a predictor of cognitive decline, this is really nothing new because we know the levels of tau in the CSF and blood positively correlate with the extent of neuronal damage (tau exist exclusively in neurons). The question is the sensitivity of detection that allow us to sound the alarm. With the more sensitive mass spectrometry we obviously are better equipped than before.

Thanks again. I will find time to answer your earlier queries.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 20, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] some development of diagnosis tool for reference

Dear Hoau :

There is some development of blood test for Alzheimer's disease to predict future cognitive decline in healthy people with levels of N-terminal fragment of tau (NT1). Data link is as <https://www.sciencedaily.com/releases/2020/12/201209115147.htm>. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, January 16, 2021 3:44 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks always for your info that keeping me in the loop of current Alzheimer's disease findings.

The problem is that this type of academic research using (genetically modified) rodent models that bear little resemblance to human Alzheimer's disease lead us to nowhere and frankly confuse & dilute our efforts. Hydrogen sulfide is no doubt playing a regulatory role in many physiological activities. Just because it is decreased with aging and replacing it can improve cognition in rodents doesn't mean it is therapeutically possible. Don't forget the hydrogen sulfide is quite toxic one should worry the accumulation can severely hurt the brain function. Most importantly, there is no evidence rodent models have neurodegeneration (unlike brains in humans with Alzheimer's disease). GSK3a/b is one of the hubs in metabolism/energy regulation and as one of the tau kinases that have a sophisticate feed forward and feedback regulators. There is no evidence there is anything change in GSK3a/b in Alzheimer's disease. In general, kinases and phosphatases are terrible targets because they all have tons of regulators once activated or inhibited in a progressively changing brain like in Alzheimer's disease is predictably short-lived and ineffective especially when the disease becomes symptomatic (much too late).

Thanks. Have a good weekend.

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 13, 2021 10:36 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

It seems to me more and more researches trying to target early pathogenesis of Alzheimer's disease which might be inspired by evidences of many clinical results. There is a recent research from John Hopkins Medicine working with University of Exeter concerning with effects of hydrogen sulfide, GSK3 β and other proteins involved in the pathogenesis of Alzheimer's disease. Their data link is https://medicalxpress.com/news/2021-01-hydrogen-sulfide-alzheimer-disease.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter. Hope that this information would be interesting to you. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 13, 2021 2:13 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Sorry for my late reply, sometimes I made a mental note to reply but I got busy and kind of putting it off. The impacts of concussion obviously vary according to the severity and frequency (multiple mild concussions can be quite damaging). It sounds like your father had a severe concussion that resulted in motor/sensory imbalance and dementia. I understand how hard it is to see your father suffer but unable to help.

There is no doubt vascular dysfunction is a risk factor and often accompanies Alzheimer's disease (cerebral amyloid angiopathy). That said, the cause-effect relationship between vascular dysfunction and Alzheimer's disease is not straight forward.

Indeed, upstream is a relative term. Abnormal filamin A can be induced by sub-chronic amyloid (soluble) infusion into brains. If abnormality in filamin A is blocked (by PTI-125), there is significant reduction in amyloid plaques (dead neurons) and neurofibrillary tangles. More importantly, brain activities with higher receptor and synaptic activities and function improve at least in mouse model of Alzheimer's disease. These data indicate reversing abnormality of filamin A especially when at the stage when mild clinical dementia is detected may be a promising way to treatment Alzheimer's disease.

Hope I answer your questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, January 4, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your comments. After two decades of researches, your important findings have a step forward which is a remarkable achievement. I do admire your courage and patience with regard to this tough disease in which early detections are probably with both natures of science and art. My father was in a healthy condition before concussion and developed with signs of body imbalance and occurrence of Alzheimer disease. It was heartbreaking without ways to lessen his burden.

My assumption of root occurrence from vascular dysfunction might be wrong. It seems to me that finding a solution with very early detection before massive degeneration occurs is more than challenging. I am wondering which events trigger the formation of abnormal filamin A. If you could come up with a diagnosis tool tracing up the root cause of abnormal filamin A, it might be a better start than random guesses. I am not sure if I am right in this direction.

BTW, you mentioned that abnormal filamin A is an upstream event. Would you shed some lights on which upstream events are already verified up to now since upstream is a relative word ? Thanks so much for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, January 5, 2021 1:07 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

There is no doubt vascular dysfunction is an important part of the Alzheimer's disease (AD) pathology. Filamin A with abnormal conformation is found in plasma from AD patients doesn't necessary mean abnormal filamin A from platelets is resulted from vascular pathology including amyloid angiopathy, infarcts. More importantly, the abnormal filamin A in peripheral may be the result of brain pathogenic changes (occurs later).

Our data indicate abnormal filamin A is an upstream event. However, AD treatment effects are better if starts earlier (hence early detection before massive degeneration occurs is the key). I always think multiple therapeutic agents may be synergistic or additive. Again, if all the treatments administered after massive degeneration there is no treatments strong enough.

Thanks.

All the best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, January 3, 2021 7:50 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks for your kindly reply. Happy New Year !

Since conformational filamin A is structurally found in palates, I therefore assume that vascular pathologies are related to this disease. Your researches in various aspects of insulin resistances were published and your comments really show how hard it is to trace pathogenic events.

I really appreciate your continued research and endeavor to find more upstream targets treating Alzheimer disease effectively. It seems to me in your comments that restoration of conformational filamin A is not strong enough to show disease modifying effects. Is it true ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, January 4, 2021 3:14 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Happy New Year. Wishing you and your family a healthy and prosperous year 2021.

It is my life time goal to help bring effective treatments and early diagnosis of the Alzheimer's disease (and other diseases with cognitive impairments). For the last two decades, I worked to identify possible drug and diagnostic targets. I'm mindful of the burden of the Alzheimer's disease caregivers, especially the potential of depression.

Regarding your question, there is no concrete data to show the function of blood platelet had changed in Alzheimer's disease (plausible of course). There are diverse pathogenic mechanisms and of course diseases such as diabetes (causes vascular pathologies) and history of concussion (multiple) had been suspected to be culprits to promote Alzheimer's disease. Surely, prevent such problems is useful but whether such measurements can reverse the damages that already done is everyone's guess. We had tried to control insulin resistance for years but the results thus far

showed not much of effects. This may indicate that brain insulin resistance is not an early pathogenic event. We will do more to find more upstream targets so that we can more effective to treat Alzheimer's disease.

Thanks for your continuing interests and communications.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, December 29, 2020 7:38 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your kindly reply. For my father, a better treatment of Alzheimer disease is motivated and caregivers deserve to be with less burden. Regarding to the timing of conformational changes, I am curious to know if this is related to conditional changes of palates which caused by blood clotting, vascular abnormality or concussion, etc. Your endeavor of this tough disease is really appreciated.

Please be safe since pandemic and cold weather persist in northern atmosphere. Have a wonderful and peaceful New Year to you and your family.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, December 30, 2020 6:56 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks for your email.

Your friend is correct regarding the difficulty of finding specific antibodies for the filamin A with altered conformation in Alzheimer's disease. Indeed, the epitope of the altered filamin A may be hidden or had been processed. Obviously, computational approaches had been used to help us find viable antibodies. We still don't know when the conformational changes occur during the Alzheimer's disease pathogenesis even though we think this event occur early. But, what is early? This timing issue also requires some attention.

Yes, one-year extension of the open-label study is well under the way. Obviously, we will be looking for cognitive improvement and reduction in pathogenic drives such as reduction in inflammatory markers and degeneration.

Thanks again for your continued interests in getting the Alzheimer's disease treatment. I am working hard to get to this goal.

Happy New Year to you and your family.

Best regards,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Monday, December 28, 2020 4:58 AM

To: Hoau-yan Wang

Subject: [EXTERNAL] Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Wish you a happy holiday and healthy new year, too. Regarding to the issue of diagnosis, my friend specialized in

chemistry of antibody suggested to me recently that an exhaustive search of appropriate antibody to be connected with conformational filamin A in human palates might be required to have a solution of universal antibody for different races. A modern equipment with computerized tools would be helpful in this exhaustive search process. Since the epitope of conformational filamin A might be structurally hidden, an appropriate antibody might be sensitively or selectively enough to be effective. Hope that this information is useful.

A one-year, open label study of PTI-125 was initiated in March 2020 and enrolled over 60% of patients as mentioned in public. Supposedly, safety issues are not a big concern since expanded clinical trials still proceed. How about attributes of reduced inflammatory cytokine levels and improved cognition/behavior in this perspective since earlier enrolled patients had been treated with more than 6 months ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 23, 2020 4:03 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Season Greetings

Dear 宜明,

Sorry for my late reply as I am deep in the semester end exam and grading.

Wow, time flies by so quickly. It has been more than a year already since we started our communication. It is my pleasure to discuss the field of neuroscience even though we actually are learning on the way. I am thankful for the opportunities you have given me to think about the questions you have posted in different angles. Truly, we all hope we have grown some in knowledge and get effective Alzheimer's disease treatments forward to contain this terrible disease. I am for one will do everything I can and work tireless toward this goal. It takes collective efforts to get this under control so that I am collaborating with academic and industrial partners to look into as many ways we can investigate and test the effectiveness. Thanks to you for keeping me informed of many new strategies other have come up with in Alzheimer's disease diagnosis and treatments.

We all hope we can better handle this COVID pandemic. With the approval of 2 vaccines, I am hopeful we are better equipped to start limiting the death tolls and eventually control this horrific virus. I sincerely hope people learn from this as we all have to play a part (wearing mask, wash hands frequently etc). This experience certainly humbles us as we humans appear more vulnerable (at least not as invincible) than we think. The fact Taiwan has done so well in controlling COVID makes me proud to be a Taiwanese.

Wishing you and your family happy holidays and a healthy, peaceful and prosperous year 2021.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, December 20, 2020 8:43 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Season Greetings

Dear Hoau-Yan :

It's been more than 1 year since I have this particular opportunity to know you. Your in-depth and insightful knowledge has given me more understandings in this tough field of neuroscience. Your assistances and comments are really appreciated. Hopefully, we will be better off with more solutions of pandemics and preventive measures next year. At this time of season, I truly wish you a Merry Christmas and happy New Year !

Best Regards,
宜明



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From: Hoau-yan Wang
Sent time: 10/11/2021 12:55:12 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your email.
Dear 宜明,

Thanks for your email. Sorry that I didn't respond to your many of your prior emails

As you know, gliosis (increased numbers of glia) is one of the biological/pathological consequence of the Alzheimer's disease. Glia do have their own functions and coordinate with neurons to keep the brain activities intact, hence one can't just say glia have functional changes during Alzheimer's disease pathogenesis that have negative impacts on the overall brain activities such as secrete inflammatory cytokines they are the bad guys. It is far more complex and not easy to be black-and-white clear. Take inflammation as an example, while prolonged inflammation harms the system we can't do without inflammation because it warns us there is something wrong. You take away the alarm, you have a false sense of security.

Regarding your mother, I am sorry to hear the Parkinson's disease diagnosis (she was diagnosed with Alzheimer's dementia first, right?). Does she have motor symptoms? Good portion of the Parkinson's patients do develop dementia. You should get a second opinion on your mother's diagnosis and have some idea of severity of the symptoms.

As you know, Rivastigmine belongs to cholinesterase inhibitor family. While it does make pharmacological sense to use in your mother's case (PD+dementia), a close monitoring is necessary (knowing you, you probably read through many papers and know a great deal of the drug and its adverse effects). What was the reason you persuade your mother to only take 1.5 mg Rivastigmine? I am sorry I don't have any say about the clinical trial. Unless, there is a trial in Taiwan, it is not possible to enroll.

Thanks again.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, October 11, 2021 3:30 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

How's going recently after all these events of speculation ? I felt deeply compassionate for your years of hardships and motives to find reliefs to people in need, Putting these aside, I have read some papers related to astrocyte which is associated with AD as below :

<https://www.nature.com/articles/s41593-020-0624-8>
<https://www.pnas.org/content/118/33/e2102191118>
[https://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914\(18\)30224-7](https://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914(18)30224-7)

Biomarkers such as apoE are mentioned in related literatures. Since many efforts with reactive glia fell short of therapeutic effectiveness, I am not sure if astrocyte is a valid pathology and target to AD. If there is a correlation, is it a possibility to find another bad guy in this complicated cascades of AD events ?

Another issue is my personal matter. My mother was diagnosed with Parkinson's disease and AD by a local clinic with brain scan. Her memory and motor conditions declined and I am very heart-broken to see her with helpless efforts after my mother took care of my father for so many years . She was prescribed to have 3mg Rivastigmine twice a day and I persuade to take 1.5mg each day. Is it possible for my mother to take part in the global study of PTI-125 if this would be helpful ? Thanks a lot for your listening to my personal matters. Your assistances are very much appreciated,

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, August 10, 2021 12:08 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your kind words. Your questions keep me thinking of my answers so that I can be as clear as possible in my answers to most. I am truly impressed with and appreciate your viewpoints. Obviously, we have a lot of unknown factors in Alzheimer's disease that harboring many pathogenic pathways. I am working as hard as I can to find other possible pathogenic triggers - bad guys (aging process is one of them, and I think mental stress may also push the brain into neurodegenerative path). Regardless, we got to find these damaging pathways as soon as we can - early diagnosis that is.

Thanks for the reminder of the COVID delta variants. I am glad that Taiwan is very cautious on this pandemic development. In US, there are people still hesitate to be vaccinated. Unlike Taiwan, the availability of vaccine is less a problem because 4 mainstream vaccines are produced in US. I think Taiwan's domestic vaccines look great and more importantly can solve the supply issues although I do not get there are politicians that constantly trying to discredit these vaccines. In any case, please be very careful still especially in Taipei and New Taipei cities.

Thanks again for your support and keeping me informed of other developments. Please also keep asking questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, August 7, 2021 2:16 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Nice to have your replies especially when you are fully occupied. Your answers to my naïve questions help me to understand more properties of PTI-125 which surely would provide viable solutions to needed patients never before. Especially for meaningful researches, PTI-125 would have more indications and implications as time goes on. If you could find additional bad guys behind AD, a Nobel prize for you is not too far away.

Stay safe when delta virus poses new threats in US. In Taiwan, we are cautious about recent pandemic developments with protective measures. Looking ahead, I would expect an oral solution with protease inhibitor or some combination therapy would truly alleviate this human dilemma. Thanks again for your insights and sharing with me.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, August 7, 2021 4:29 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

As always, I am completely booked up with research activities. Your questions kept me thinking. I answer your questions directly underneath each of your queries.

Hope all is well,

Thank you.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, July 31, 2021 2:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Thanks for your kindly reply during busy hours as always. Knocking off hard nuts is especially tough especially there was no precedent before. Your persistence and genuine contributions to global AD community is obvious. I am happy that your finding of the bad guy will eventually be a history of AD and even mankind. Your family and friends will be certainly proud of you after so many tough years spent in lab and related researches.

Your answers to my naïve questions are plain and understandable. To my personal curiosity which might be common to most people, I have additional questions as below.

1. Is there any plateau effect after months of oral treatment of PTI-125 since biomarkers of neuroinflammation and neurodegeneration will eventually reach their peaks ? Will responded patients need to take oral treatments of PTI-125 in their lifetime ? *True. neuroinflammation and neurodegeneration will reach a breaking point down the road without treatments. Our hope is that this treatment will delay the neuroinflammation and neurodegeneration so that brain can recover (those not dead yet) some so that brain can function better. My guess is that there is some sort of limitations (not plateau per se). We hope the window is big enough (beyond the nature life span).*
2. When temporal changes of individual patient during the span of treatments will be revealed ? This information might show more consistent and clearer trend of treatment effects. *I am not sure what you are referring to. It would be difficult to gauge patient's response rate since each patient is different in many aspects (other diseases, genetic make up etc). Very difficult to tell.*
3. For neurons already beyond repairs or dead, is there any viable therapeutic or complimentary solution ? *No. Raise from death is NOT any humans can do.*
4. Would mental or physical rehabilitations for patients during or after treatments add more values to their health ? *We have evidence to show exercise and good nutrients (diet) help to elevate the treatment effects.*

There must be lots of works needed to be done after this stage. For all your dedication, I believe that all time spent in search of better treatments will be meaningful and greatly appreciated. Thanks again in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, July 31, 2021 1:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your encouragements always and giving your opinions and questions as I need such reminders to keep my comments plain and understandable.

I will **answer your questions directly underneath each query you posted**. Since I am blind to all patient related info, I can only answer in general terms.

Hope all is well with you and your family.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Thursday, July 29, 2021 10:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Congratulation to your researches going with a gigantic step forward. After reading updated PTI-125 related papers in CCAI 2021, I had a feeling that your lab works have gradually verified the MOA of Filamin A with abnormal conformation. There are thoughts with results of SavaDx and 9-month data as follows :

- 1) Correlation studies of Abnormal Filamin A in phase 2b patients is a positive step. That is a great findings and direction in the framework of diagnosis tool. However, taking Abnormal Filamin A as a biomarker needs more works to establish that which level of Abnormal Filamin A should be detected as an early sign of AD. I am wondering if a totally new or compatible antibody in your earlier works of SavaDx is employed in this study.
- Indeed, this is just the initial steps. The antibodies used obviously required constant verifications using that was used earlier. It is a tedious work but there are no short cuts. We need to define the timeline when the abnormal FLNA can be detected (not an easy task because we don't even know when is early).
- 2) Cognition Improvement of 3.0 Points on ADAS-Cog at 9 Months ($p < 0.001$) is great for patients as a process of Filamin A normalization. However, most people are wondering why NPI score in 9 month improved less than in 6 month by 0.6 points. All tested biomarkers are consistent with improvements which relieved lots of overhangs.
- People forget Alzheimer's disease is a progressive neurodegenerative disease with multiple factors at play. As patients deteriorate cognitively due to brain function declines, there are added factors hence the magnitude of improvements become less comparing the the baseline. The 0.6 points less at 9 month reflects just that (obviously it also depends on the stage of disease when patients first enrolled) but the curve will be stabilize for period of time.
- 3) 22% of patients declined less than reported in the science literature at 9 months. Why these patients are so hard to respond to treatment of simufilam ? Any other upstream catalyst for these patients ?
- Well, we don't actually know but my guess is that these patients have other issues or they were selected at later stage of the disease even though their MMSE or ADAS-Cog when enrolled were not bad. While we like to have 100% responsive rate, it is an unrealistic expectation. This drive home the importance of early diagnosis. I am sure if we treat earlier, we will see a better result.
- 4) As reported earlier, Evonik will supply Cassava Sciences with large-scale, clinical-grade quantities of simufilam. I am wondering if Evonik will produce good qualities of simufilam as in phase 2b study and it should be carefully verified before entering phase 3.
- Clearly, QC will be done carefully.
- 5) Finally, is abnormal filamin A responsible for the symptom or modifying answer to AD ?
- While we all want to find the "bad" guy (abnormal FLNA is a critical but one of the bad guys I am sure there are many others). Fortunately, fixing abnormal FLNA promotes healthier and more resilient brain but unfortunately can't fix anything already beyond repairs or dead. I am a realistic person by showing people what I saw but I don't want to give a wrong impression that fixing abnormal FLNA can bring back what have already damaged.

I am honored to be with your ongoing researches and contributions to AD patients. Thanks for your hard works.

Best Regards,

宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, June 30, 2021 8:29 PM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Sorry for my late reply. I often just get occupied by too many tasks in hand and consequently delay in my response to you and many.

Yes, lots efforts had been on the multiple fronts and there should be an update in phase 2b study. I will be interest in learning of your comments.

I watch the COVID-19 situation in Taiwan closely. It is most unfortunately some careless acts led to such a spread. Even though it is pale by comparison to US and EU, it is still very concerning especially in Taipei (the worst in transparency) and New Taipei. A solution to this monumental disaster must include understand the pathogen (virus) so that more effective medications together with vaccination can put this pandemic out for good.

Best wishes to you and your family, it is looking better recently so that normalcy is near.

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, June 22, 2021 12:18 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After reading a recent news from Cassava Sciences, I realized that there will be a presentation at AAIC during the week of July 26-30th about SavaDx clinical dataset from PTI-125's Phase 2b study of 64 patients. Look forward to seeing more updates of SavaDx developments which you must devote lots of time and energy.

Affected by recent COVID-19 impacts in Taiwan, I have been working from home more than 1 month. Hope that this history-making pandemics will be alleviated or solved by pharmaceutical solutions. The same goes to PTI-125 to help patients in need. Thanks.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 23, 2021 10:26 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

The MOA for PTI-125 is very different from that of ANVS401. PTI-125 reverses an abnormal filamin A thereby reducing the toxic signaling pathways that drive neurodegeneration and inflammation. ANVS401 functions as a translational blockers that presumably (based on cell and transgenic models) to reduce toxic substances such as amyloid beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. The major problem is that reducing those "toxic" substances do not work in humans. In fact, ANVS401 blocks APP (amyloid precursor protein) to reduce amyloid beta. APP is a known trophic factor whose expression increases when brain is injured. More of the problem, we know reduction in amyloid beta by beta or gamma secretase inhibitors do not stop Alzheimer's disease progression and in some cases actually worsen cognitive impairments. Hence, I don't predict any synergy between PTI-125 and ANVS401.

Postmortem brains are not suitable to study metabolic dysfunction because one can only show there is metabolic disturbance but can not conclusively show the source, when and how the metabolic dysfunction occur. Transgenic animal models are partial models at best and are very different from actual disease, therefore they are inheritably insufficient to any pathogenic pathway questions just about any diseases.

I hope my explanations help answering your questions.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, February 21, 2021 3:05 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

I had some thoughts again regarding to the upstream causes of Alzheimer disease and MOA of PTI-125.

As you mentioned earlier, there were complicated lab works deriving chemical compounds of PTI-125 to restore of Filamin A with abnormal conformation. I am curious to know what is the chemical MOA of PTI-125 which differentiates from other approaches such as ANVS401 of Annovis Bio Inc. to decrease multiple neurotoxic in Cerebrospinal Fluid (CSF) and improve axonal transport of nerve cell. Their therapeutic target also aims for reductions of neuroinflammation and neurodegeneration. Is there any synergetic effect to combine PTI-125 and ANVS401 ?

As in previous email, I am skeptical about causes of metabolic dysfunction related to Alzheimer disease. Is there any direct proof from human postmortem model instead of mouse model ?
Thanks again for your insights in advance.

Best Regards,

宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 16, 2021 1:08 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

First, Happy Lunar New Year. Wishing you and your family a happy, healthy and prosperous year of Ox.

Regarding your question, Donepezil's ADAS-cog score you are referring to are raw score. Once taking placebo control into consideration, the improvement achieved by 24 months of 5 mg and 10 mg daily dose of donepezil were around 0.35 and 0.39 (page 16 stat significant). By now we know donepezil's clinical effectiveness eventually diminished as disease progresses. Obviously, we hope the cognitive benefit of PTI-125 continues based on the biomarker data. The improvement in cognition is depending on the baseline state of the patients (how severe the dementia and obviously the accuracy of diagnosis). I can't say too much and frankly nobody is all that certain.

Based on the mechanism of action, we predict the therapeutic effects of PTI-125 are applicable to a broad range of Alzheimer's disease patients. Again, the magnitude of benefits depend on the severity of dementia - the earlier the better. Hence, it is important to have a reliable early diagnosis tool though we still not entirely sure how to define "early".

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, February 15, 2021 10:32 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After some thoughts and review of data during Chinese New Year, I have some questions needed for your comments as follows :

1. ADAS-Cog Improvement between ARICEPT and PTI-125 : In https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively after 24 weeks of treatment. These differences were statistically significant for 473 patients. Compared with baseline, 5 mg/day and 10 mg/day treatments of donepezil at 24 weeks showed 1.06 and 1.6 benefits in a controlled study. However, the press release of Cassava Sciences on Feb. 2, 2021 mentioned that six months of PTI-125 treatment improved cognition scores by 1.6 points on ADAS-Cog11.

These comparative improvements did not clearly distinguish the therapeutic advantage of PTI-125 compared with ARICEPT in 24 weeks of treatment. Is it true for this simple observation as above ? Is there any indication that PTI-125 will have better effects after prolonged period of time (such as 1 year) by restoring of Filamin A with abnormal conformation ?

2. You mentioned that collective efforts try to bring some solutions for Alzheimer's disease patients. Does it mean that a subset of Alzheimer patients would be appropriate for therapeutic effects of PTI-125 and diagnosis tool of SavaDx ? While other patients are not ideal enough ?

Thanks so much for your insights again.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Thursday, February 4, 2021 4:39 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thank you for your well wishes and positive comments. Your continued interests in finding solutions for Alzheimer's disease research motivate us and I can truly say I am trying my very best. I thank you for keeping me informed and discussions on the findings from other investigators. We will keep moving forward and hope our collective efforts can bring some solutions for Alzheimer's disease patients.

Will keep safe the best I can as the COVID pandemic is still very bad here. Hopefully, with vaccination the situation improves in the coming months.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, February 2, 2021 7:54 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

Nice to know that the interim result of PTI-125 is positive and brings lights to the Alzheimer community. Congratulation to your continued efforts. There must be lots of persons sending emails to you regarding to this matter. To continue your clinical endeavors, I truly wish you to keep safe in this covid-19 epidemics. Your academic and real-word contributions are very much appreciated.

Best Regards,

宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Thursday, January 21, 2021 11:55 PM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for keeping me informed of the recent development. I am all tied up by my extensive teaching load and research activities (this pandemic has caused tremendous pain with limited access).

Regarding the levels of N-terminal fragment of tau in the blood as a predictor of cognitive decline, this is really nothing new because we know the levels of tau in the CSF and blood positively correlate with the extent of neuronal damage (tau exist exclusively in neurons). The question is the sensitivity of detection that allow us to sound the alarm. With the more sensitive mass spectrometry we obviously are better equipped than before.

Thanks again. I will find time to answer your earlier queries.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Wednesday, January 20, 2021 7:54 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] some development of diagnosis tool for reference

Dear Hoau :

There is some development of blood test for Alzheimer's disease to predicte future cognitive decline in healthy people with levels of N-terminal fragment of tau (NT1). Data link is as <https://www.sciencedaily.com/releases/2020/12/201209115147.htm>. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, January 16, 2021 3:44 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks always for your info that keeping me in the loop of current Alzheimer's disease findings.

The problem is that this type of academic research using (genetically modified) rodent models that bear little resemblance to human Alzheimer's disease lead us to nowhere and frankly confuse & dilute our efforts. Hydrogen sulfide is no doubt playing a regulatory role in many physiological activities. Just because it is decreased with aging and replacing it can improve cognition in rodents doesn't mean it is therapeutically possible. Don't forget the hydrogen sulfide is quite toxic one should worry the accumulation can severely hurt the brain function. Most importantly, there is no evidence rodent models have neurodegeneration (unlike brains in humans with Alzheimer's disease). GSK3a/b is one of the hubs in metabolism/energy regulation and as one of the tau kinases that have a sophisticate feed forward and feedback regulators. There is no evidence there is anything change in GSK3a/b in Alzheimer's disease. In general, kinases and phosphatases are terrible targets because they all have tons of regulators once activated or inhibited in a progressively changing brain like in Alzheimer's disease is predictably short-lived and ineffective especially when the disease becomes symptomatic (much too late).

Thanks. Have a good weekend.

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 13, 2021 10:36 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

It seems to me more and more researches trying to target early pathogenesis of Alzheimer's disease which might be inspired by evidences of many clinical results. There is a recent research from John Hopkins Medicine working with University of Exeter concerning with effects of hydrogen sulfide, GSK3 β and other proteins involved in the pathogenesis of Alzheimer's disease. Their data link is https://medicalxpress.com/news/2021-01-hydrogen-sulfide-alzheimer-disease.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter. Hope that this information would be interesting to you. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 13, 2021 2:13 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Sorry for my late reply, sometimes I made a mental note to reply but I got busy and kind of putting it off. The impacts of concussion obviously vary according to the severity and frequency (multiple mild concussions can be quite damaging). It sounds like your father had a severe concussion that resulted in motor/sensory imbalance and dementia. I understand how hard it is to see your father suffer but unable to help.

There is no doubt vascular dysfunction is a risk factor and often accompanies Alzheimer's disease (cerebral amyloid angiopathy). That said, the cause-effect relationship between vascular dysfunction and Alzheimer's disease is not straight forward.

Indeed, upstream is a relative term. Abnormal filamin A can be induced by sub-chronic amyloid (soluble) infusion into brains. If abnormality in filamin A is blocked (by PTI-125), there is significant reduction in amyloid plaques (dead neurons) and neurofibrillary tangles. More importantly, brain activities with higher receptor and synaptic activities and function improve at least in mouse model of Alzheimer's disease. These data indicate reversing abnormality of filamin A especially when at the stage when mild clinical dementia is detected may be a promising way to treatment Alzheimer's disease.

Hope I answer your questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Monday, January 4, 2021 7:54 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your comments. After two decades of researches, your important findings have a step forward which is a remarkable achievement. I do admire your courage and patience with regard to this tough disease in which early detections are probably with both natures of science and art. My father was in a healthy condition before concussion and developed with signs of body imbalance and occurrence of Alzheimer disease. It was heartbreaking without ways to lessen his burden.

My assumption of root occurrence from vascular dysfunction might be wrong. It seems to me that finding a solution with very early detection before massive degeneration occurs is more than challenging. I am wondering which events trigger the formation of abnormal filamin A. If you could come up with a diagnosis tool tracing up the root cause of abnormal filamin A, it might be a better start than random guesses. I am not sure if I am right in this direction.

BTW, you mentioned that abnormal filamin A is an upstream event. Would you shed some lights on which upstream events are already verified up to now since upstream is a relative word ? Thanks so much for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Tuesday, January 5, 2021 1:07 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

There is no doubt vascular dysfunction is an important part of the Alzheimer's disease (AD) pathology. Filamin A with abnormal conformation is found in plasma from AD patients doesn't necessary mean abnormal filamin A from platelets is resulted from vascular pathology including amyloid angiopathy, infarcts. More importantly, the abnormal filamin A in peripheral may be the result of brain pathogenic changes (occurs later).

Our data indicate abnormal filamin A is an upstream event. However, AD treatment effects are better if starts earlier (hence early detection before massive degeneration occurs is the key). I always think multiple therapeutic agents may be synergistic or additive. Again, if all the treatments administered after massive degeneration there is no treatments strong enough.

Thanks.

All the best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, January 3, 2021 7:50 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks for your kindly reply. Happy New Year !

Since conformational filamin A is structurally found in palates, I therefore assume that vascular pathologies are related to this disease. Your researches in various aspects of insulin resistances were published and your comments really show how hard it is to trace pathogenic events.

I really appreciate your continued research and endeavor to find more upstream targets treating Alzheimer disease effectively. It seems to me in your comments that restoration of conformational filamin A is not strong enough to show disease modifying effects. Is it true ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, January 4, 2021 3:14 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Happy New Year. Wishing you and your family a healthy and prosperous year 2021.

It is my life time goal to help bring effective treatments and early diagnosis of the Alzheimer's disease (and other diseases with cognitive impairments). For the last two decades, I worked to identify possible drug and diagnostic targets. I'm mindful of the burden of the Alzheimer's disease caregivers, especially the potential of depression.

Regarding your question, there is no concrete data to show the function of blood platelet had changed in Alzheimer's disease (plausible of course). There are diverse pathogenic mechanisms and of course diseases such as diabetes (causes vascular pathologies) and history of concussion (multiple) had been suspected to be culprits to promote Alzheimer's disease. Surely, prevent such problems is useful but whether such measurements can reverse the damages that already done is everyone's guess. We had tried to control insulin resistance for years but the results thus far showed not much of effects. This may indicate that brain insulin resistance is not an early pathogenic event. We will do more to find more upstream targets so that we can more effective to treat Alzheimer's disease.

Thanks for your continuing interests and communications.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, December 29, 2020 7:38 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your kindly reply. For my father, a better treatment of Alzheimer disease is motivated and caregivers deserve to be with less burden. Regarding to the timing of conformational changes, I am curious to know if this is related to conditional changes of palates which caused by blood clotting, vascular abnormality or concussion, etc. Your endeavor of this tough disease is really appreciated.

Please be safe since pandemic and cold weather persist in northern atmosphere. Have a wonderful and peaceful New Year to you and your family.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 30, 2020 6:56 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks for your email.

Your friend is correct regarding the difficulty of finding specific antibodies for the filamin A with altered conformation in Alzheimer's disease. Indeed, the epitope of the altered filamin A may be hidden or had been processed. Obviously, computational approaches had been used to help us find viable antibodies. We still don't know when the conformational changes occur during the Alzheimer's disease pathogenesis even though we think this event occur early. But, what is early? This timing issue also requires some attention.

Yes, one-year extension of the open-label study is well under the way. Obviously, we will be looking for cognitive improvement and reduction in pathogenic drives such as reduction in inflammatory markers and degeneration.

Thanks again for your continued interests in getting the Alzheimer's disease treatment. I am working hard to get to this goal.

Happy New Year to you and your family.

Best regards,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, December 28, 2020 4:58 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Wish you a happy holiday and healthy new year, too. Regarding to the issue of diagnosis, my friend specialized in chemistry of antibody suggested to me recently that an exhaustive search of appropriate antibody to be connected with conformational filamin A in human palates might be required to have a solution of universal antibody for different races. A modern equipment with computerized tools would be helpful in this exhaustive search process. Since the epitope of conformational filamin A might be structurally hidden, an appropriate antibody might be sensitively or selectively enough to be effective. Hope that this information is useful.

A one-year, open label study of PTI-125 was initiated in March 2020 and enrolled over 60% of patients as mentioned in public. Supposedly, safety issues are not a big concern since expanded clinical trials still proceed. How about attributes of reduced inflammatory cytokine levels and improved cognition/behavior in this perspective since earlier enrolled patients had been treated with more than 6 months ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 23, 2020 4:03 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Season Greetings

Dear 宜明,

Sorry for my late reply as I am deep in the semester end exam and grading.

Wow, time flies by so quickly. It has been more than a year already since we started our communication. It is my pleasure to discuss the field of neuroscience even though we actually are learning on the way. I am thankful for the opportunities you have given me to think about the questions you have posted in different angles. Truly, we all hope we

have grown some in knowledge and get effective Alzheimer's disease treatments forward to contain this terrible disease. I am for one will do everything I can and work tirelessly toward this goal. It takes collective efforts to get this under control so that I am collaborating with academic and industrial partners to look into as many ways we can investigate and test the effectiveness. Thanks to you for keeping me informed of many new strategies other have come up with in Alzheimer's disease diagnosis and treatments.

We all hope we can better handle this COVID pandemic. With the approval of 2 vaccines, I am hopeful we are better equipped to start limiting the death tolls and eventually control this horrific virus. I sincerely hope people learn from this as we all have to play a part (wearing mask, wash hands frequently etc). This experience certainly humbles us as we humans appear more vulnerable (at least not as invincible) than we think. The fact Taiwan has done so well in controlling COVID makes me proud to be a Taiwanese.

Wishing you and your family happy holidays and a healthy, peaceful and prosperous year 2021.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, December 20, 2020 8:43 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] Season Greetings

Dear Hoau-Yan :

It's been more than 1 year since I have this particular opportunity to know you. Your in-depth and insightful knowledge has given me more understandings in this tough field of neuroscience. Your assistances and comments are really appreciated. Hopefully, we will be better off with more solutions of pandemics and preventive measures next year. At this time of season, I truly wish you a Merry Christmas and happy New Year !

Best Regards,
宜明



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From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent time: 10/11/2021 09:26:22 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Appreciate a lot for your kindly reply. My mom has dementia sometimes and needed to be reminded afterwards. Her motor and memory functions as mentioned decline as days go on. I keep reminding from your earlier suggestions that exercises, social contacts and healthy food are essential to daily life. She was prescribed with 1.5g Rivastigmine for a period of time and had some mental fluctuations after vaccination with AZ 3 weeks ago. Then, doctor changed prescriptions with 3g Rivastigmine b.i.d. after knowing recent behavior changes. However, I noticed that her mental fluctuations are stabilized recently with daily regular rests and good conversations improved her conditions. Thanks for your reminding me to monitor her conditions closely and that is what I could do at this moment.

Thanks a lot for your teaching me lots of information which is essential to this neurological complex beyond average understandings. I personally wish that an improved therapeutic support could alleviate and help people in need. It's my personal experiences to appreciate all these efforts of medical community overcoming this tough subject. Your devotion is very much appreciated.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, October 12, 2021 12:55 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your email.

Dear 宜明,

Thanks for your email. Sorry that I didn't respond to your many of your prior emails

As you know, gliosis (increased numbers of glia) is one of the biological/pathological consequence of the Alzheimer's disease. Glia do have their own functions and coordinate with neurons to keep the brain activities intact, hence one can't just say glia have functional changes during Alzheimer's disease pathogenesis that have negative impacts on the overall brain activities such as secrete inflammatory cytokines they are the bad guys. It is far more complex and not easy to be black-and-white clear. Take inflammation as an example, while prolonged inflammation harms the system we can't do without inflammation because it warns us there is something wrong. You take away the alarm, you have a false sense of security.

Regarding your mother, I am sorry to hear the Parkinson's disease diagnosis (she was diagnosed with Alzheimer's dementia first, right?). Does she have motor symptoms? Good portion of the Parkinson's patients do develop dementia. You should get a second opinion on your mother's diagnosis and have some idea of severity of the symptoms.

As you know, Rivastigmine belongs to cholinesterase inhibitor family. While it does make pharmacological sense to use in your mother's case (PD+dementia), a close monitoring is necessary (knowing you, you probably read through many papers and know a great deal of the drug and its adverse effects). What was the reason you persuade your mother to only take 1.5 mg Rivastigmine? I am sorry I don't have any say about the clinical trial. Unless, there is a trial in Taiwan, it is not possible to enroll.

Thanks again.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, October 11, 2021 3:30 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

How's going recently after all these events of speculation ? I felt deeply compassionate for your years of hardships and motives to find reliefs to people in need, Putting these aside, I have read some papers related to astrocyte which is associated with AD as below :

<https://www.nature.com/articles/s41593-020-0624-8>
<https://www.pnas.org/content/118/33/e2102191118>
[https://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914\(18\)30224-7](https://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914(18)30224-7)

Biomarkers such as apoE are mentioned in related literatures. Since many efforts with reactive glia fell short of therapeutic effectiveness, I am not sure if astrocyte is a valid pathology and target to AD. If there is a correlation, is it a possibility to find another bad guy in this complicated cascades of AD events ?

Another issue is my personal matter. My mother was diagnosed with Parkinson's disease and AD by a local clinic with brain scan. Her memory and motor conditions declined and I am very heart-broken to see her with helpless efforts after my mother took care of my father for so many years . She was prescribed to have 3mg Rivastigmine twice a day and I persuade to take 1.5mg each day. Is it possible for my mother to take part in the global study of PTI-125 if this would be helpful ? Thanks a lot for your listening to my personal matters. Your assistances are very much appreciated,

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, August 10, 2021 12:08 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your kind words. Your questions keep me thinking of my answers so that I can be as clear as possible in my answers to most. I am truly impressed with and appreciate your viewpoints. Obviously, we have a lot of unknown factors in Alzheimer's disease that harboring many pathogenic pathways. I am working as hard as I can to find other possible pathogenic triggers - bad guys (aging process is one of them, and I think mental stress may also push the brain into neurodegenerative path). Regardless, we got to find these damaging pathways as soon as we can - early diagnosis that is.

Thanks for the reminder of the COVID delta variants. I am glad that Taiwan is very cautious on this pandemic development. In US, there are people still hesitate to be vaccinated. Unlike Taiwan, the availability of vaccine is less a problem because 4 mainstream vaccines are produced in US. I think Taiwan's domestic vaccines look great and more importantly can solve the supply issues although I do not get there are politicians that constantly trying to discredit these vaccines. In any case, please be very careful still especially in Taipei and New Taipei cities.

Thanks again for your support and keeping me informed of other developments. Please also keep asking questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, August 7, 2021 2:16 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Nice to have your replies especially when you are fully occupied. Your answers to my naïve questions help me to understand more properties of PTI-125 which surely would provide viable solutions to needed patients never before. Especially for meaningful researches, PTI-125 would have more indications and implications as time goes on. If you could find additional bad guys behind AD, a Nobel prize for you is not too far away.

Stay safe when delta virus poses new threats in US. In Taiwan, we are cautious about recent pandemic developments with protective measures. Looking ahead, I would expect an oral solution with protease inhibitor or some combination therapy would truly alleviate this human dilemma. Thanks again for your insights and sharing with me.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, August 7, 2021 4:29 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

As always, I am completely booked up with research activities. Your questions kept me thinking. I answer your questions directly underneath each of your queries.

Hope all is well,

Thank you.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Saturday, July 31, 2021 2:49 AM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Thanks for your kindly reply during busy hours as always. Knocking off hard nuts is especially tough especially there was no precedent before. Your persistence and genuine contributions to global AD community is obvious. I am happy that your finding of the bad guy will eventually be a history of AD and even mankind. Your family and friends will be certainly proud of you after so many tough years spent in lab and related researches.

Your answers to my naïve questions are plain and understandable. To my personal curiosity which might be common to most people, I have additional questions as below.

1. Is there any plateau effect after months of oral treatment of PTI-125 since biomarkers of neuroinflammation and neurodegeneration will eventually reach their peaks ? Will responded patients need to take oral treatments of PTI-125 in their lifetime ? *True. neuroinflammation and neurodegeneration will reach a breaking point down the road without treatments. Our hope is that this treatment will delay the neuroinflammation and neurodegeneration so that brain can recover (those not dead yet) some so that brain can function better. My guess is that there is some sort of limitations (not plateau per se). We hope the window is big enough (beyond the nature life span).*
2. When temporal changes of individual patient during the span of treatments will be revealed ? This information might show more consistent and clearer trend of treatment effects. *I am not sure what you are referring to. It would be difficult to gauge patient's response rate since each patient is different in many aspects (other diseases, genetic make up etc). Very difficult to tell.*
3. For neurons already beyond repairs or dead, is there any viable therapeutic or complimentary solution ? *No. Raise from death is NOT any humans can do.*
4. Would mental or physical rehabilitations for patients during or after treatments add more values to their health ? *We have evidence to show exercise and good nutrients (diet) help to elevate the treatment effects.*

There must be lots of works needed to be done after this stage. For all your dedication, I believe that all time spent in search of better treatments will be meaningful and greatly appreciated. Thanks again in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Saturday, July 31, 2021 1:39 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for your encouragements always and giving your opinions and questions as I need such reminders to keep my comments plain and understandable.

I will **answer your questions directly underneath each query you posted**. Since I am blind to all patient related info, I can only answer in general terms.

Hope all is well with you and your family.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Thursday, July 29, 2021 10:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

Congratulation to your researches going with a gigantic step forward. After reading updated PTI-125 related papers in CCAI 2021, I had a feeling that your lab works have gradually verified the MOA of Filamin A with abnormal conformation. There are thoughts with results of SavaDx and 9-month data as follows :

- 1) Correlation studies of Abnormal Filamin A in phase 2b patients is a positive step. That is a great findings and direction in the framework of diagnosis tool. However, taking Abnormal Filamin A as a biomarker needs more works to establish that which level of Abnormal Filamin A should be detected as an early sign of AD. I am wondering if a totally new or compatible antibody in your earlier works of SavaDx is employed in this study.
- Indeed, this is just the initial steps. The antibodies used obviously required constant verifications using that was used earlier. It is a tedious work but there are no short cuts. We need to define the timeline when the abnormal FLNA can be detected (not an easy task because we don't even know when is early).
- 2) Cognition Improvement of 3.0 Points on ADAS-Cog at 9 Months ($p < 0.001$) is great for patients as a process of Filamin A normalization. However, most people are wondering why NPI score in 9 month improved less than in 6 month by 0.6 points. All tested biomarkers are consistent with improvements which relieved lots of overhangs.
- People forget Alzheimer's disease is a progressive neurodegenerative disease with multiple factors at play. As patients deteriorate cognitively due to brain function declines, there are added factors hence the magnitude of improvements become less comparing the the baseline. The 0.6 points less at 9 month reflects just that (obviously it also depends on the stage of disease when patients first enrolled) but the curve will be stabilize for period of time.
- 3) 22% of patients declined less than reported in the science literature at 9 months. Why these patients are so hard to respond to treatment of simufilam ? Any other upstream catalyst for these patients ?
- Well, we don't actually know but my guess is that these patients have other issues or they were selected at later stage of the disease even though their MMSE or ADAS-Cog when enrolled were not bad. While we like to have 100% responsive rate, it is an unrealistic expectation. This drive home the importance of early diagnosis. I am sure if we treat earlier, we will see a better result.
- 4) As reported earlier, Evonik will supply Cassava Sciences with large-scale, clinical-grade quantities of simufilam. I am wondering if Evonik will produce good qualities of simufilam as in phase 2b study and it should be carefully verified before entering phase 3.
- Clearly, QC will be done carefully.
- 5) Finally, is abnormal filamin A responsible for the symptom or modifying answer to AD ?
- While we all want to find the "bad" guy (abnormal FLNA is a critical but one of the bad guys I am sure there are many others). Fortunately, fixing abnormal FLNA promotes healthier and more resilient brain but unfortunately can't fix anything already beyond repairs or dead. I am a realistic person by showing people what I saw but I don't want to give a wrong impression that fixing abnormal FLNA can bring back what have already damaged.

I am honored to be with your ongoing researches and contributions to AD patients. Thanks for your hard works.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, June 30, 2021 8:29 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Sorry for my late reply. I often just get occupied by too many tasks in hand and consequently delay in my response to you and many.

Yes, lots efforts had been on the multiple fronts and there should be an update in phase 2b study. I will be interest in

learning of your comments.

I watch the COVID-19 situation in Taiwan closely. It is most unfortunately some careless acts led to such a spread. Even though it is pale by comparison to US and EU, it is still very concerning especially in Taipei (the worst in transparency) and New Taipei. A solution to this monumental disaster must include understand the pathogen (virus) so that more effective medications together with vaccination can put this pandemic out for good.

Best wishes to you and your family, it is looking better recently so that normalcy is near.

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, June 22, 2021 12:18 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After reading a recent news from Cassava Sciences, I realized that there will be a presentation at AAIC during the week of July 26-30th about SavaDx clinical dataset from PTI-125's Phase 2b study of 64 patients. Look forward to seeing more updates of SavaDx developments which you must devote lots of time and energy.

Affected by recent COVID-19 impacts in Taiwan, I have been working from home more than 1 month. Hope that this history-making pandemics will be alleviated or solved by pharmaceutical solutions. The same goes to PTI-125 to help patients in need. Thanks.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 23, 2021 10:26 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

The MOA for PTI-125 is very different from that of ANVS401. PTI-125 reverses an abnormal filamin A thereby reducing the toxic signaling pathways that drive neurodegeneration and inflammation. ANVS401 functions as a translational blockers that presumably (based on cell and transgenic models) to reduce toxic substances such as amyloid beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. The major problem is that reducing those "toxic" substances do not work in humans. In fact, ANVS401 blocks APP (amyloid precursor protein) to reduce amyloid beta. APP is a known trophic factor whose expression increases when brain is injured. More of the problem, we know reduction in amyloid beta by beta or gamma secretase inhibitors do not stop Alzheimer's disease progression and in some cases actually worsen cognitive impairments. Hence, I don't predict any synergy between PTI-125 and ANVS401.

Postmortem brains are not suitable to study metabolic dysfunction because one can only show there is metabolic disturbance but can not conclusively show the source, when and how the metabolic dysfunction occur. Transgenic animal models are partial models at best and are very different from actual disease, therefore they are inheritably insufficient to any pathogenic pathway questions just about any diseases.

I hope my explanations help answering your questions.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, February 21, 2021 3:05 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

I had some thoughts again regarding to the upstream causes of Alzheimer disease and MOA of PTI-125.

As you mentioned earlier, there were complicated lab works deriving chemical compounds of PTI-125 to restore of Filamin A with abnormal conformation. I am curious to know what is the chemical MOA of PTI-125 which differentiates from other approaches such as ANVS401 of Annovis Bio Inc. to decrease multiple neurotoxic in Cerebrospinal Fluid (CSF) and improve axonal transport of nerve cell. Their therapeutic target also aims for reductions of neuroinflammation and neurodegeneration. Is there any synergetic effect to combine PTI-125 and ANVS401 ?

As in previous email, I am skeptical about causes of metabolic dysfunction related to Alzheimer disease. Is there any direct proof from human postmortem model instead of mouse model ?
Thanks again for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, February 16, 2021 1:08 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

First, Happy Lunar New Year. Wishing you and your family a happy, healthy and prosperous year of Ox.

Regarding your question, Donepezil's ADAS-cog score you are referring to are raw score. Once taking placebo control into consideration, the improvement achieved by 24 months of 5 mg and 10 mg daily dose of donepezil were around 0.35 and 0.39 (page 16 stat significant). By now we know donepezil's clinical effectiveness eventually diminished as disease progresses. Obviously, we hope the cognitive benefit of PTI-125 continues based on the biomarker data. The improvement in cognition is depending on the baseline state of the patients (how severe the dementia and obviously the accuracy of diagnosis). I can't say too much and frankly nobody is all that certain.

Based on the mechanism of action, we predict the therapeutic effects of PTI-125 are applicable to a broad range of Alzheimer's disease patients. Again, the magnitude of benefits depend on the severity of dementia - the earlier the better. Hence, it is important to have a reliable early diagnosis tool though we still not entirely sure how to define "early".

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, February 15, 2021 10:32 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan,

After some thoughts and review of data during Chinese New Year, I have some questions needed for your comments as follows :

1. ADAS-Cog Improvement between ARICEPT and PTI-125 : In https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively after 24 weeks of treatment. These differences were statistically significant for 473 patients. Compared with baseline, 5 mg/day and 10 mg/day treatments of donepezil at 24 weeks showed 1.06 and 1.6 benefits in a controlled study. However, the press release of Cassava Sciences on Feb. 2, 2021 mentioned that six months of PTI-125 treatment improved cognition scores by 1.6 points on ADAS-Cog11.

These comparative improvements did not clearly distinguish the therapeutic advantage of PTI-125 compared with ARICEPT in 24 weeks of treatment. Is it true for this simple observation as above ? Is there any indication that PTI-125 will have better effects after prolonged period of time (such as 1 year) by restoring of Filamin A with abnormal conformation ?

2. You mentioned that collective efforts try to bring some solutions for Alzheimer's disease patients. Does it mean that a subset of Alzheimer patients would be appropriate for therapeutic effects of PTI-125 and diagnosis tool of SavaDx ? While other patients are not ideal enough ?

Thanks so much for your insights again.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, February 4, 2021 4:39 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thank you for your well wishes and positive comments. Your continued interests in finding solutions for Alzheimer's disease research motivate us and I can truly say I am trying my very best . I thank you for keeping me informed and discussions on the findings from other investigators. We will keep moving forward and hope our collective efforts can bring some solutions for Alzheimer's disease patients.

Will keep safe the best I can as the COVID pandemic is still very bad here. Hopefully, with vaccination the situation improves in the coming months.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Tuesday, February 2, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: some development of diagnosis tool for reference

Dear Hoau-Yan :

Nice to know that the interim result of PTI-125 is positive and brings lights to the Alzheimer community. Congratulation to your continued efforts. There must be lots of persons sending emails to you regarding to this matter. To continue your clinical endeavors, I truly wish you to keep safe in this covid-19 epidemics. Your academic and real-word contributions are very much appreciated.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, January 21, 2021 11:55 PM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: some development of diagnosis tool for reference

Dear 宜明,

Thanks for keeping me informed of the recent development. I am all tied up by my extensive teaching load and research activities (this pandemic has caused tremendous pain with limited access).

Regarding the levels of N-terminal fragment of tau in the blood as a predictor of cognitive decline, this is really nothing new because we know the levels of tau in the CSF and blood positively correlate with the extent of neuronal damage (tau exist exclusively in neurons). The question is the sensitivity of detection that allow us to sound the alarm. With the more sensitive mass spectrometry we obviously are better equipped than before.

Thanks again. I will find time to answer your earlier queries.

Best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Wednesday, January 20, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] some development of diagnosis tool for reference

Dear Hoau :

There is some development of blood test for Alzheimer's disease to predicte future cognitive decline in healthy people with levels of N-terminal fragment of tau (NT1). Data link is as
<https://www.sciencedaily.com/releases/2020/12/201209115147.htm>. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Saturday, January 16, 2021 3:44 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks always for your info that keeping me in the loop of current Alzheimer's disease findings.

The problem is that this type of academic research using (genetically modified) rodent models that bear little resemblance to human Alzheimer's disease lead us to nowhere and frankly confuse & dilute our efforts. Hydrogen sulfide is no doubt playing a regulatory role in many physiological activities. Just because it is decreased with aging and replacing it can improve cognition in rodents doesn't mean it is therapeutically possible. Don't forget the hydrogen sulfide is quite toxic one should worry the accumulation can severely hurt the brain function. Most importantly, there is no evidence rodent models have neurodegeneration (unlike brains in humans with Alzheimer's disease). GSK3a/b is one of the hubs in metabolism/energy regulation and as one of the tau kinases that have a sophisticated feed forward and feedback regulators. There is no evidence there is anything change in GSK3a/b in Alzheimer's disease. In general, kinases and phosphatases are terrible targets because they all have tons of regulators once activated or inhibited in a progressively changing brain like in Alzheimer's disease is predictably short-lived and ineffective especially when the disease becomes symptomatic (much too late).

Thanks. Have a good weekend.

Best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Wednesday, January 13, 2021 10:36 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

It seems to me more and more researches trying to target early pathogenesis of Alzheimer's disease which might be inspired by evidences of many clinical results. There is a recent research from John Hopkins Medicine working with University of Exeter concerning with effects of hydrogen sulfide, GSK3 β and other proteins involved in the pathogenesis of Alzheimer's disease. Their data link is https://medicalxpress.com/news/2021-01-hydrogen-sulfide-alzheimer-disease.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter. Hope that this information would be interesting to you. FYI.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, January 13, 2021 2:13 PM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Sorry for my late reply, sometimes I made a mental note to reply but I got busy and kind of putting it off. The impacts of concussion obviously vary according to the severity and frequency (multiple mild concussions can be quite damaging). It sounds like your father had a severe concussion that resulted in motor/sensory imbalance and dementia. I understand how hard it is to see your father suffer but unable to help.

There is no doubt vascular dysfunction is a risk factor and often accompanies Alzheimer's disease (cerebral amyloid angiopathy). That said, the cause-effect relationship between vascular dysfunction and Alzheimer's disease is not straight forward.

Indeed, upstream is a relative term. Abnormal filamin A can be induced by sub-chronic amyloid (soluble) infusion into brains. If abnormality in filamin A is blocked (by PTI-125), there is significant reduction in amyloid plaques (dead neurons) and neurofibrillary tangles. More importantly, brain activities with higher receptor and synaptic activities and function improve at least in mouse model of Alzheimer's disease. These data indicate reversing abnormality of filamin A especially when at the stage when mild clinical dementia is detected may be a promising way to treatment Alzheimer's disease.

Hope I answer your questions.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, January 4, 2021 7:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your comments. After two decades of researches, your important findings have a step forward which is a remarkable achievement. I do admire your courage and patience with regard to this tough disease in which early detections are probably with both natures of science and art. My father was in a healthy condition before concussion and developed with signs of body imbalance and occurrence of Alzheimer disease. It was heartbreaking without ways to lessen his burden.

My assumption of root occurrence from vascular dysfunction might be wrong. It seems to me that finding a solution with very early detection before massive degeneration occurs is more than challenging. I am wondering which events trigger the formation of abnormal filamin A. If you could come up with a diagnosis tool tracing up the root cause of abnormal filamin A, it might be a better start than random guesses. I am not sure if I am right in this direction.

BTW, you mentioned that abnormal filamin A is an upstream event. Would you shed some lights on which upstream events are already verified up to now since upstream is a relative word ? Thanks so much for your insights in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Tuesday, January 5, 2021 1:07 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

There is no doubt vascular dysfunction is an important part of the Alzheimer's disease (AD) pathology. Filamin A with abnormal conformation is found in plasma from AD patients doesn't necessary mean abnormal filamin A from platelets is resulted from vascular pathology including amyloid angiopathy, infarcts. More importantly, the abnormal filamin A in peripheral may be the result of brain pathogenic changes (occurs later).

Our data indicate abnormal filamin A is an upstream event. However, AD treatment effects are better if starts earlier (hence early detection before massive degeneration occurs is the key). I always think multiple therapeutic agents may be synergistic or additive. Again, if all the treatments administered after massive degeneration there is no treatments strong enough.

Thanks.

All the best,

Hoau

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Sunday, January 3, 2021 7:50 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks for your kindly reply. Happy New Year !

Since conformational filamin A is structurally found in palates, I therefore assume that vascular pathologies are related to this disease. Your researches in various aspects of insulin resistances were published and your comments really show how hard it is to trace pathogenic events.

I really appreciate your continued research and endeavor to find more upstream targets treating Alzheimer disease effectively. It seems to me in your comments that restoration of conformational filamin A is not strong enough to show disease modifying effects. Is it true ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, January 4, 2021 3:14 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Happy New Year. Wishing you and your family a healthy and prosperous year 2021.

It is my life time goal to help bring effective treatments and early diagnosis of the Alzheimer's disease (and other diseases with cognitive impairments). For the last two decades, I worked to identify possible drug and diagnostic targets. I'm mindful of the burden of the Alzheimer's disease caregivers, especially the potential of depression.

Regarding your question, there is no concrete data to show the function of blood platelet had changed in Alzheimer's disease (plausible of course). There are diverse pathogenic mechanisms and of course diseases such as diabetes (causes vascular pathologies) and history of concussion (multiple) had been suspected to be culprits to promote Alzheimer's disease. Surely, prevent such problems is useful but whether such measurements can reverse the damages that already done is everyone's guess. We had tried to control insulin resistance for years but the results thus far

showed not much of effects. This may indicate that brain insulin resistance is not an early pathogenic event. We will do more to find more upstream targets so that we can more effective to treat Alzheimer's disease.

Thanks for your continuing interests and communications.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Tuesday, December 29, 2020 7:38 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] RE: Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Thanks again for your kindly reply. For my father, a better treatment of Alzheimer disease is motivated and caregivers deserve to be with less burden. Regarding to the timing of conformational changes, I am curious to know if this is related to conditional changes of palates which caused by blood clotting, vascular abnormality or concussion, etc. Your endeavor of this tough disease is really appreciated.

Please be safe since pandemic and cold weather persist in northern atmosphere. Have a wonderful and peaceful New Year to you and your family.

Best Regards,

宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Wednesday, December 30, 2020 6:56 AM

To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Subject: Re: Some comments from my friend regarding to diagnosis

Dear 宜明,

Thanks for your email.

Your friend is correct regarding the difficulty of finding specific antibodies for the filamin A with altered conformation in Alzheimer's disease. Indeed, the epitope of the altered filamin A may be hidden or had been processed. Obviously, computational approaches had been used to help us find viable antibodies. We still don't know when the conformational changes occur during the Alzheimer's disease pathogenesis even though we think this event occur early. But, what is early? This timing issue also requires some attention.

Yes, one-year extension of the open-label study is well under the way. Obviously, we will be looking for cognitive improvement and reduction in pathogenic drives such as reduction in inflammatory markers and degeneration.

Thanks again for your continued interests in getting the Alzheimer's disease treatment. I am working hard to get to this goal.

Happy New Year to you and your family.

Best regards,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Sent: Monday, December 28, 2020 4:58 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Some comments from my friend regarding to diagnosis

Dear Hoau-Yan :

Wish you a happy holiday and healthy new year, too. Regarding to the issue of diagnosis, my friend specialized in chemistry of antibody suggested to me recently that an exhaustive search of appropriate antibody to be connected with conformational filamin A in human palates might be required to have a solution of universal antibody for different races. A modern equipment with computerized tools would be helpful in this exhaustive search process. Since the epitope of conformational filamin A might be structurally hidden, an appropriate antibody might be sensitively or selectively enough to be effective. Hope that this information is useful.

A one-year, open label study of PTI-125 was initiated in March 2020 and enrolled over 60% of patients as mentioned in public. Supposedly, safety issues are not a big concern since expanded clinical trials still proceed. How about attributes of reduced inflammatory cytokine levels and improved cognition/behavior in this perspective since earlier enrolled patients had been treated with more than 6 months ?

Thanks again for your comments in advance.

Best Regards,
宜明

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, December 23, 2020 4:03 AM
To: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>
Subject: Re: Season Greetings

Dear 宜明,

Sorry for my late reply as I am deep in the semester end exam and grading.

Wow, time flies by so quickly. It has been more than a year already since we started our communication. It is my pleasure to discuss the field of neuroscience even though we actually are learning on the way. I am thankful for the opportunities you have given me to think about the questions you have posted in different angles. Truly, we all hope we have grown some in knowledge and get effective Alzheimer's disease treatments forward to contain this terrible disease. I am for one will do everything I can and work tireless toward this goal. It takes collective efforts to get this under control so that I am collaborating with academic and industrial partners to look into as many ways we can investigate and test the effectiveness. Thanks to you for keeping me informed of many new strategies other have come up with in Alzheimer's disease diagnosis and treatments.

We all hope we can better handle this COVID pandemic. With the approval of 2 vaccines, I am hopeful we are better equipped to start limiting the death tolls and eventually control this horrific virus. I sincerely hope people learn from this as we all have to play a part (wearing mask, wash hands frequently etc). This experience certainly humbles us as we humans appear more vulnerable (at least not as invincible) than we think. The fact Taiwan has done so well in

controlling COVID makes me proud to be a Taiwanese.

Wishing you and your family happy holidays and a healthy, peaceful and prosperous year 2021.

All the best,

Hoau-Yan

From: 鄭宜明 Eddy Jeng - CDIB <yiming_j@cdibcapital.com>

Sent: Sunday, December 20, 2020 8:43 PM

To: Hoau-yan Wang

Subject: [EXTERNAL] Season Greetings

Dear Hoau-Yan :

It's been more than 1 year since I have this particular opportunity to know you. Your in-depth and insightful knowledge has given me more understandings in this tough field of neuroscience. Your assistances and comments are really appreciated. Hopefully, we will be better off with more solutions of pandemics and preventive measures next year. At this time of season, I truly wish you a Merry Christmas and happy New Year !

Best Regards,
宜明



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