The Role of Innate Immunity in Brain Health and Alzheimer's Disease

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Disclosures:

- ***Financial Interest: Neurogenetics, Inc / React Neuro, Inc / Cognitive Clarity, Inc / Verge Genomics, Inc/ Alterity, Inc / Cognoptix, Inc / Genomind, Inc / DRADS Capital / Interaxon, Inc***

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- **None**

Learning Objectives:

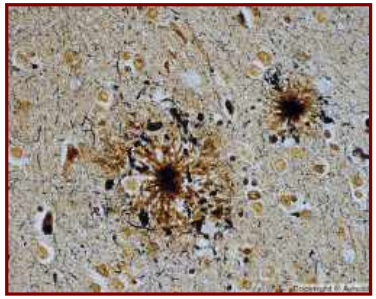
- ***Update on the Etiology and Pathogenesis of Alzheimer's Disease***
- ***How to treat the right Alzheimer's Pathology at the Right Stage of the Disease***
- ***Update on the genetic basis of neuroinflammation in Alzheimer's disease***
- ***Review of lifestyle Interventions to reduce risk for Alzheimer's disease***

Alzheimer's Disease

- Most common *form* of dementia in the elderly
- 5.5 million patients in U.S.: Medical Cost $300B/Year!
- Pre-symptomatic AD – brain pathology before symptoms: 38M!!
- Risk: Age, Family History, Head Injury, Stroke, High BP, Gender
- Women make up 2/3 of Alzheimer's disease patients
- 30-40% >85 have AD - Current lifespan~80 years
- Number of cases will triple by 2050 → Epidemic!

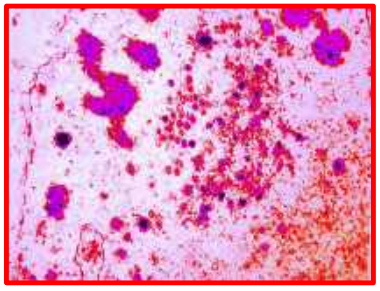
Alzheimer's Pathology → Amyloid Hypothesis → Genes → Amyloid Cascade Hypothesis

Beta-Amyloid Deposition



NFT/Tauopathy

Neuro-inflammation



Biochemical and Biophysical Research Communications

Volume 122, Issue 1, 16 August 1984, Pages 1131-1135

Alzheimer's disease and Down's syndrome: Sharing of a unique cerebrovascular amyloid fibril protein

George G. Glenner M.D., Caine W. Wong

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Abstract

The cerebrovascular amyloid protein from a case of adult Down's syndrome was isolated and purified. Amino acid sequence analysis showed it to be homologous to that of the β protein of Alzheimer's disease. This is the first chemical evidence of a relationship between Down's syndrome and Alzheimer's disease. It suggests that Down's syndrome may be a predictable model for Alzheimer's disease. Assuming the β protein is a human gene product, it also suggests that the genetic defect in Alzheimer's disease is localized on chromosome 21.

Proc. Natl. Acad. Sci. USA
Vol. 82, pp. 4245–4249, June 1985
Medical Sciences

Amyloid plaque core protein in Alzheimer disease and Down syndrome

(protein sequence/HPLC/congophilic angiopathy/unconventional virus infection/scrapie)

COLIN L. MASTERS*†, GAIL SIMMS*, NICOLA A. WEINMAN*, GERD MULTHAUP‡, BRIAN L. MCDONALD*, AND KONRAD BEYREUTHER‡

*Laboratory of Molecular and Applied Neuropathology, Neuroscience Research Institute, Department of Pathology, University of Western Australia, Nedlands, Western Australia, 6009; †Department of Neuropathology, Royal Perth Hospital, Perth, Western Australia, 6001; and ‡Institute of Genetics, University of Cologne, Cologne, Federal Republic of Germany

Amyloid β Protein Gene: cDNA, mRNA Distribution, and Genetic Linkage Near the Alzheimer Locus

RUDOLPH E. TANZI, JAMES F. GUSELLA, PAUL C. WATKINS, GAIL A. P. BRUNS, PETER ST GEORGE-HYSLOP, MARGARET L. VAN KEUREN, DAVID PATTERSON, SUSAN PAGAN, DAVID M. KURNIT, RACHAEL L. NEVE*

The amyloid β protein has been identified as an important component of both cerebrovascular amyloid and amyloid plaques of Alzheimer's disease and Down

NATURE VOL. 325 19 FEBRUARY 1987

The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor

Jie Kang, Hans-Georg Lemaire, Axel Unterbeck, J. Michael Salbaum, Colin L. Masters*, Karl-Heinz Grzeschik†, Gerd Multhaup, Konrad Beyreuther & Renno Müller-Hill

Characterization and Chromosomal Localization of a cDNA Encoding Brain Amyloid of Alzheimer's Disease

DMITRY GOLDGABER, MICHAEL I. LERMAN, O. WESLEY MCBRIDE, UMBERTO SAFFIOTTI, D. CARLETON GAJDUSEK

Four clones were isolated from an adult human brain complementary DNA library with an oligonucleotide probe corresponding to the first 20 amino acids of the β peptide of brain amyloid from Alzheimer's disease. The open reading frame of the

Mutation of the Alzheimer's Disease Amyloid Gene in Hereditary Cerebral Hemorrhage, Dutch Type

EFRAT LEVY,* MARK D. CARMAN, IVAN J. FERNANDEZ-MADRID, MICHAEL D. POWER, IVAN LIEBERBURG, SJOERD G. VAN DUINEN, GERARD TH. A. M. BOTS, WILLEM LUYENDIJK, BLAS FRANGIONE

Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease

Alison Goate*, Marie-Christine Chartier-Harlin*, Mike Mullan*, Jeremy Brown*, Fiona Crawford*, Liana Fidani*, Luis Giuffra†, Andrew Haynes‡, Nick Irving*, Louise James‡, Rebecca Mant‖, Phillipa Newton*, Karen Rooke*, Penelope Roques*, Chris Talbot*, Margaret Pericak-Vance‖, Allen Roses‖, Robert Williamson*, Martin Rossor*, Mike Owen‖ & John Hardy*†

Missense mutations in *APP*, *PS1*, or *PS2* genes

↓

Increased Aβ42 production and accumulation

↓

Aβ42 oligomerization and deposition as diffuse plaques

↓

Subtle effects of Aβ oligomers on synapses

↓

Microglial and astrocytic activation (complement factors, cytokines, etc.)

↓

Progressive synaptic and neuritic injury

↓

Altered neuronal ionic homeostasis; oxidative injury

↓

Altered kinase/phosphatase activities ▶ tangles

↓

Widespread neuronal/neuritic dysfunction and cell death with transmitter deficits

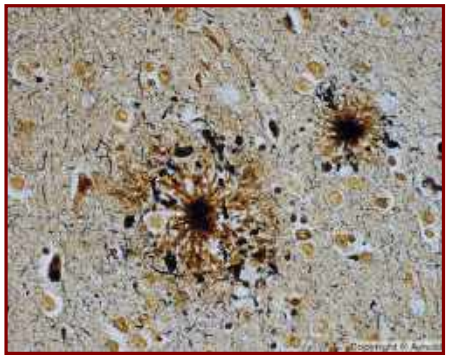
↓

Dementia

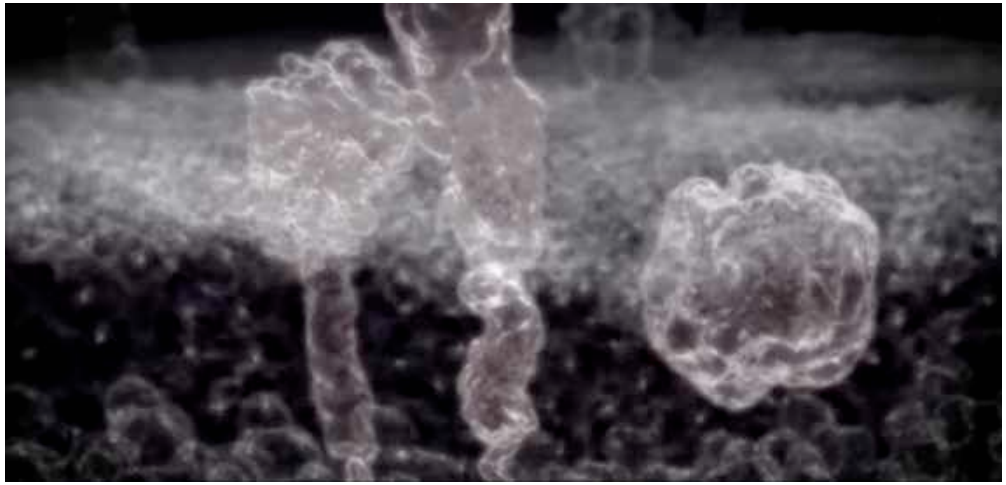
Original AD Genes Support the Amyloid Hypothesis of AD

Onset	Gene	Mutation/Variant	Consequence
Early Onset <60 yr	***APP*** ***PSEN1*** ***PSEN2***	***Mutations Guarantee EO FAD*** **18** **180** **16**	**↑ Ratio of Aβ42:Aβ40 (Aβ42 seeds β-amyloid)** **↑ Aggregation of Aβ** **↑ Production of Aβ**
Late Onset >60 yr	***APOE***	***ε4 Increases Risk for AD:*** **ε4 - 3.7 (het) to 14-fold (hom) increased risk**	**↑ Aβ Deposition**

Alzheimer's Disease Pathology



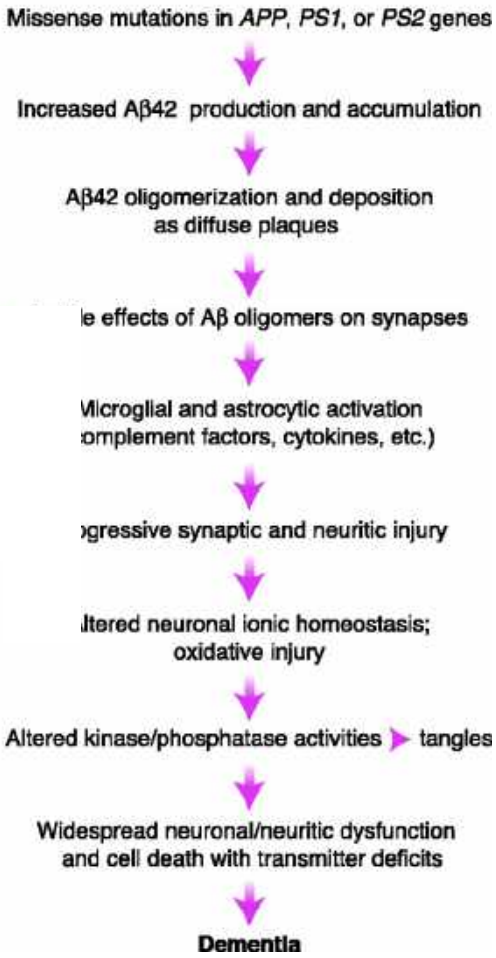
Plaques

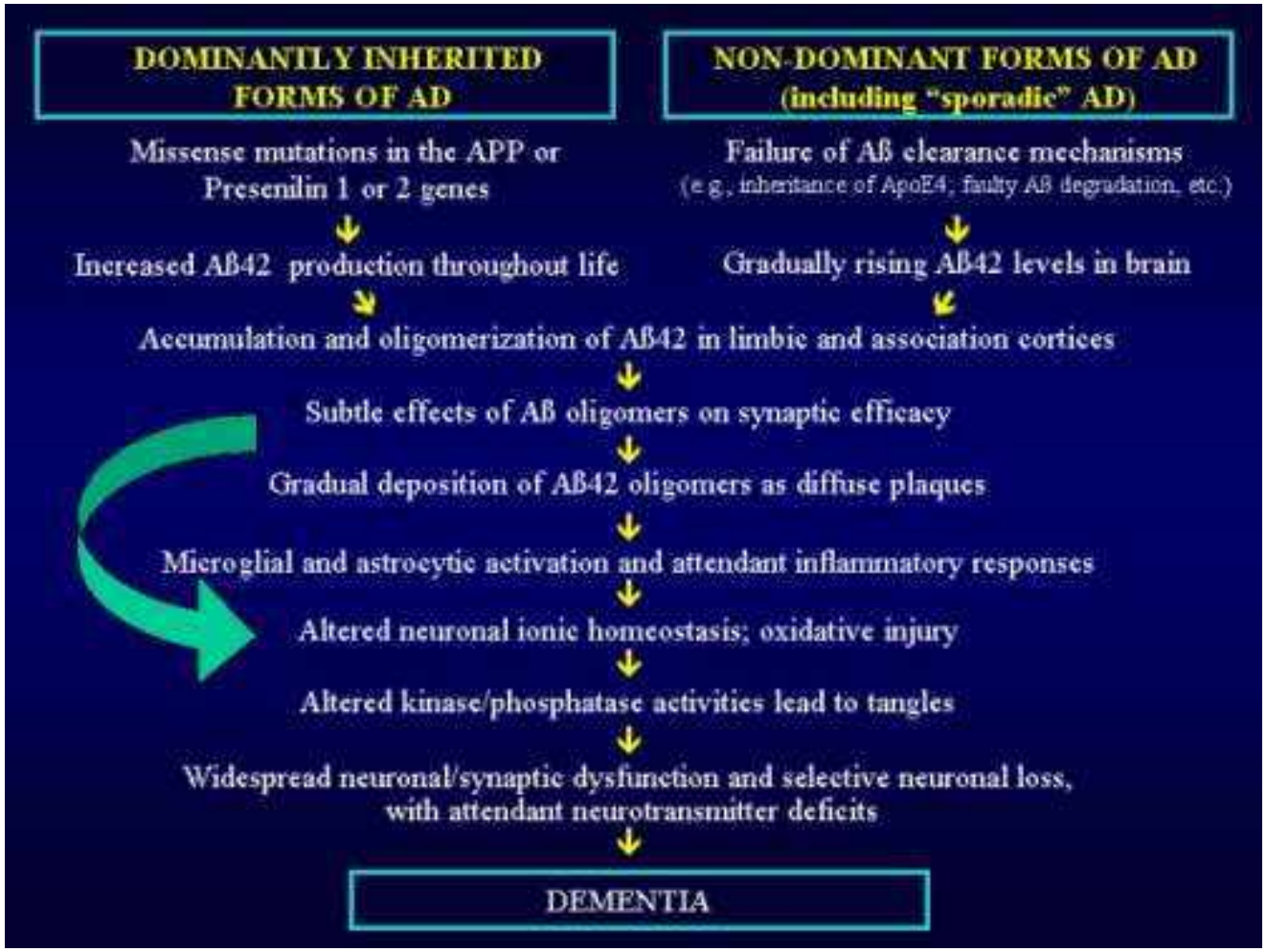


Tangles

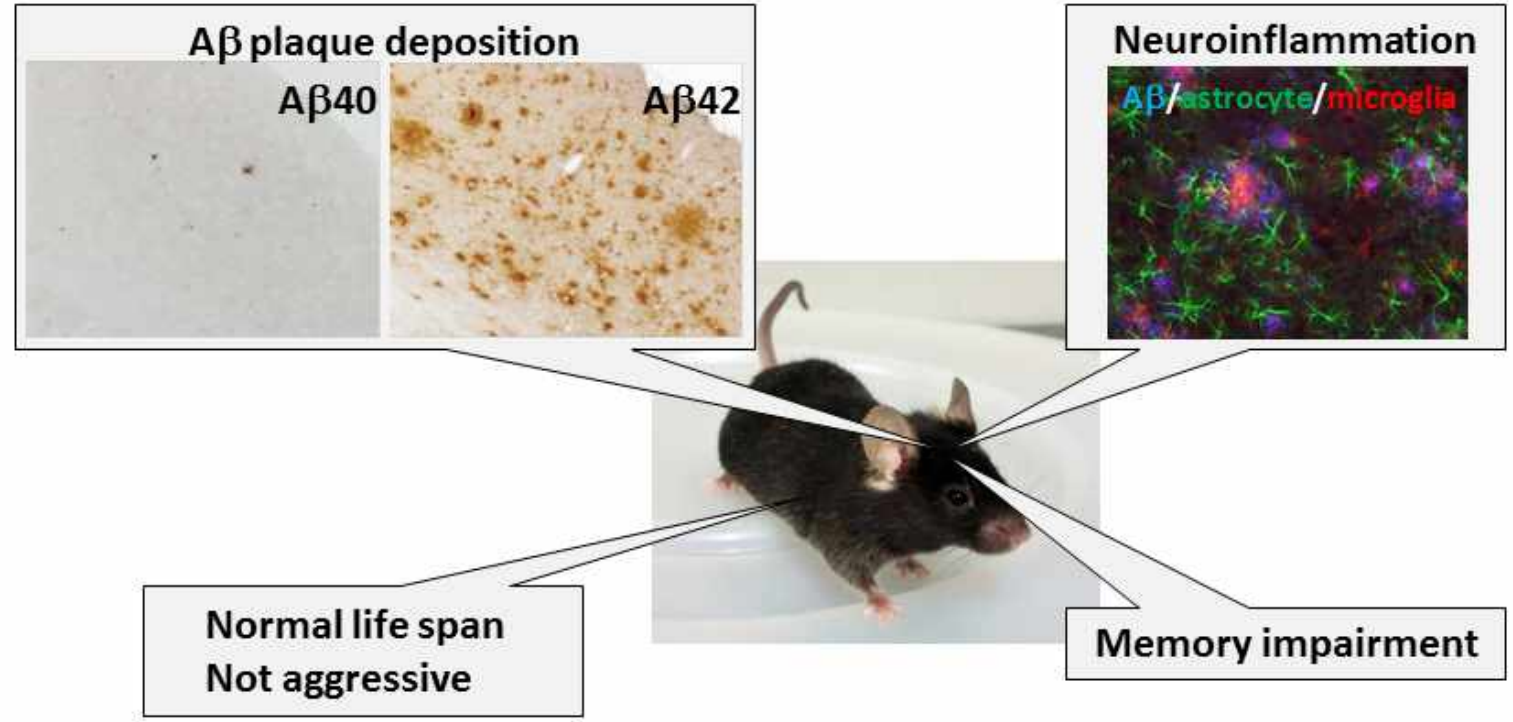
Video: Visual MD

Amyloid Cascade Hypothesis

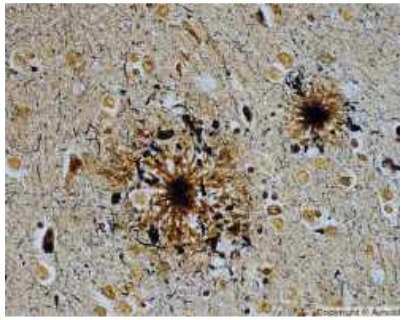


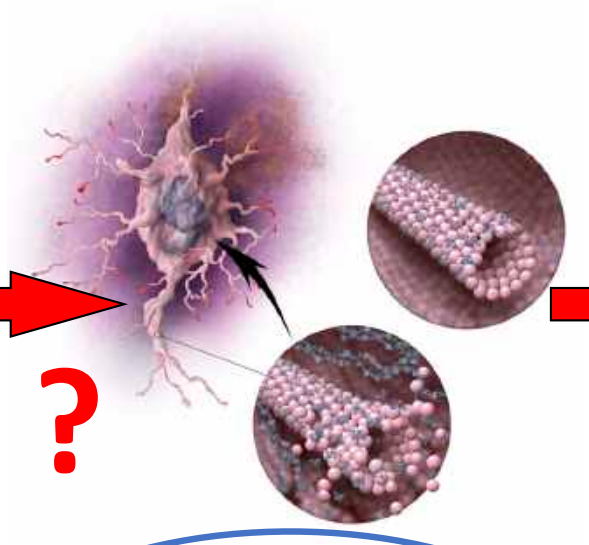


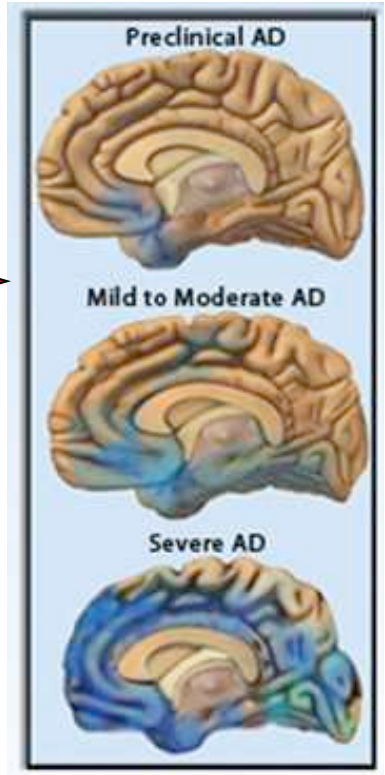
Despite strong genetic evidence in favor of the amyloid hypothesis:
Tg AD mice expressing FAD gene mutations have β-amyloid plaques and inflammation but *no* tangles..questioning amyloid hypothesis



Amyloid Hypothesis: Amyloid plaques cause tangles that kill nerve cells





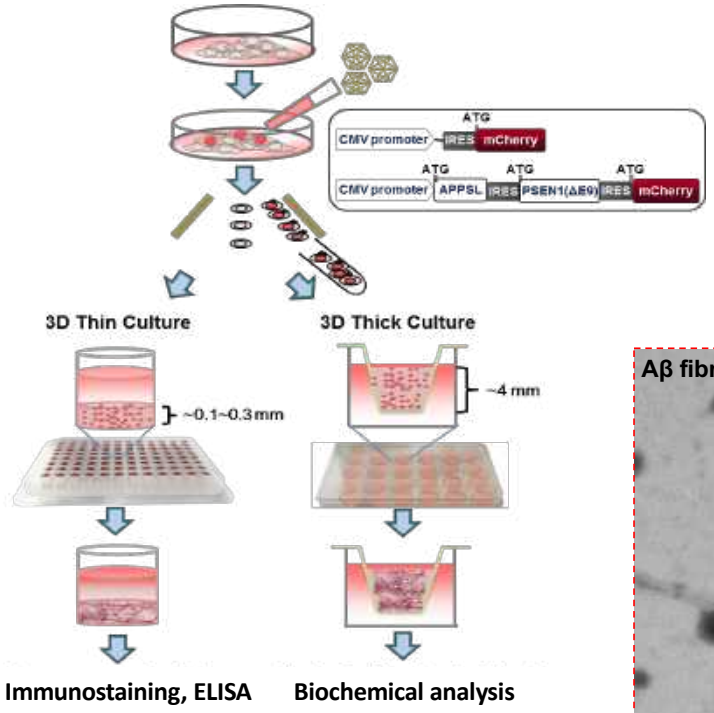


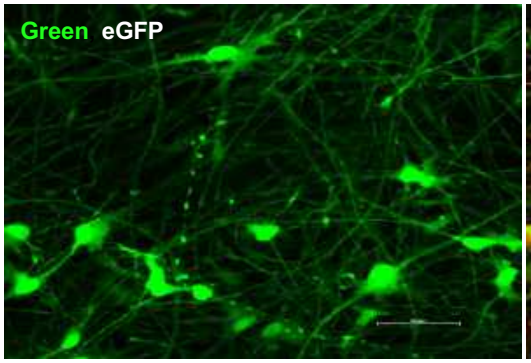
My brain has lots of amyloid plaques and neuroinflammation…but NO tangles!!!!

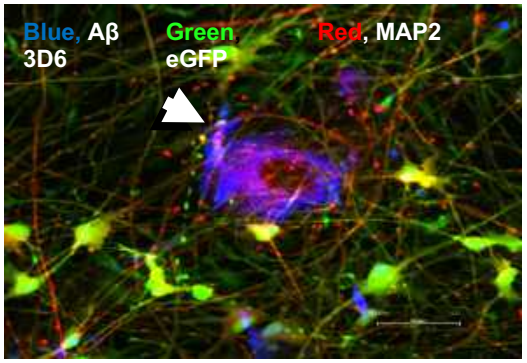
Mice are *NOT* Good Models for Alzheimer's Disease

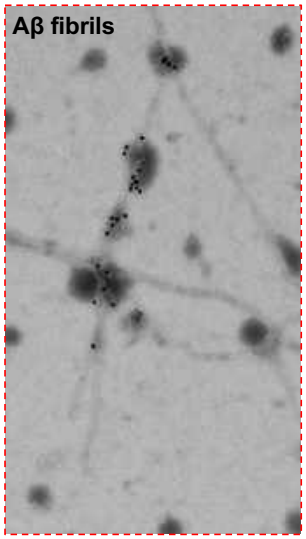
We are not big mice!

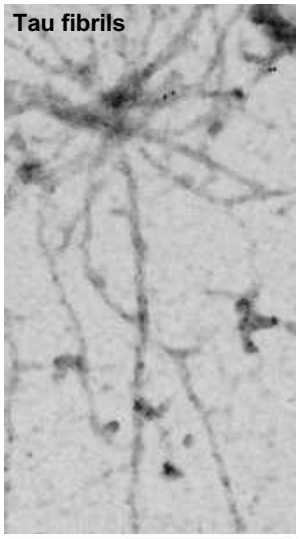
3D Human Neural Cell Culture Model of AD: Aβ Directly Induces Tangles
Plaques (4 Weeks) → Tangles (5 Weeks)

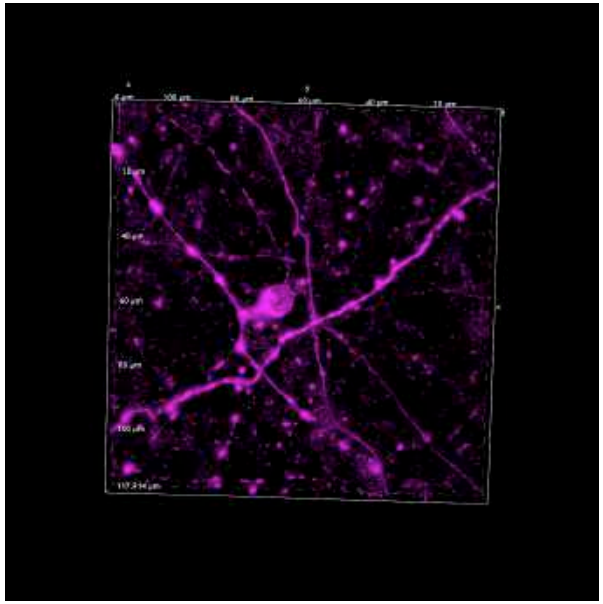






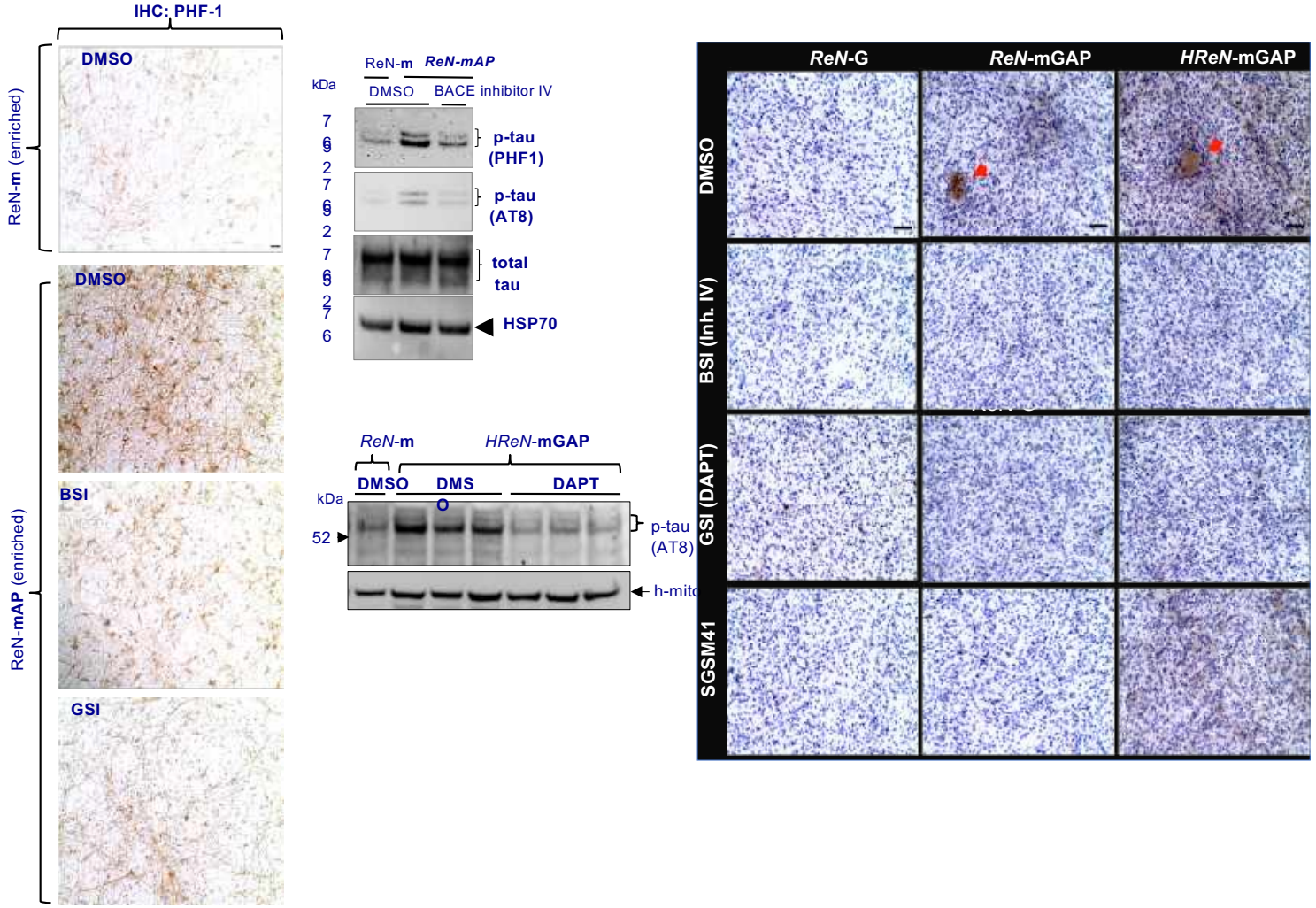






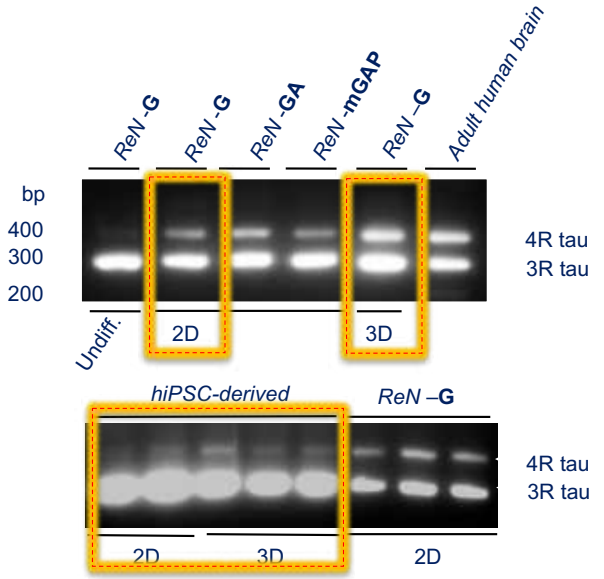
Choi et al., Nature, 2014; Kim *et al.*, Nature Prot., *2015*

β– and γ–secretase inhibitors/modulators lower β-amyloid (6 wks) and lead to dramatic reductions in phospho-tau and tangles (8 wks)



Tangle Formation depends on 3R:4R ratio: 2D vs. 3D; ReN vs. hiPSC

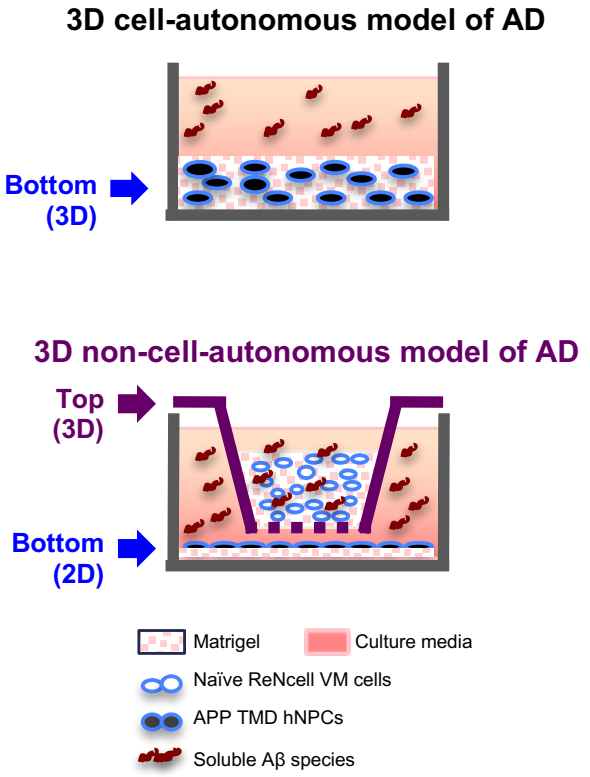
Type	Gene Name	ReN-G 2D-differentiated (fold increases)	ReN-G, 3D-differentiated (fold increases)
Neuronal	NCAM1	15.1 ± 2.9	39.7 ± 25.7
	SYT5	7.2 ± 0.6	3.6 ± 1.2
	SLC17A7 (VGLUT1)	3.8 ± 0.7	184.3 ± 64.5
	GRIN2A (NR2A))	2.6 ± 1.2	134.1 ± 63.4
	EAAT3	2.1 ± 0.5	45.1 ± 9.4
	ACHE	4.8 ± 1.9	4.6 ± 1.3
	SLC6A4	3.3 ± 1.7	87.0 ± 33.9
	GABRA1	4.9 ± 0.7	239.3 ± 57.9
	MAPT	**33.0 ± 5.4**	**525.3 ± 156.9**
Glial	S100β	7.6 ± 1	138.8 ± 42.2
	GFAP	17.3 ± 4.8	118.0 ± 34.9
	EAAT2	3.3 ± 0.3	107.1 ± 18.9
	MBP	4.1 ± 1.0	2.4 ± 1.5

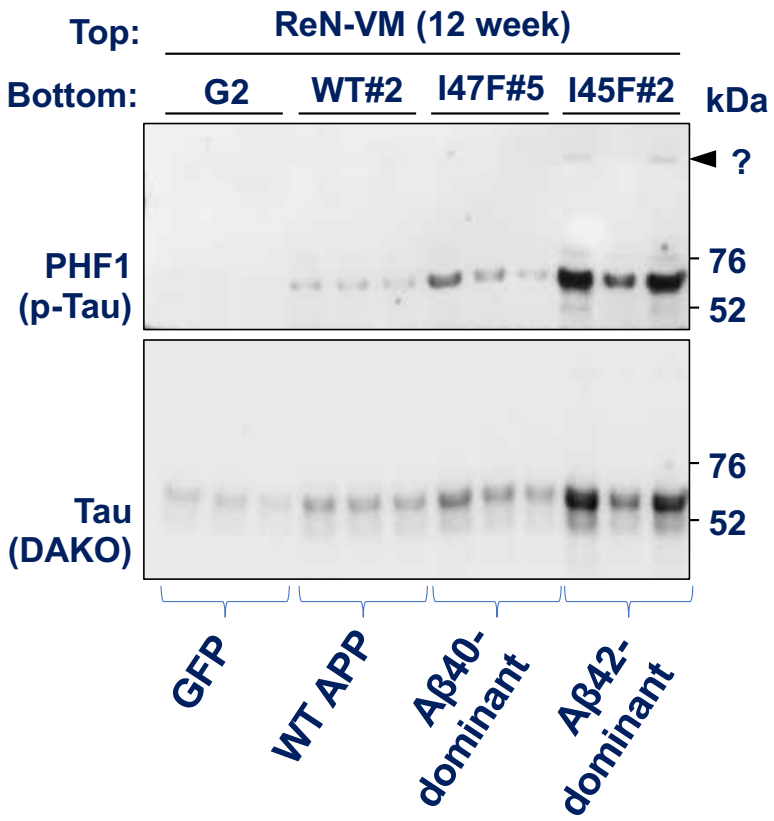


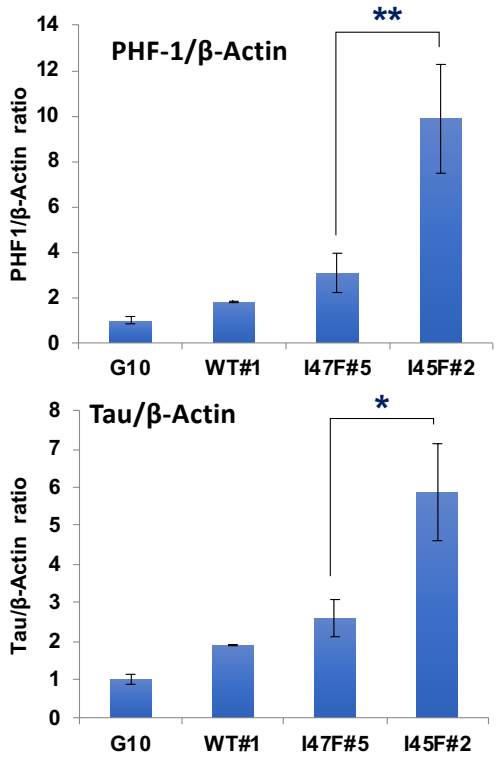
Control ReN cells:
ReN-G, GFP
FAD ReN cells:
ReN-GA, $APP^{Sw/Lon}$
ReN-mGAP, $APP^{Sw/Lon}$+$PS1^{\Delta E9}$

3D non-cell-autonomous model of AD: Aβ Oligomers Cause Tangles

3D non-cell-autonomous model of AD Western Blot analysis of tau in 1% sarkosyl-insoluble fractions

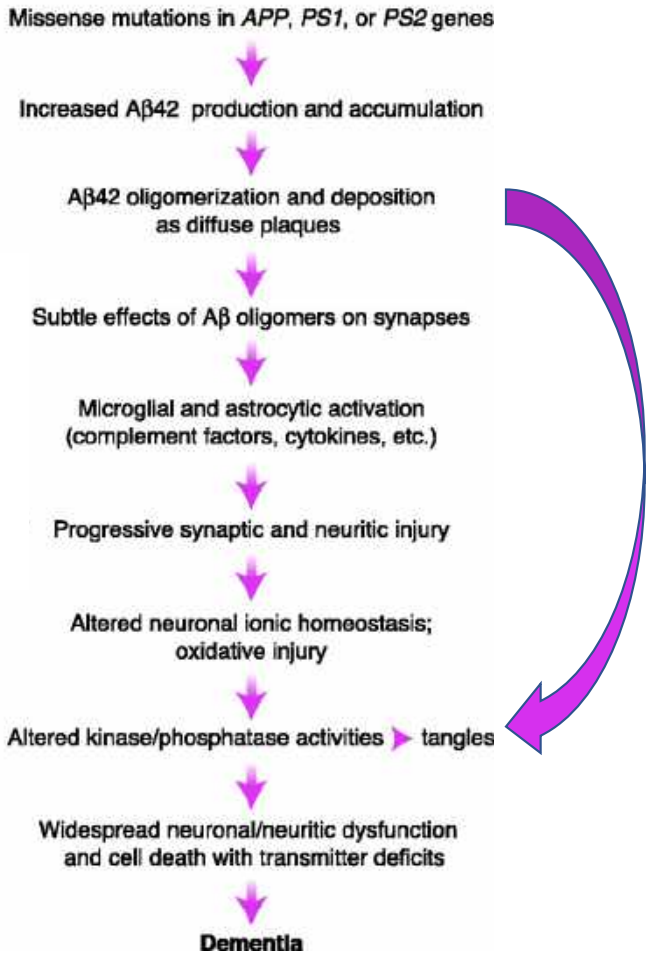


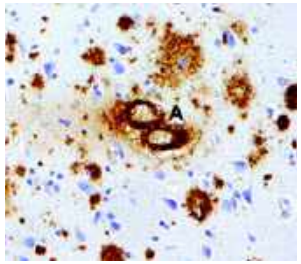




Kwak et al. 2020

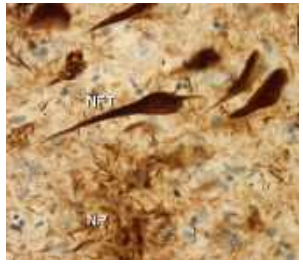
The β-amyloid Cascade Hypothesis (Redefined in 3D Human Neural Cultures)





β-Amyloid

GSK3β
Elevated Intracellular Calcium

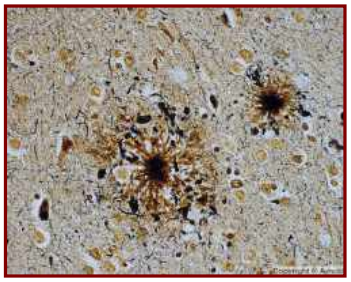


Neurofibrillary Tangles (NFT)

Hardy, J. and Selkoe, D. J. *Science* **2002**, *297*, 353-356.

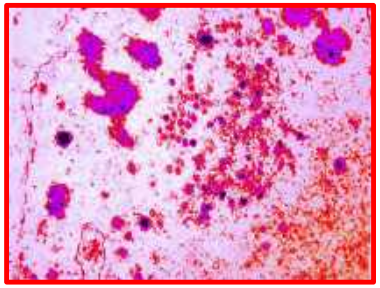
FTLD, Pick's, SSPE..

Alzheimer's Disease



CTE

Amyloid-β



Neuroinflammation

Pro-inflammatory Microglia
Astrogliosis
Neuronal Loss
Synapse Loss

Tauopathy

HEALTH

The New York Times

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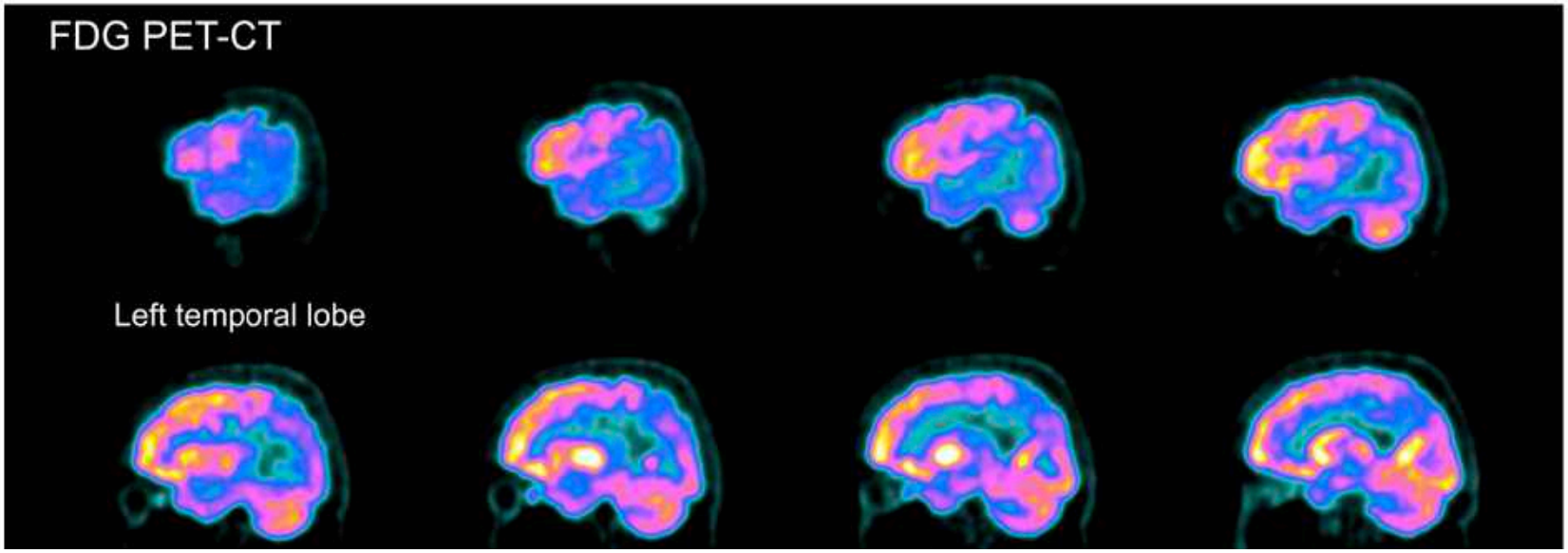
'Amazing, Isn't It?' Long-Sought Blood Test for Alzheimer's in Reach

Scientists say such tests could be available in a few years, speeding research for treatments and providing a diagnosis for dementia patients who want to know if they have Alzheimer's disease.

Phospho-Tau217: Biomarker for β-amyloid-induced tauopathy (AD)



The Spectrum of *Induced Tauopathies*:

- *Alzheimer's disease is an amyloid-induced tauopathy* that triggers an insidious and vicious cycle of neuroinflammation and neurodegeneration gradually leading to cognitive decline and dementia.

- *Frontotemporal Lobe Dementia (FTLD) is a direct (often genetic-induced) tauopathy* that trigger an insidious and vicious cycle of neuroinflammation and neurodegeneration gradually leading to cognitive decline and dementia.

- *Chronic Traumatic Encephalopathy is a head trauma-induced tauopathy* that triggers an insidious and vicious cycle of neuroinflammation and neurodegeneration gradually leading to cognitive decline and dementia.

- All three of these *induced tauopathies require decades* of tangles and neuroinflammation spreading through the brain eventually leading to dementia, which likely begins early in life, e.g. CTE and playing football as a young adult.

All Alzheimer's clinical trials targeting amyloid have failed to improve cognition in AD: *Exception: Biogen – Aducanumab ??*

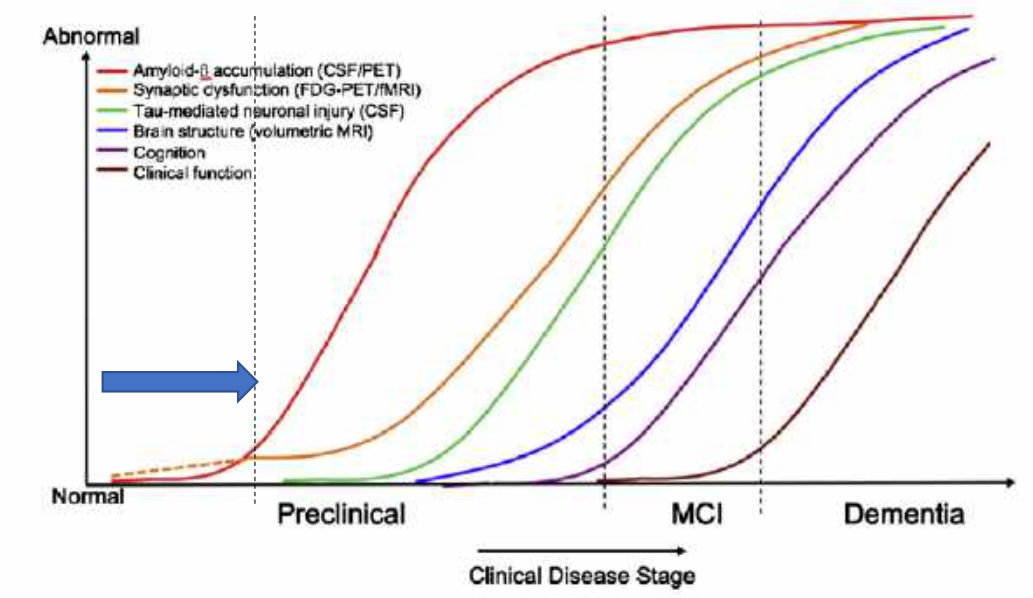
Table 1. Discontinued Phase 3 Disease-Modifying Drug Trials in AD, Excluding ChEI and Memantine Trials

Drug (Study Name)	Study Population	Target/Mechanism	Type of Molecule	Outcome	ClinicalTrials.gov NCT Identifier	Reference
Bapineuzumab	Mild-to-moderate AD	Soluble and fibrillar Aβ	Monoclonal antibody	No effect on cognition or ADL	NCT00575055 NCT00574132	(Salloway et al., 2014)
Solanezumab (EXPEDITION-1, 2 and 3)	Mild-to-moderate AD; mild AD	Soluble monomeric Aβ	Monoclonal antibody	No effect on cognition or ADL	NCT00905372 NCT00904683	(Doody et al., 2014; Honig et al., 2018)
Crenezumab (CREAD-1/2)	very-mild-to-mild AD with amyloid positive biomarkers	Oligomeric, fibrillar and plaque-based Aβ	Monoclonal antibody	No effect on cognition or ADL on preliminary analysis	NCT03114657	
Aducanumab (ENGAGE; EMERGE)	Mild AD	Conformation-specific Aβ aggregates	Monoclonal Antibody	No change in rate of cognitive decline	NCT03639987	(Selkoe, 2019)
AN-1792	Mild-to-moderate AD	Active immunization	Full-length Aβ42 immunogen	Trial halted due to development of meningoencephalitis in 4 patients	NCT00021723	
Semagacestat (IDENTITY-1/2)	Mild-to-moderate AD	γ-secretase inhibitor	Small molecule	No effect on cognition or ADL; increased risk of skin cancer	NCT01035138 NCT00594568	(Doody et al., 2013)
Tarenflurbil	Mild AD	γ-secretase modulator	Small molecule	No effect on cognition or ADL	NCT00105547	(Green et al., 2009)
CNP520 (Umibecestat) (API Generation)	Cognitively normal *APOE* ε4/ ε4 carriers	BACE1 inhibitor	Small molecule	Worse cognitive performance, weight loss	NCT03131453 NCT02565511	(Lopez Lopez et al., 2019)
Lanabecestat (AMARANTH; DAYBREAK-ALZ)	Very-mild-to-mild AD	BACE1 inhibitor	Small molecule	No effect on cognition or ADL	NCT02783573 NCT02245737	
Atabecestat	Preclinical AD; positive amyloid, normal cognition	BACE1 inhibitor	Small molecule	Worse performance on some cognitive tests; in some cases, prominent side effects	NCT02569398	(Henley et al., 2019)
Verubecestat (APECS)	Prodromal AD	BACE1 inhibitor	Small molecule	Worse performance on some cognitive tests and in ADL	NCT01953601	(Egan et al., 2018, 2019)
Elenbecestat (MISSION-AD1/2)	Mild AD	BACE1 inhibitor	Small molecule	Unspecified safety concerns upon interim review	NCT02956486 NCT03036280	

??

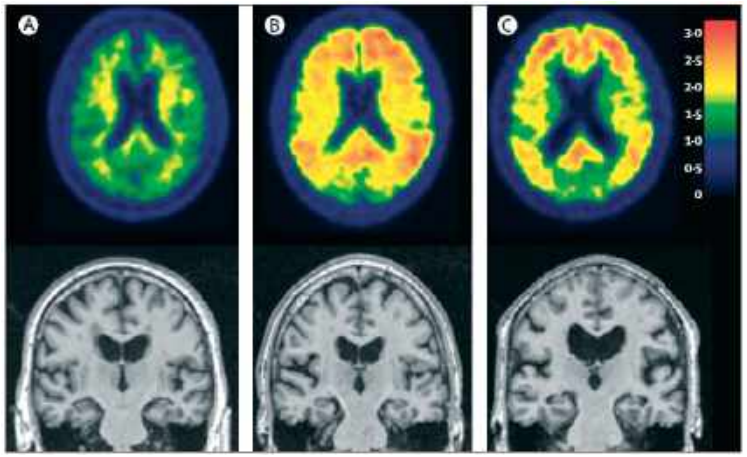
Long JM, Holtzman D, *Cell*, 2019

Aβ and Tau-Tangle Pathology Precedes Symptoms by Decades



Primary prevention	2nd prevention	Tertiary prevention/treatment
• Pathology -; • Symptoms -	• Pathology +; • Symptoms -	• Pathology ++; • Symptoms+

Cognitively normal PIB -/MRI-	Cognitively normal PIB +; MRI-	Dementia/AD PIB +; MRI+

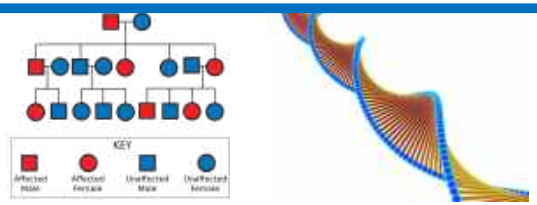


Primary prevention	2nd prevention	Tertiary prevention / treatment
• Pathology -; • Symptoms -	• Pathology +; • Symptoms -	• Pathology ++; • Symptoms+

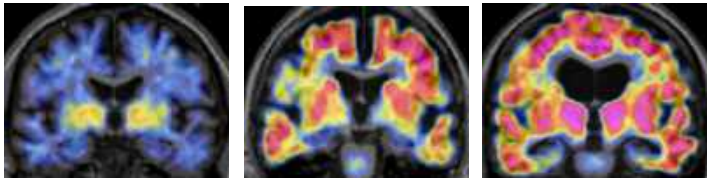
•Jack et al., 2010
•Sperling et al., 2011

Preventing Alzheimer's

***Early Prediction** (Family History, Gene Testing)*

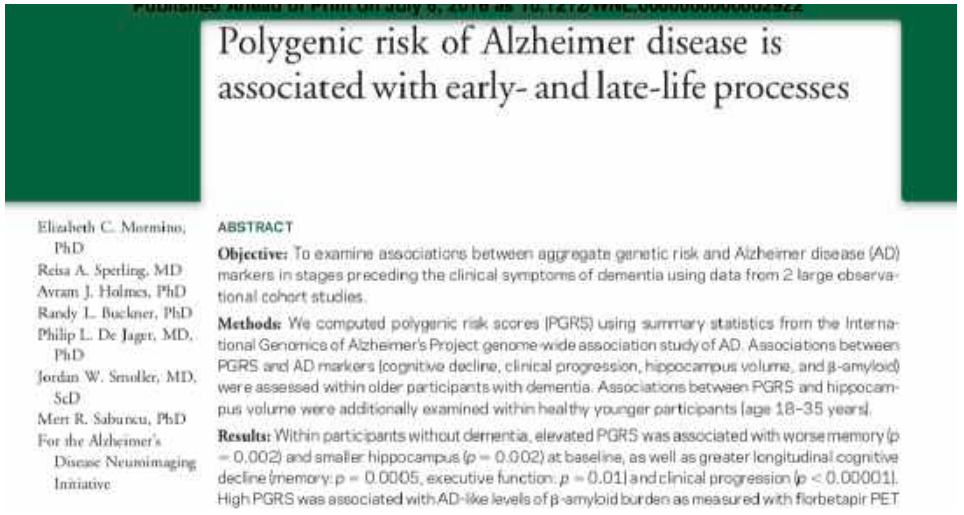


***Early Detection** (Imaging, Biomarkers, Digital)*



***Early Intervention** (Stop Pathology a Decade before Dementia)*

rs6656401	rs4844610	1	CR1
rs4575098	rs4663096	1	ADAMTS4
rs6733839		2	BIN1
rs35349669	rs10933431	2	INPP5D
rs18438474			
6		3	HESX1
rs6448453	rs6448799	4	HS3ST1
rs10948363	rs9473117	6	CD2AP
rs78738018		6	HLA-DQB1
rs75932628	rs385758, rs114812713	6	TREM2
rs11771145	rs11762262	7	EPHA1
rs1476679	rs12539172 rs1859788	7	NYAP1
rs11436049			
2		7	CNTNAP2
rs9331896	rs867230	8	CLU
rs28834970	rs73223431	8	PTK2B
rs7920721		10	ECHDC3
rs983392		11	MS4A6A
rs10792832 rs3851179	rs867611	11	PICALM
rs11218343		11	SORL1
rs10838725	rs3740688	11	SPI1
rs10498633	rs12881735	14	SLC24A4
rs17125944	rs17125924	14	FERMT2
rs442495	rs593742	15	ADAM10
rs11761801			
7		15	APH1B
rs72824905		16	PLCG2
rs59735493		16	KAT8
rs616338	rs28394864	17	ABI3
rs7225151		17	SCIMP
rs13819008			
6	rs6504163, rs6504163	17	ACE
rs76726049		18	ALPK2
	rs12151021, rs3752246		
rs4147929	rs111278892	19	ABCA7
rs3865444		19	CD33
rs76320948		19	BHMG1
rs7274581	rs6024870	20	CASS4
rs2830500		21	ADAMTS1
rs7185636			IQCK1



Polygenic risk of Alzheimer disease is associated with early- and late-life processes

Elizabeth C. Mormino, PhD
Reisa A. Sperling, MD
Avram J. Holmes, PhD
Randy L. Buckner, PhD
Philip L. De Jager, MD, PhD
Jordan W. Smoller, MD, ScD
Mert R. Sabuncu, PhD
For the Alzheimer's Disease Neuroimaging Initiative

ABSTRACT

Objective: To examine associations between aggregate genetic risk and Alzheimer disease (AD) markers in stages preceding the clinical symptoms of dementia using data from 2 large observational cohort studies.

Methods: We computed polygenic risk scores (PGRS) using summary statistics from the International Genomics of Alzheimer's Project genome-wide association study of AD. Associations between PGRS and AD markers (cognitive decline, clinical progression, hippocampus volume, and β-amyloid) were assessed within older participants with dementia. Associations between PGRS and hippocampus volume were additionally examined within healthy younger participants (age 18–35 years).

Results: Within participants without dementia, elevated PGRS was associated with worse memory ($p = 0.002$) and smaller hippocampus ($p = 0.002$) at baseline, as well as greater longitudinal cognitive decline (memory: $p = 0.0005$, executive function: $p = 0.01$) and clinical progression ($p < 0.00001$). High PGRS was associated with AD-like levels of β-amyloid burden as measured with florbetapir PET

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BRAIN
A JOURNAL OF NEUROLOGY

Polygenic hazard score, amyloid deposition and Alzheimer's neurodegeneration

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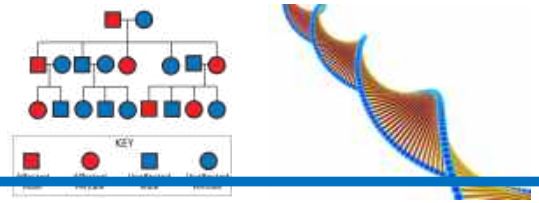
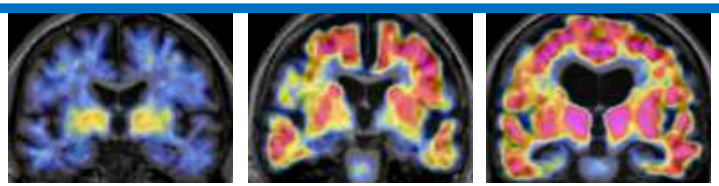
Preventing Alzheimer's

Early Prediction (Family History, Gene Testing)



Early Detection (Imaging, Biomarkers, Digital)



Early Intervention (Stop Pathology a Decade before Dementia)

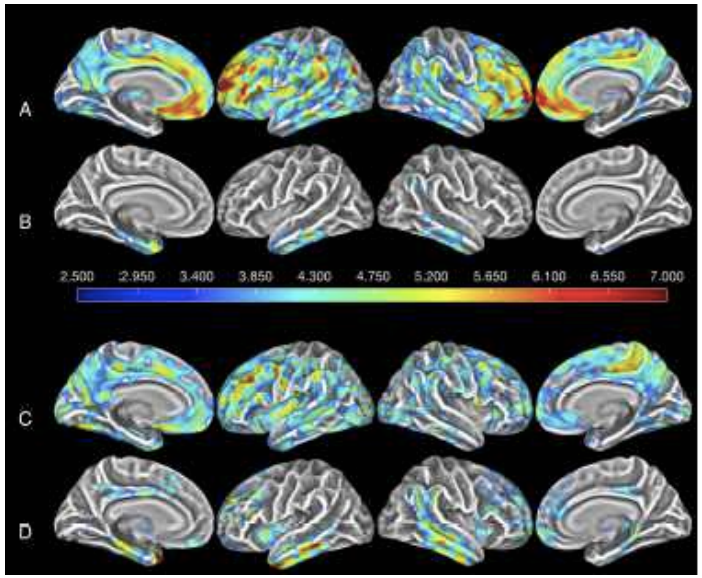
BRAIN IMAGING – PET &MRI

BLOOD TESTS

DIGITAL & EYE TESTS

The Impact of Amyloid-Beta and Tau on Prospective Cognitive Decline in Older Individuals

Reisa A. Sperling, MD,[1,2†] Elizabeth C. Mormino, PhD,[1,3†] Aaron P. Schultz, PhD,[1] Rebecca A. Betensky, PhD,[1,4] Kathryn V. Papp, PhD,[1,2] Rebecca E. Amariglio, PhD,[1,2] Bernard J. Hanseeuw, MD, PhD,[1,5] Rachel Buckley, PhD[1,6] Jasmeer Chhatwal, MD, PhD,[1] Trey Hedden, PhD,[1,3] Gad A. Marshall, MD,[1,2] Yakeel T. Quiroz, PhD,[1,7] Nancy J. Donovan, MD,[1,2,7] Jonathan Jackson, PhD,[1] Jennifer R. Gatchel, MD, PhD,[1,7,8] Jennifer S. Rabin, PhD,[1,7] Heidi Jacobs, PhD[9,1] Hyun-Sik Yang, MD,[1,2] Michael Properzi, BS,[1] Dylan R. Kirn, MPH,[1] Dorene M. Rentz, PsyD,[1,2] and Keith A. Johnson, MD[1,2,3,9†]



HEALTH

The New York Times

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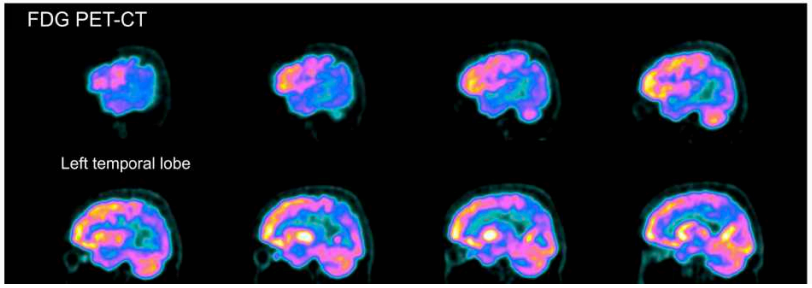
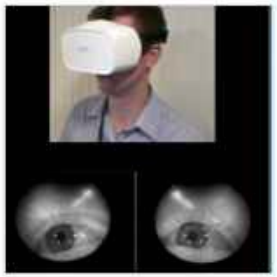
'Amazing, Isn't It?' Long-Sought Blood Test for Alzheimer's in Reach

Scientists say such tests could be available in a few years, speeding research for treatments and providing a diagnosis for dementia patients who want to know if they have Alzheimer's disease.



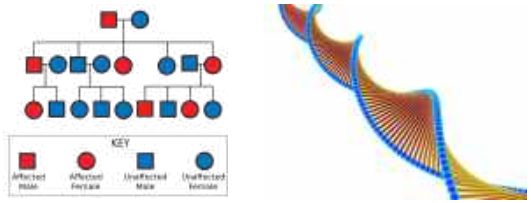
- ***Phospho-Tau217: Biomarker for β-amyloid-induced tauopathy (AD-specific)***
- ***NFL – Biomarker for neurodegeneration***



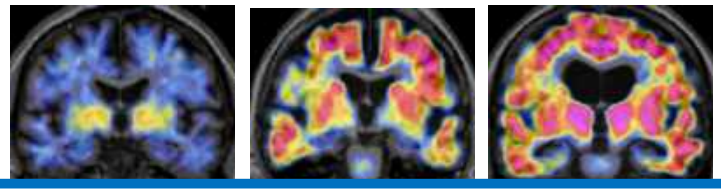
*Financial Interest/Co-Founder of React Neuro

Preventing Alzheimer's

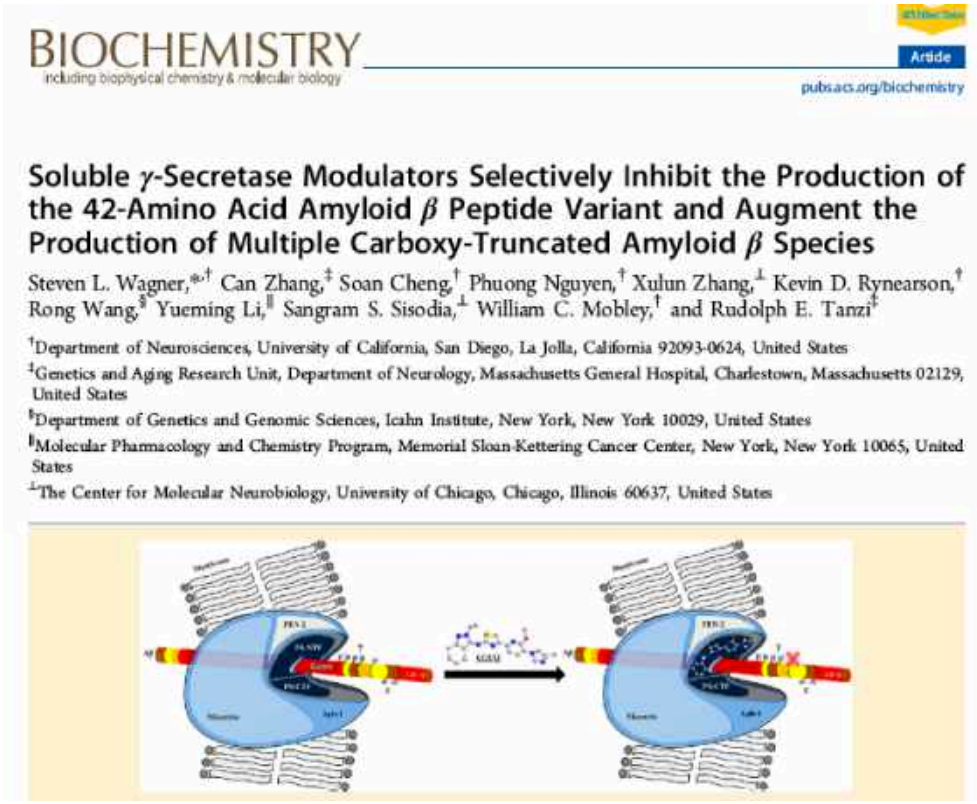
Early Prediction (Family History, Gene Testing)



Early Detection (Imaging, Biomarkers, Digital)



Early Intervention (Stop Pathology a Decade before Dementia)



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Soluble γ-Secretase Modulators Selectively Inhibit the Production of the 42-Amino Acid Amyloid β Peptide Variant and Augment the Production of Multiple Carboxy-Truncated Amyloid β Species

Steven L. Wagner,*[,†] Can Zhang,[‡] Soan Cheng,[†] Phuong Nguyen,[†] Xulun Zhang,[⊥] Kevin D. Rynearson,[†] Rong Wang,[§] Yueming Li,[∥] Sangram S. Sisodia,[⊥] William C. Mobley,[†] and Rudolph E. Tanzi[‡]

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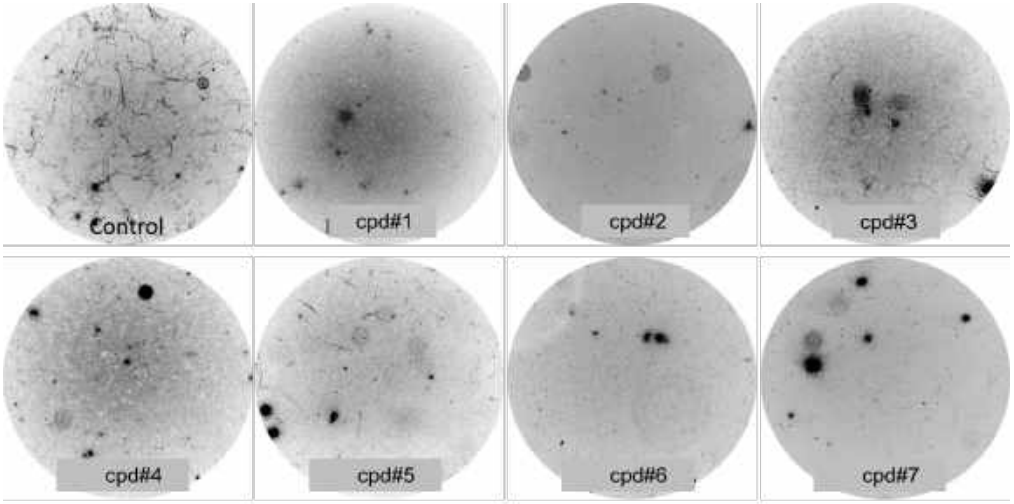
[⊥]The Center for Molecular Neurobiology, University of Chicago, Chicago, Illinois 60637, United States

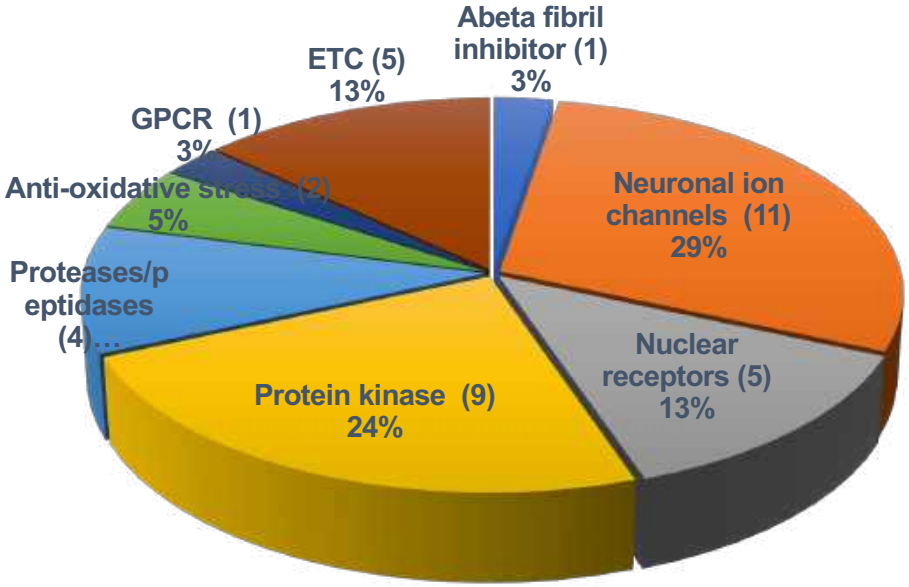
Gamma Secretase Modulators:

- Allosteric Modulators of Docking Site
- Reduce Aβ42:Aβ40 Ratio
- Ic50 ~5 nM for Aβ42
- These are *not* Gamma Secretase Inhibitors
  - *No* inhibition of cleavage of other γ-secretase substrates, e.g. Notch
- Best used pre-symptomatically
- Phase 1 Trials Planned in Early 2021 at MGH and UCSD

Drug repositioning: FDA-approved drugs

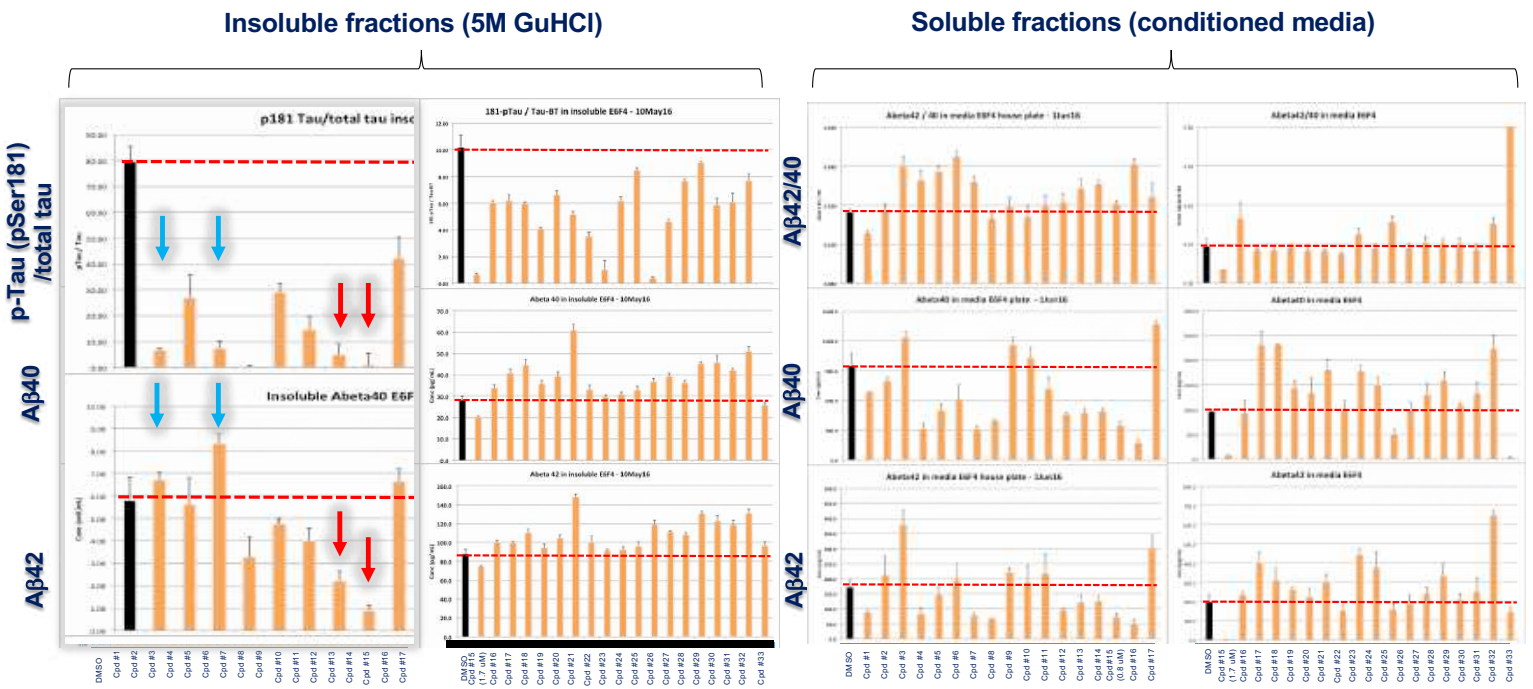
1. We finished primary screening of 2,640 drug library including most FDA-approved drugs (LOPAC+Tocriscreen+240 kinase inhibitors) using high content screening of p-tau/NFT accumulation.
2. We identified 38 primary hits that dramatically reduce p-tau-positive neurites and cell bodies by >90% in a 6-week-differentiated 3D ReN-GA2 AD model.





Courtesy of Dr. Steve Wong

3D Human Stem Cell-Derived Neural Culture - High Content Screening: 38 drugs lower P-Tau/tangles by ≥90%

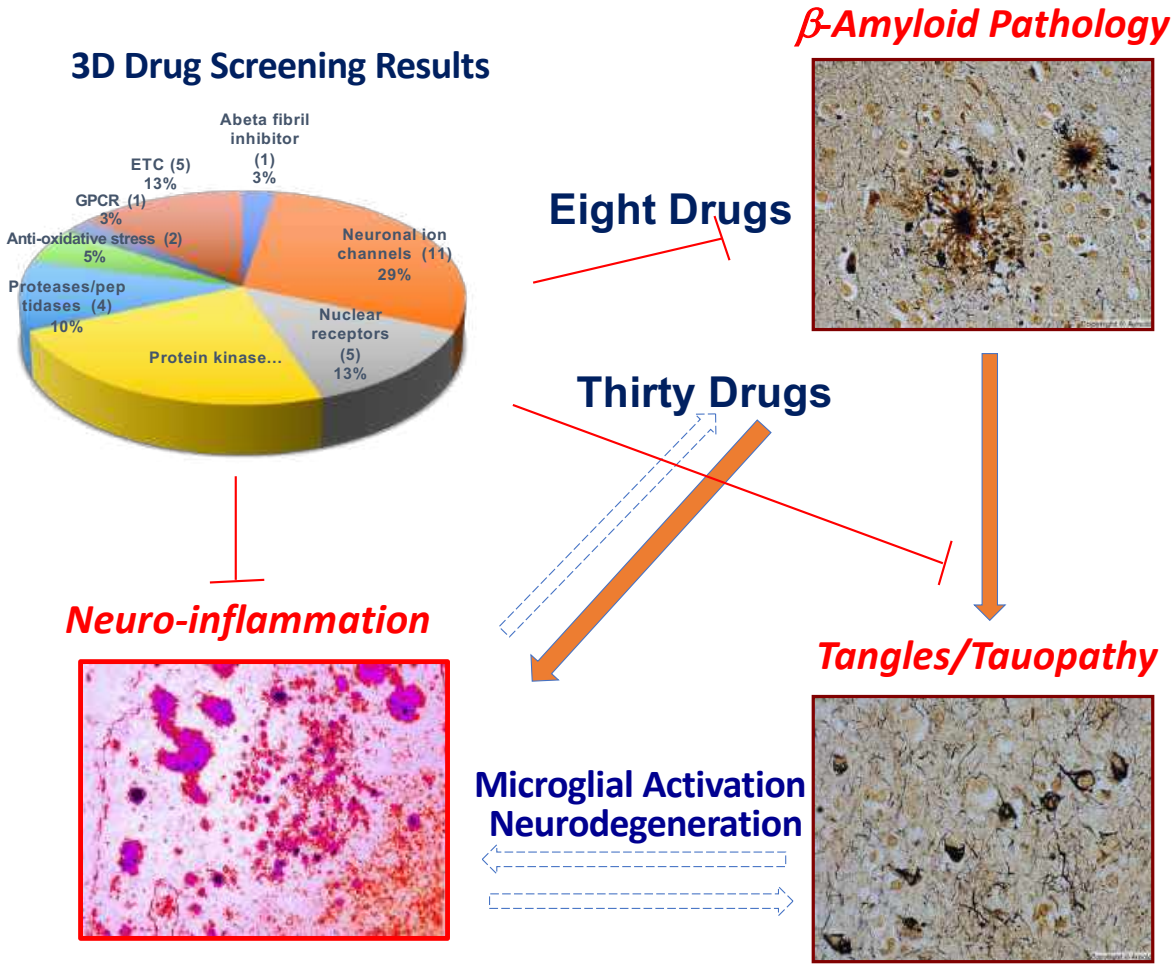


30 drugs: Inhibitory effect on p-tau/tangles is independent of Aβ deposition

8 drugs: Inhibitory effect on p-tau/tangles is dependent on reduced Aβ deposition

Steve Wong and Doo Yeon Kim, Unpublished

Targeting Alzheimer's Pathology: Repositioning Safe Drugs



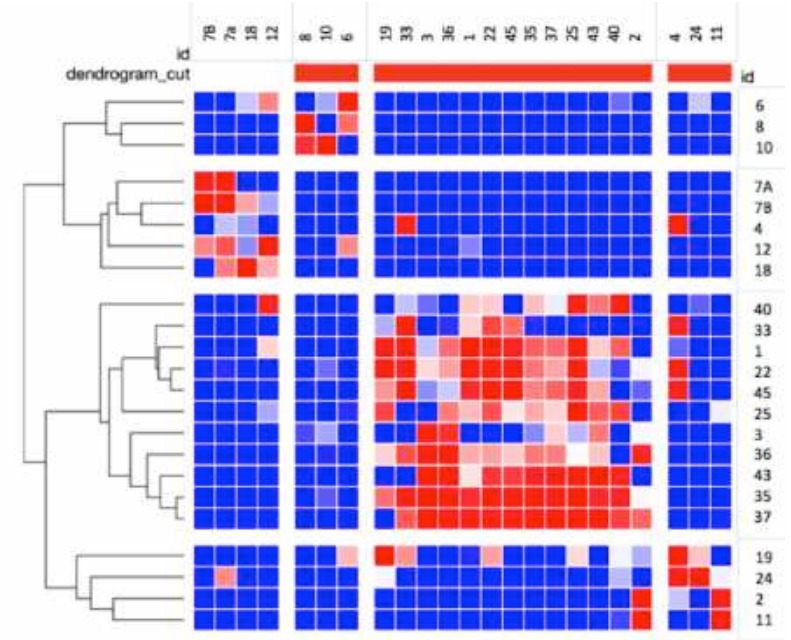
- We screened 2,640 drugs including all FDA-approved drugs plus other safe brain-permeable drugs.
- We identified 38 drugs that reduce tangle formation by >90% in our 3D human stem cell-derived neural cell cultures - (Alzheimers-in-a Dish)

Drug repositioning: Expanding library screening capacity using bioinformatics

1. Transcriptomic profiles for 22 out of the 38 primary hits (for~20 different cell lines) were available in CLUE.IO (LINCS) transcriptome database (Broad Institute).

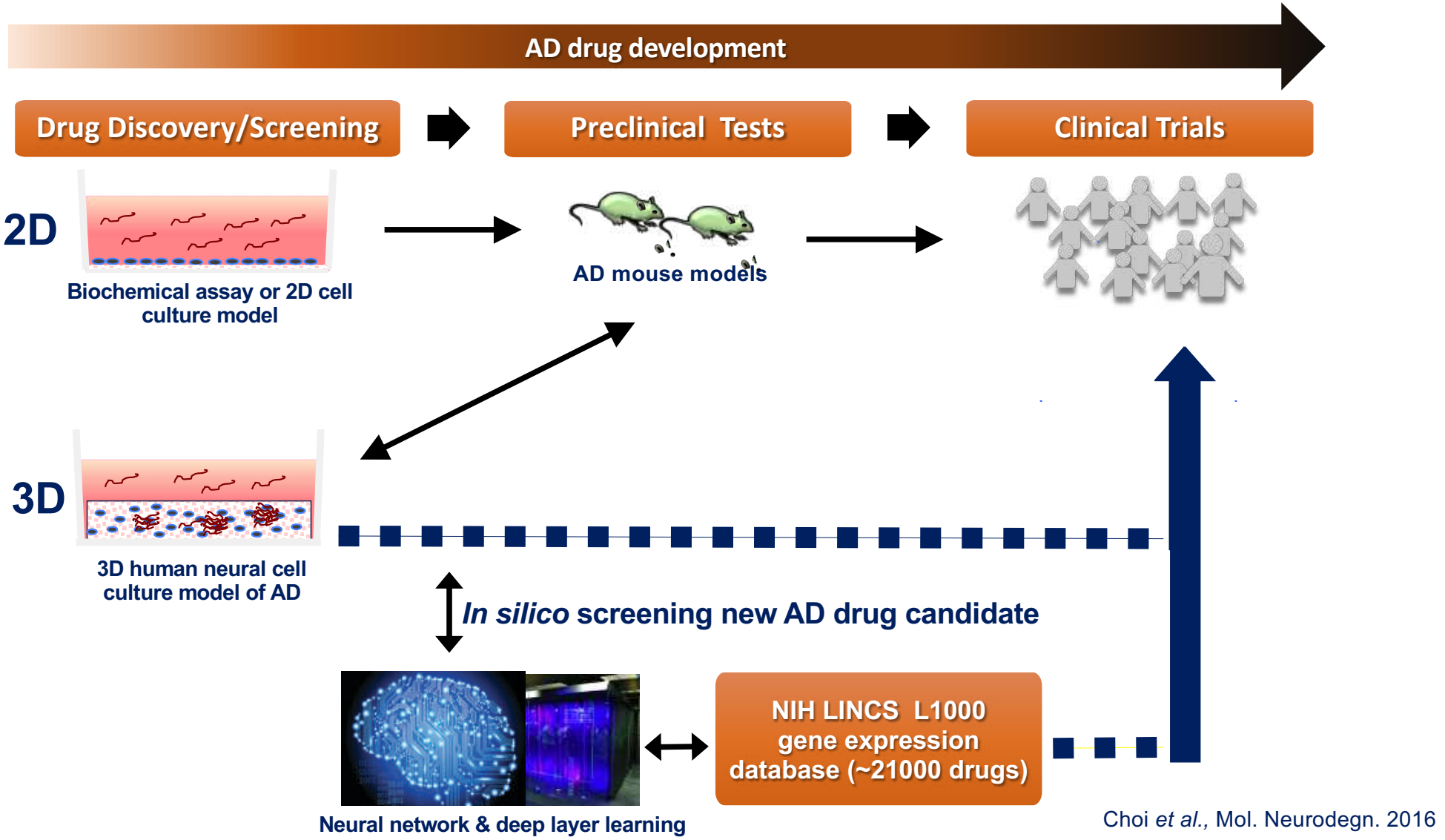
2. *In silico* drug screening against ~20,413 compounds in CLUE.IO database library, using shared transcriptome patterns of the 4 seed compounds.

3. 59 new drug candidates, 10 of which were positive in their HCS screening.



CLUE.IO perturbation database (~20,403 drugs in)

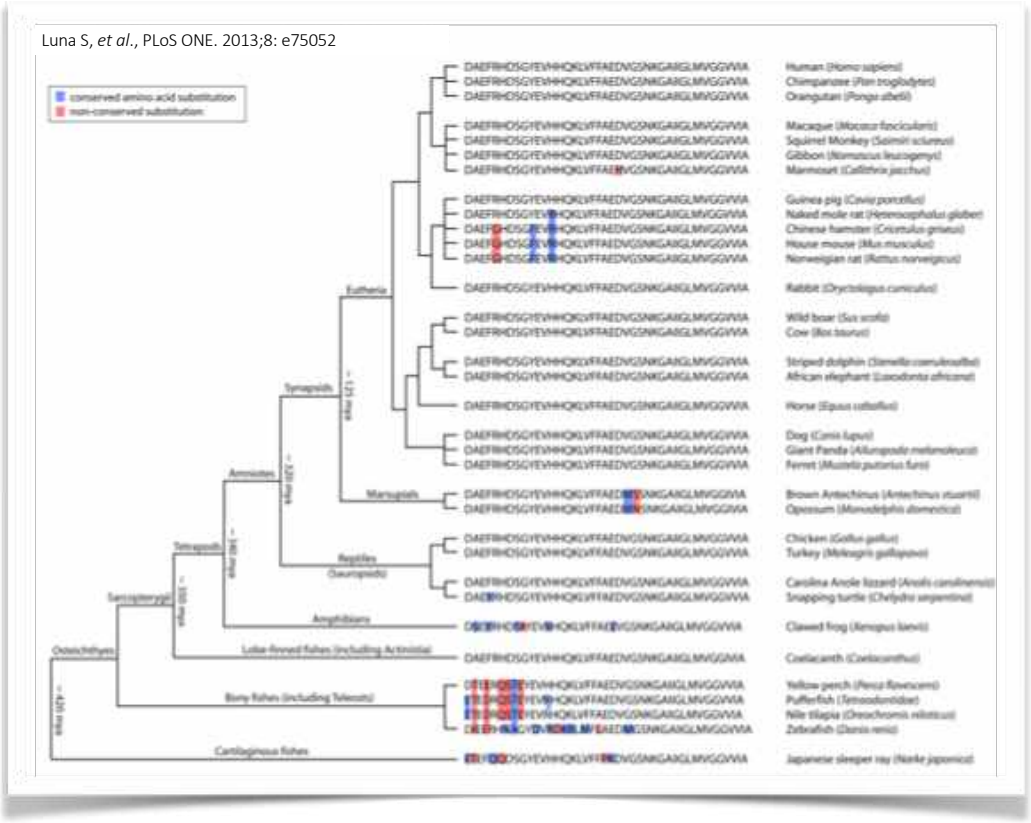
Drs. Stephan Wong and Zheng Ying



Choi *et al.*, Mol. Neurodegn. 2016

Aβ function?

- **Human Aβ: Highly conserved across at least 400 million years - Coelacanth fish has human Aβ sequence**
- **Nearly all vertebrates express Aβ and 60-70% species have human Aβ sequence**



Aβ is an Antimicrobial Peptide (AMP) in the Brain

Antimicrobial Protection Hypothesis: Alzheimer's pathology is an orchestrated innate immune response that has evolved along with AD susceptibility gene variants to protect the brain against acute and low-grade microbial infections.

Rob Moir

1961-2019

- **AMP: Host defense peptides - "Foot Soldiers of Innate Immunity"**
  - **LL-37, defensins, protegrins, temporins, etc.**
- **Effective Against:**
  - **Bacteria, Enveloped viruses, Fungi, Tumor Cells**
- **Typical AMP structure:**
  - **12 and 50 amino acid charged peptides**
  - **α-helix, β-sheet, or combination**
- **Known AMPs that cause clinical amyloidosis;**
  - **lactoferrin- corneal amyloidosis**
  - **semenogelin - seminal vesicle amyloid**
  - **Lactadherin - aortic medial amyloid**

Aβ: Highly Effective AMP against 8 clinical pathogens

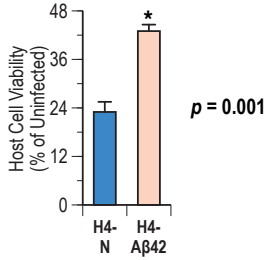
- ***Candida albicans***
- ***Escherichia coli***
- ***Staphylococcus epidermidis***
- ***Streptococcus pneumoniae***
- ***Staphylococcus aureus***
- ***Listeria monocytogenes***
- ***Enterococcus faecalis***
- ***Streptococcus agalactiae***

Soscia et al, 2010

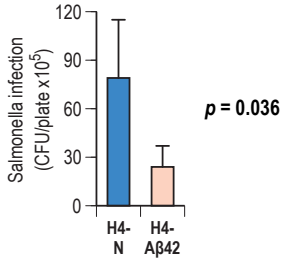
Amyloid-β Protects Against Infection in Animal Models of Alzheimer's Disease

H4-Aβ42 Vs naïve (H4-N) cultured cells

a) *Candida* infection

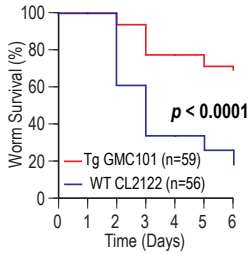


b) *Salmonella* infection

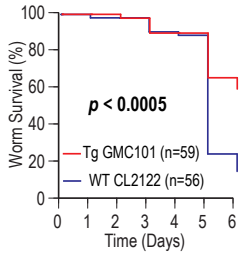


Transgenic (GMC101) Vs control (CL2122) *C. elegans*

a) *Candida* infection

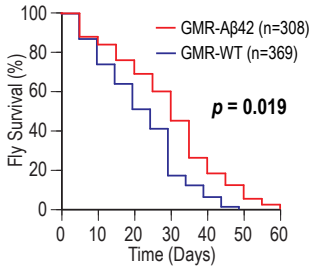


a) *Salmonella* Typhimurium infection



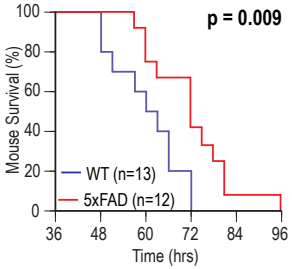
Transgenic (GMR-Aβ42) Vs control (GMR-WT) *Drosophila*

Candida infection

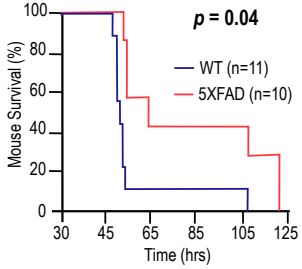


Survival of high (5XFAD) and low (APP-KO) mice Vs WT littermates following intracranial pathogen injection

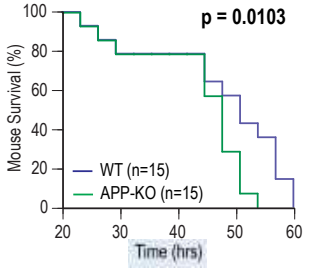
a) High Aβ expression *Salmonella* infection



b) High Aβ expression HSV-1 infection



c) Low Aβ expression *Salmonella* infection



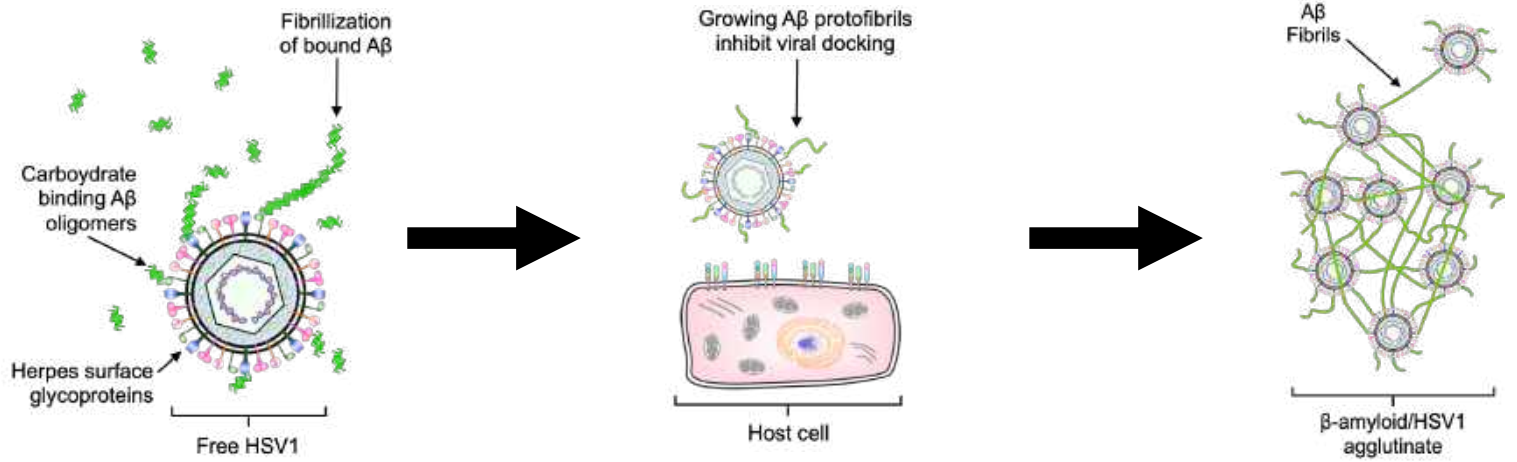
D.K.V. Kumar et al. / Science Translational Medicine (2016)

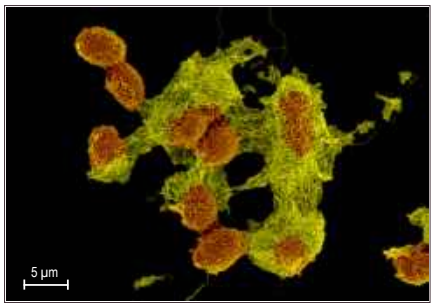
Amyloid-β is Rapidly Seeded into Plaques by Bacteria and Virus - Overnight !!

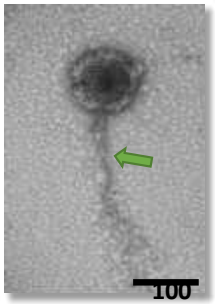
a) Oligomers target and bind herpes glycoproteins

b. Growing protofibrils disrupt virus/host docking

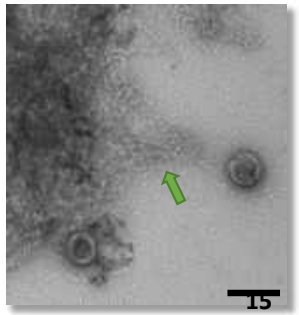
c. Fibrils agglutinate & entrap virus particles



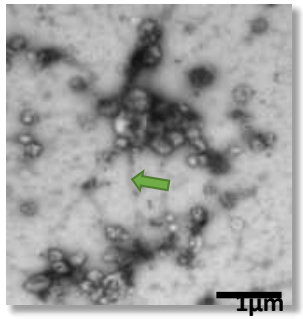




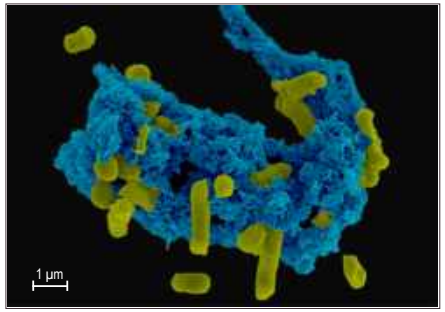
15 min



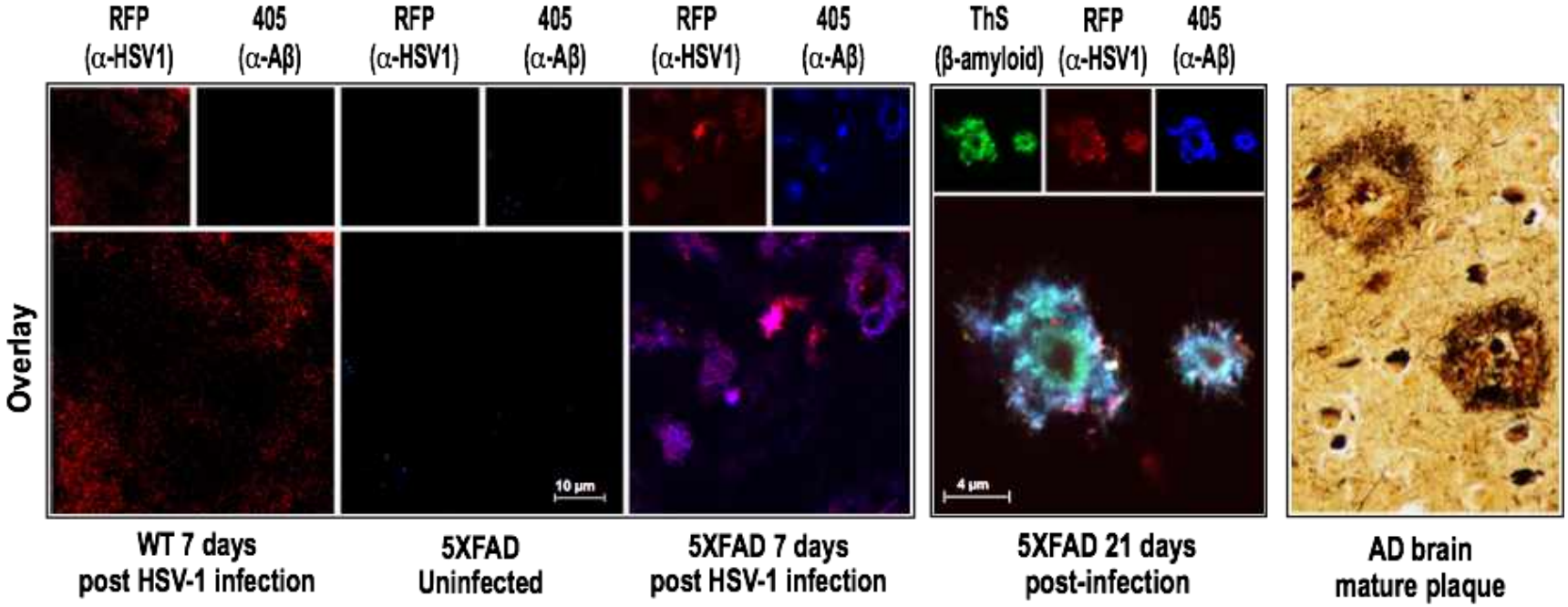
30 min



2 hr



HSV1 rapidly “seeds” diffuse β-amyloid in 36 hours in 1.5 month-old 5XFAD mice; neuritic plaques in 21 days



HSV1-seeded amyloid in 5XFAD Tg mice; co-localization of herpes and Aβ immunosignal

The Innate Immune Hypothesis of Alzheimer's Disease

Innate Immune Protection Hypothesis Pt. 1: Role of AD Pathology

Alzheimer's pathology (plaques, tangles, neuroinflammation) is an orchestrated innate immune response that has evolved to protect the brain against the microbial infection.

- **Aβ is an antimicrobial peptide that can protect the brain against microbes.**
- **Sub-clinical infections in the brain rapidly "seed" toxic β-amyloid to trap microbes**
- **Infection drives Aβ opsonization ("Eat Me" signal for microglia)**
- **Aβ also blocks neurotransmission (LTP) and induces vasoconstriction**
- **Tangles form in response to virus and Aβ – blocks neurotropic viral spread**
- **Aβ plus neuronal cell death induce neuroinflammation leading to neurodegeneration**

Innate Immune Protection Hypothesis Pt. 2: Role of AD Risk Genes

AD-associated genetic risk variants were evolutionarily conserved to keep β-amyloid deposition, tangle formation, and gliosis/neuroinflammation on a "hair trigger" to protect a subset of the human species in the advent of a major epidemic of brain infection.

Key Questions:

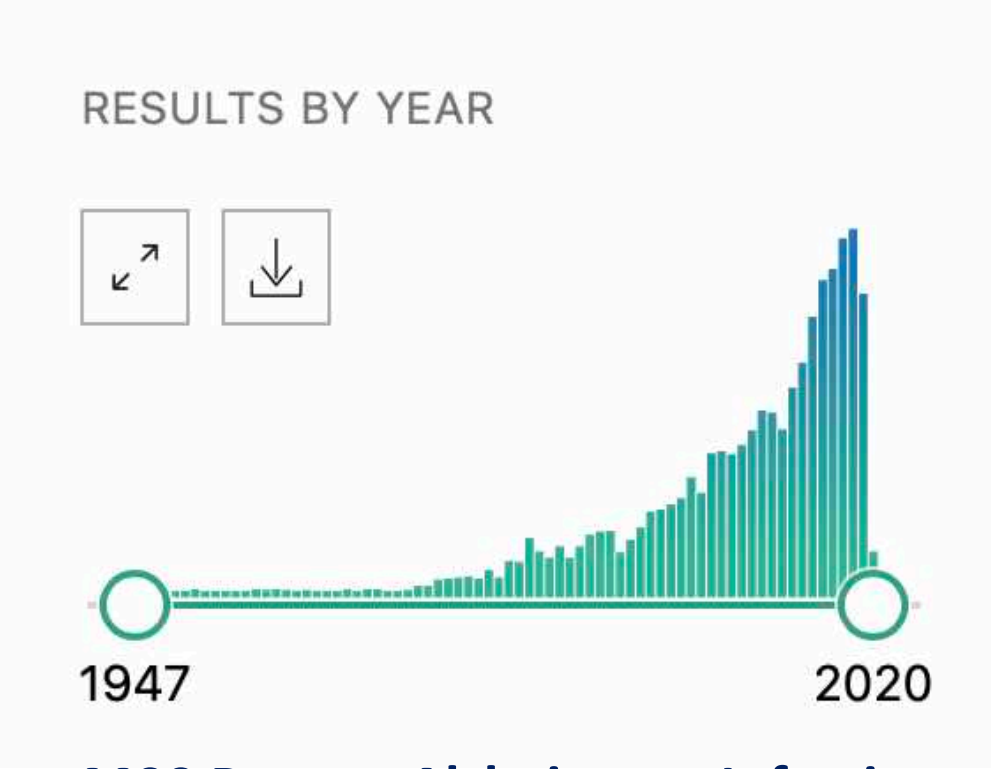
If AD pathology has evolved to protect the brain from microbial infection, and AD genetic risk variants have been evolutionarily conserved to promote this pathology when necessary…

Which microbes (if any) may drive AD pathology? When?

What are the relative contributions of *microbes, genes*, and *lifestyle* in driving Alzheimer's disease pathology, today?

Alzheimer's Disease and Infection

- **Fungal infections**
  - (Prusiner, 2013; Alonso et al.,2014; Heintz and Mair, 2014)
- **Herpes (HSV1)**
  - (Jamieson et al., 1991; Kammerman et al., 2006; Itzhaki and Wozniak, 2008; Toma et al., 2008; Lukiw et al., 2010; Ball et al., 2012; Agostini et al., 2014; Mancuso et al., 2014)
- **Chlamydophila pneumoniae**
  - (Balin and Hudson, 2014; Wunderink and Waterer, 2014, Pisa, 2017)
- **HIV and HAND**
  - (Borjabad and Volsky, 2012; Widera et al.,2014)
- **Toxoplasma**
  - (Prandota, 2014)
- **Hepatitis**
  - (Chiu et al., 2013; Karim et al.,2014)
- **Cytomegalovirus**
  - (Lurain et al., 2013)



>4400 Papers: Alzheimer + Infection

Parkinsonism Relat Disord. 2010 November ; 16(9): 566–571. doi:10.1016/j.parkreldis.2010.06.012.

Parkinsonism and Neurological Manifestations of Influenza Throughout the 20th and 21st Centuries

Julie Henry, B.S.,
Department of Neurolog

Richard J. Smeyne, Ph
Department of Developr
TN

Haeman Jang, PhD.,
Department of Developr
TN

Bayard Miller, M.D., an
Department of Neurolog

Michael S. Okun, M.D.
Departments of Neurolo
Gainesville FL

viruses

MDPI

Review

Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System?

Marc Desforges [1,*], Alain Le Coupanec [1], Philippe Dubeau [1], Andréanne Bourgouin [1], Louise Lajoie [2], Mathieu Dubé [1,3] and Pierre J. Talbot [1,*]

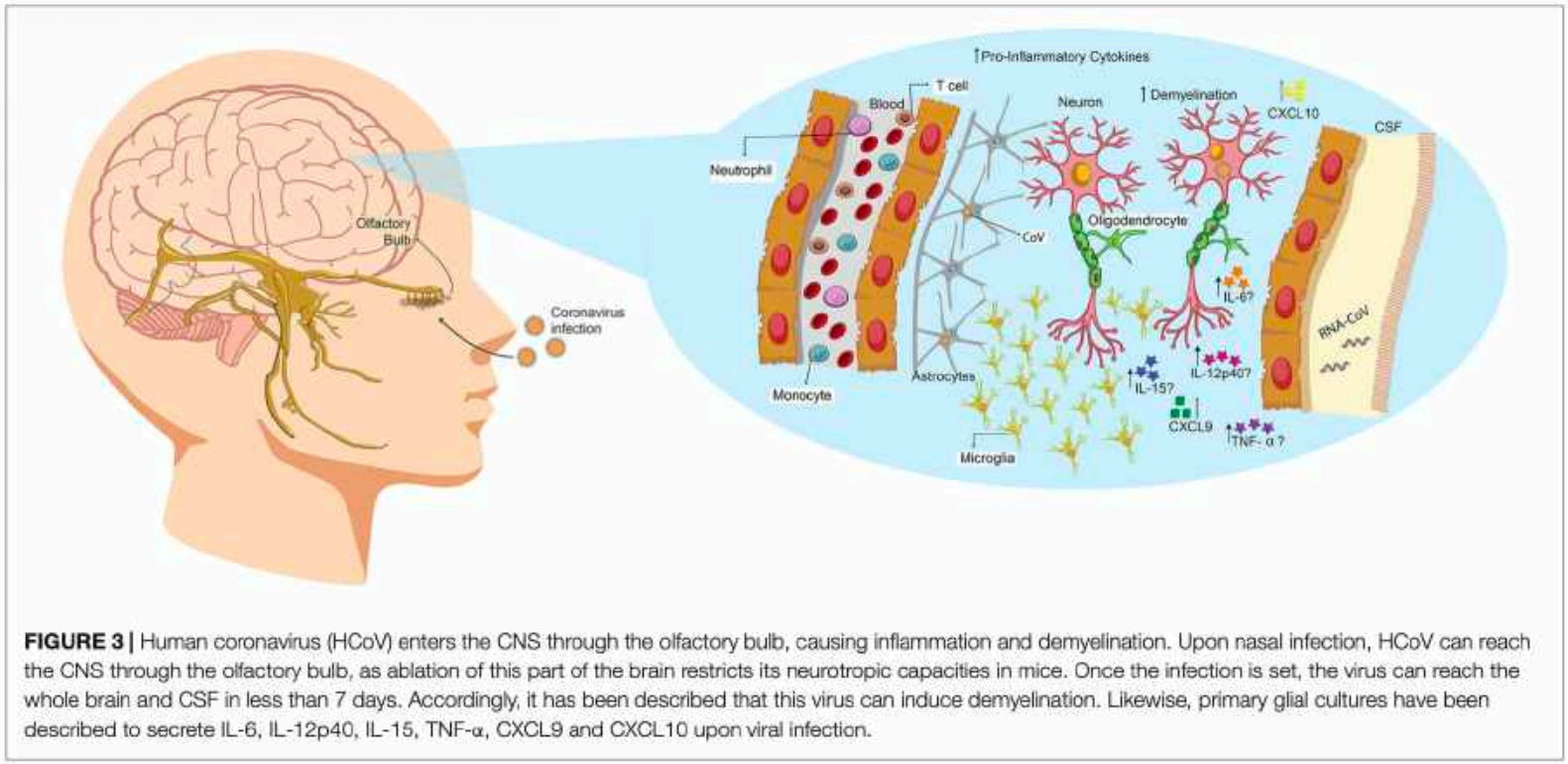


FIGURE 3 | Human coronavirus (HCoV) enters the CNS through the olfactory bulb, causing inflammation and demyelination. Upon nasal infection, HCoV can reach the CNS through the olfactory bulb, as ablation of this part of the brain restricts its neurotropic capacities in mice. Once the infection is set, the virus can reach the whole brain and CSF in less than 7 days. Accordingly, it has been described that this virus can induce demyelination. Likewise, primary glial cultures have been described to secrete IL-6, IL-12p40, IL-15, TNF-α, CXCL9 and CXCL10 upon viral infection.

Resilient (*Mismatch*) Brains: Plaque and Tangle Counts Consistent with Alzheimer's, but.. but *No* Neuronal Loss or Dementia *If* there are minimal activated microglia and astrocytes

Resilient AD

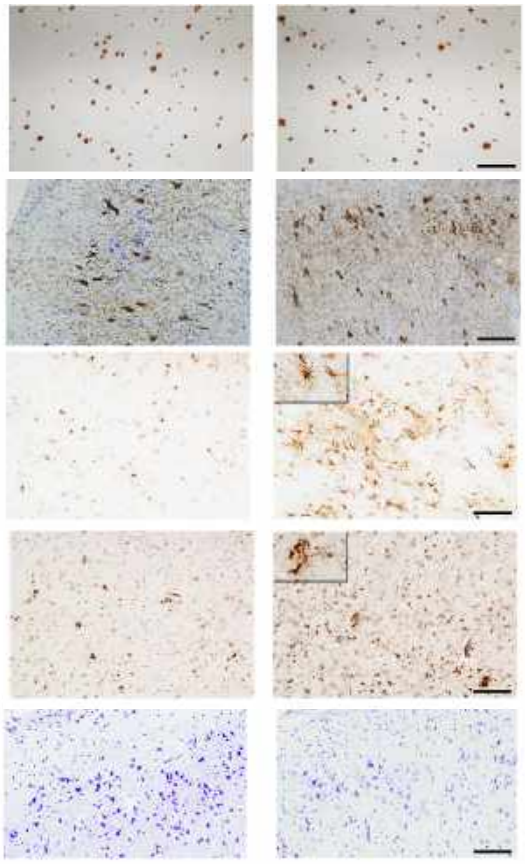
Plaques

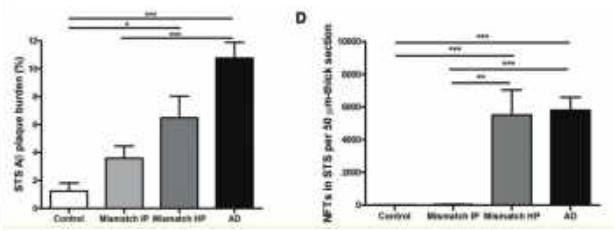
Tangles

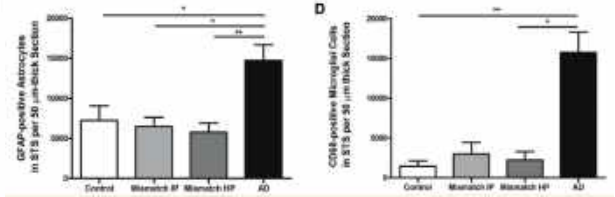
Neuroinflammatory Astrocytes

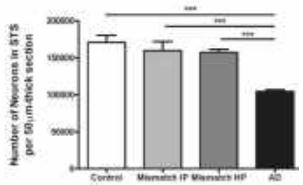
Neuroinflammatory Microglia

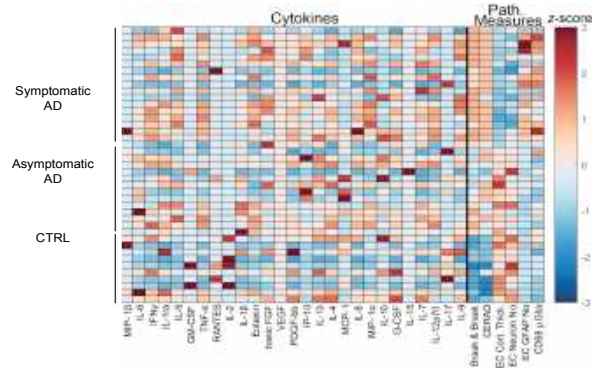
Neurons











One can have abundant plaques and tangles, but *without* neuroinflammation

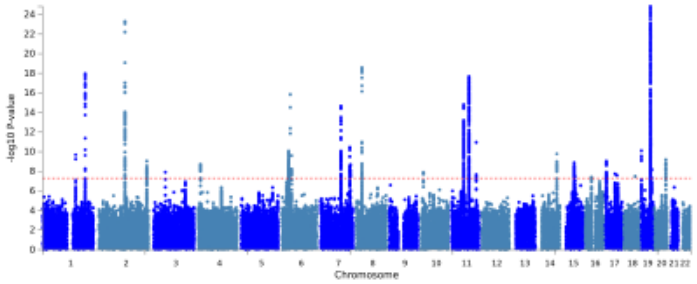
↓

No dementia!

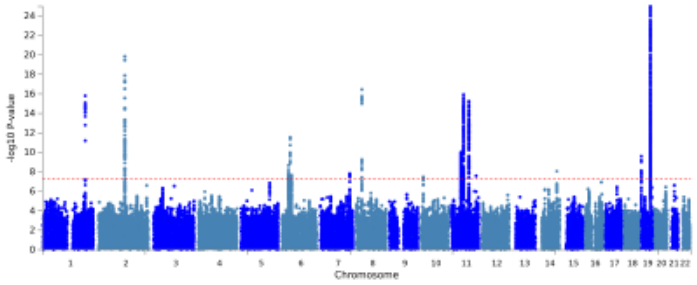
:-Nievas et al. 2013

AD-Associated Genes by GWAS 2008-2019

Jansen et al (2019)



Kunkle et al (2019)



Bertram and Tanzi, Nature Rev. Neurosci, 2019

rs6656401	rs4844610	1	CR1
rs4575098	rs4663096	1	ADAMTS4
rs6733839		2	BIN1
rs35349669	rs10933431	2	INPP5D
rs18438474			
6		3	HESX1
rs6448453	rs6448799	4	HS3ST1
rs10948363	rs9473117	6	CD2AP
rs78738018		6	HLA-DQB1
rs75932628	rs385758, rs114812713	6	TREM2
rs11771145	rs11762262	7	EPHA1
rs1476679	rs12539172 rs1859788	7	NYAP1
rs11436049			
2		7	CNTNAP2
rs9331896	rs867230	8	CLU
rs28834970	rs73223431	8	PTK2B
rs7920721		10	ECHDC3
rs983392		11	MS4A6A
rs10792832 rs3851179	rs867611	11	PICALM
rs11218343		11	SORL1
rs10838725	rs3740688	11	SPI1
rs10498633	rs12881735	14	SLC24A4
rs17125944	rs17125924	14	FERMT2
rs442495	rs593742	15	ADAM10
rs11761801			
7		15	APH1B
rs72824905		16	PLCG2
rs59735493		16	KAT8
rs616338	rs28394864	17	ABI3
rs7225151		17	SCIMP

Fastest growing group of AD Genes involved with innate immunity:

CD33

TREM2

CR1

HLA Cluster

CLU

MS4A Cluster

SPI1

PLCG2

ABI3

ABCA7

ADAMTS4

CD2AP

CASS4

INPP5D

CD33 5’ UTR SNP is protective for AD by reducing CD33 expression

Co-segregates with protective *CD33* mutation deleting exon 2 - inactivating CD33

The American Journal of Human Genetics 83, 1–10, November 7, 2008

Genome-wide Association Analysis Reveals Putative Alzheimer’s Disease Susceptibility Loci in Addition to *APOE*

CD33

Lars Bertram,[1,6] Christoph Lange,[2,6] Kristina Mullin,[1] Michele Parkinson,[1] Monica Hsiao,[1] Meghan F. Hogan,[1] Brit M.M. Schjeide,[1] Basavaraj Hooli,[1] Jason DiVito,[1] Iuliana Ionita,[2] Hongyu Jiang,[2] Nan Laird,[2] Thomas Moscarillo,[4] Kari L. Ohlsen,[5] Kathryn Elliott,[5] Xin Wang,[5] Diane Hu-Lince,[5] Marie Ryder,[5] Amy Murphy,[5] Steven L. Wagner,[5] Deborah Blacker,[3,4] K. David Becker,[5] and Rudolph E. Tanzi[1,*]

Please cite this article in press as: Griciuc et al., Alzheimer’s Disease Risk Gene CD33 Inhibits Microglial Uptake of Amyloid Beta, Neuron (2013), http://dx.doi.org/10.1016/j.neuron.2013.04.014

Neuron
Article

Alzheimer’s Disease Risk Gene *CD33* Inhibits Microglial Uptake of Amyloid Beta

Ana Griciuc,[1] Alberto Serrano-Pozo,[2] Antonio R. Parrado,[1] Andrea N. Lesinski,[1] Caroline N. Asselin,[1] Kristina Mullin,[1] Basavaraj Hooli,[1] Se Hoon Choi,[1] Bradley T. Hyman,[2] and Rudolph E. Tanzi[1,*]
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Neuron
Article

TREM2 Acts Downstream of CD33 in Modulating Microglial Pathology in Alzheimer’s Disease

Ana Griciuc,[1] Shaun Patel,[1] Anthony N. Federico,[1] Se Hoon Choi,[1] Brendan J. Innes,[1] Mary K. Oram,[1] Gea Cereghetti,[1,2] Danielle McGinty,[1] Anthony Anselmo,[3] Ruslan I. Sadreyev,[3] Suzanne E. Hickman,[4] Joseph El Khoury,[4] Marco Colonna,[5] and Rudolph E. Tanzi[1,6,7,*]
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[2]Institute of Biochemistry, Department of Biology, ETH Zürich, 8093 Zürich, Switzerland
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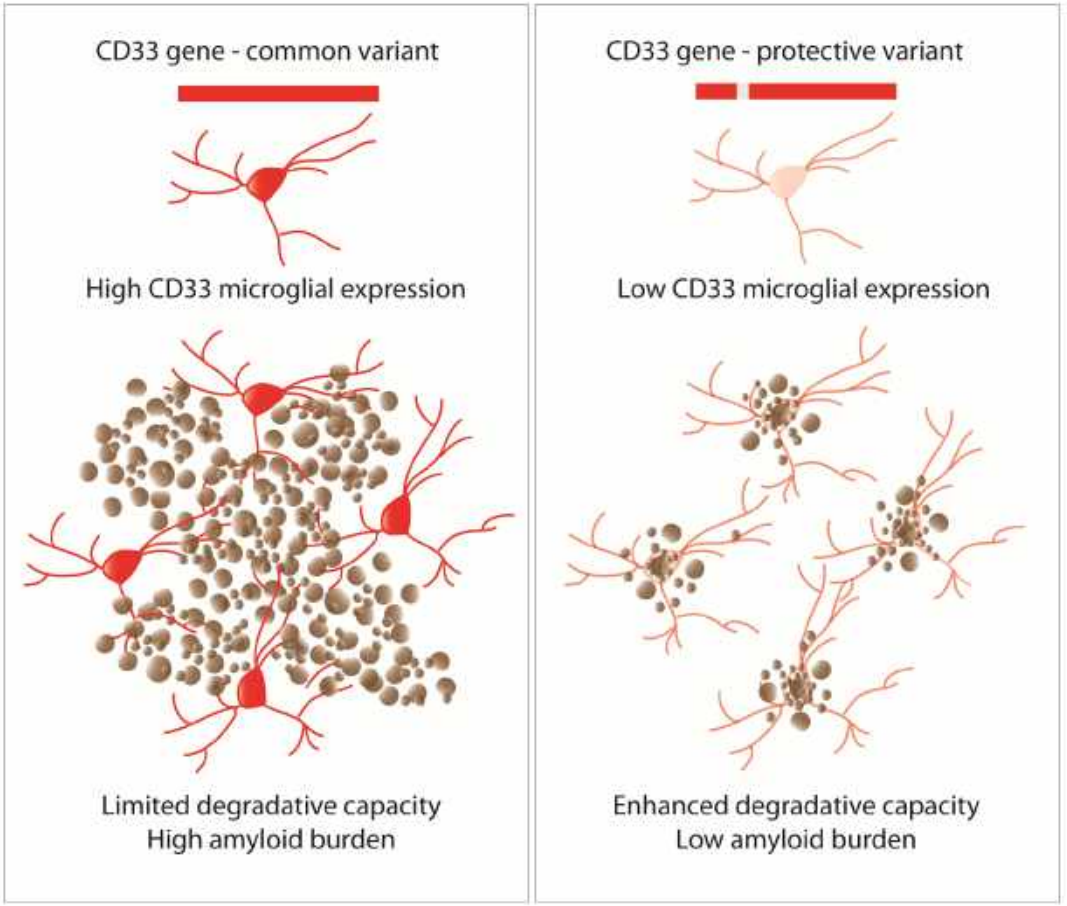
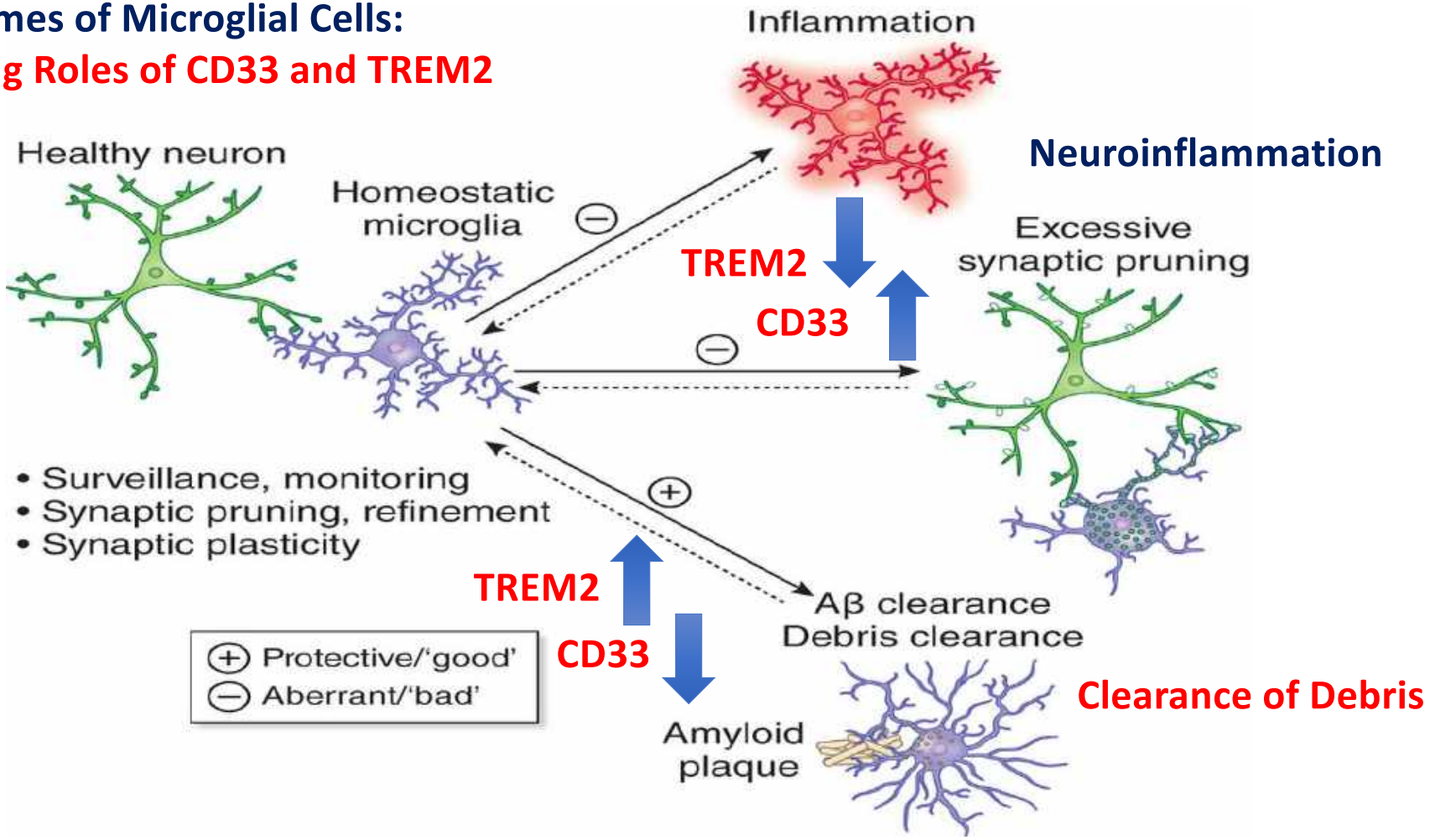
[4]Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA
[5]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO 63110, USA
[6]Lead Contact
*Correspondence: tanzi@helix.mgh.harvard.edu



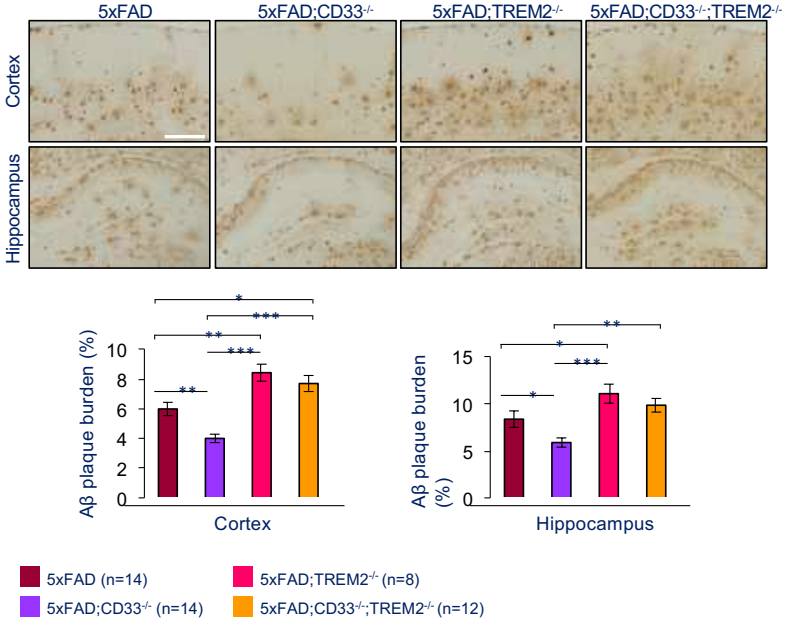
Polar Extremes of Microglial Cells:
Yin and Yang Roles of CD33 and TREM2

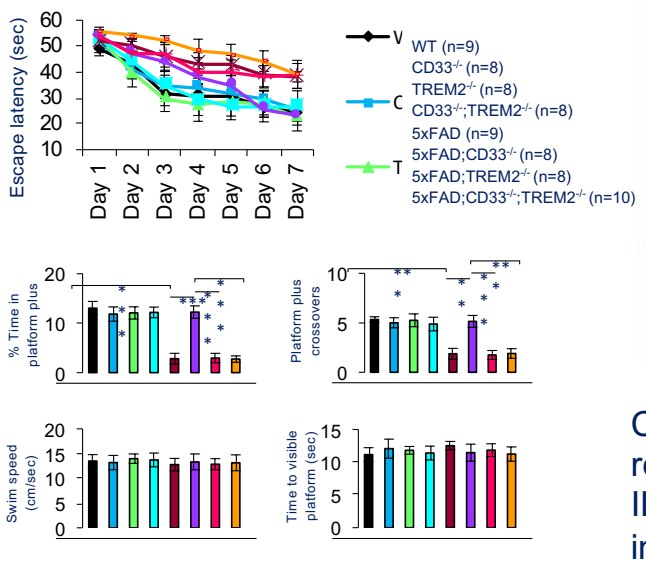


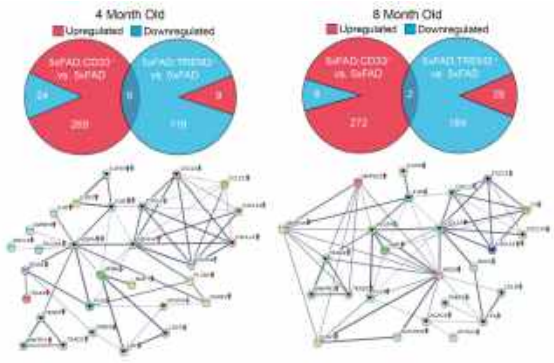
Modified from Stevens et al

TREM2 Regulates Microglial Activation Downstream of CD33

Knock-out of *CD33* in 5XFAD *decreases* Aβ plaque burden and improves cognition
Knock-out of *TREM2* in 5XFAD *increases* Aβ plaque burden and worsens cognition
Double *CD33/TREM2* knock-out in 5XFAD *mimics* *TREM2* knock-out in 5XFAD
***CD33/TREM2* knock-out-5XFAD transcriptome *mimics* *TREM2* knock-out-5XFAD**



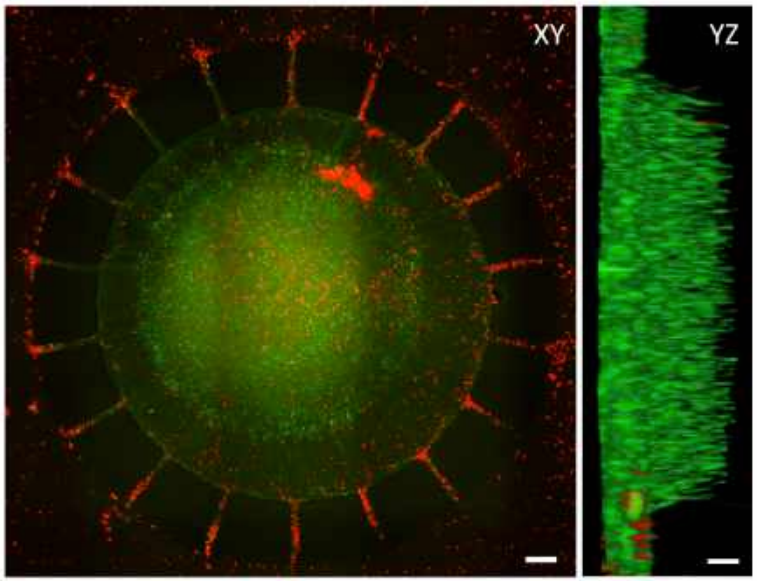




CD33 and TREM2 display opposite regulatory effects, with IL-1β and IL-1RN at the center of overlapping inflammation pathways

Griciuc et al, *Neuron*, 2019

Human Microglial-Neuronal-Astrocyte 3D Tri-Culture Model of AD



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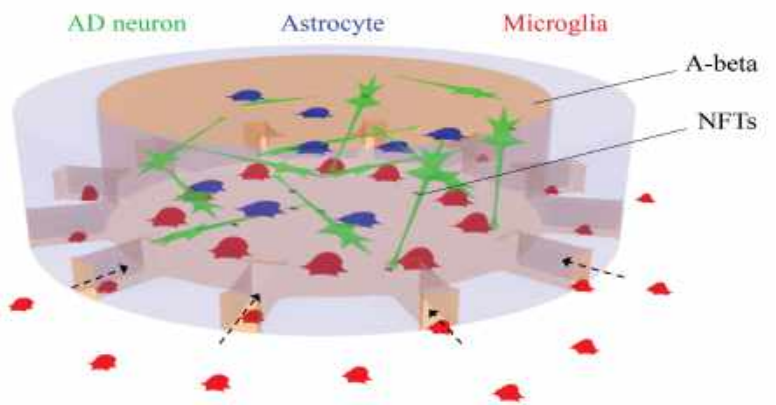
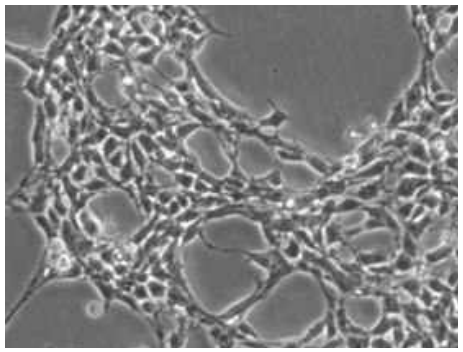
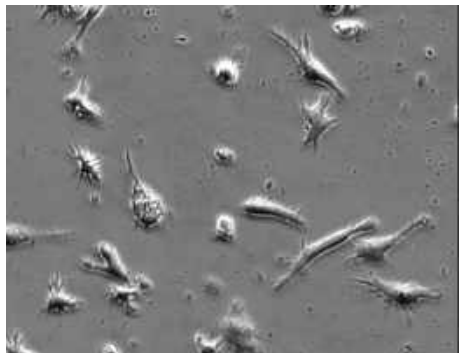
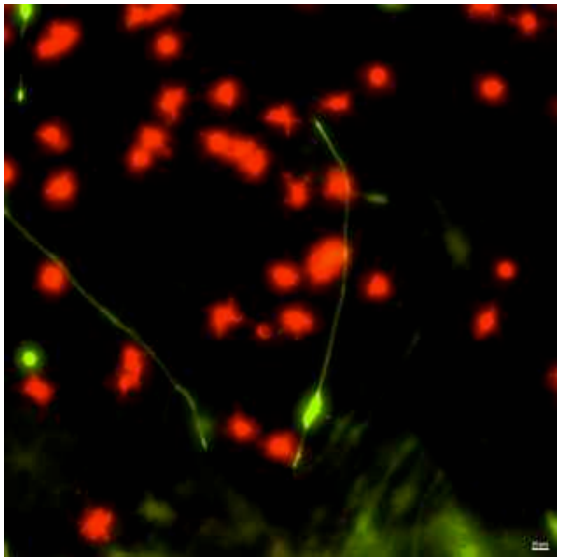


Human SV40



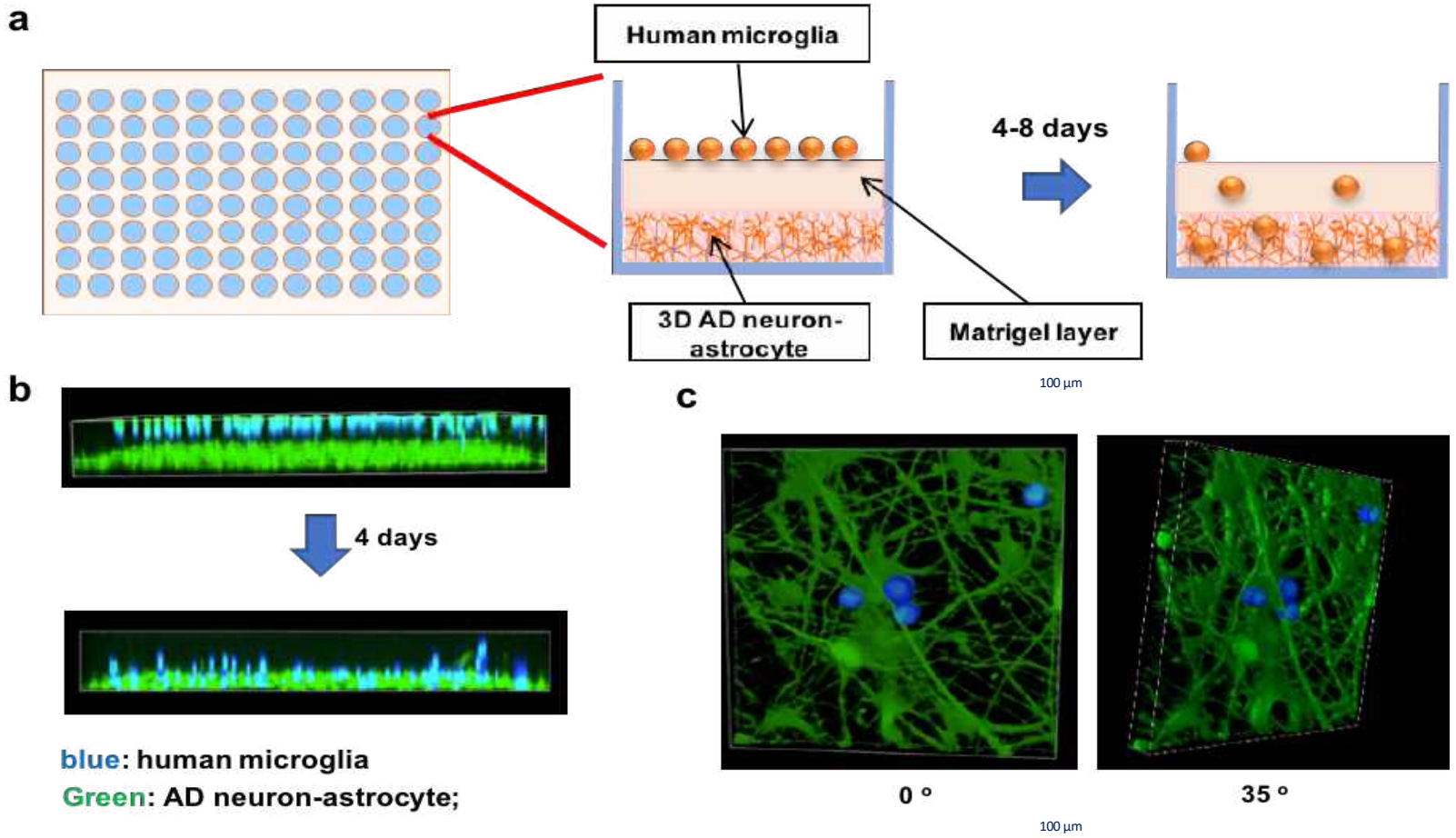
iMGL





Park et al., *Nature Neurosci*. 2018

3D Triculture Platform : Gel-Layered 3D Triculture in 96 Well Plate with iMGL's



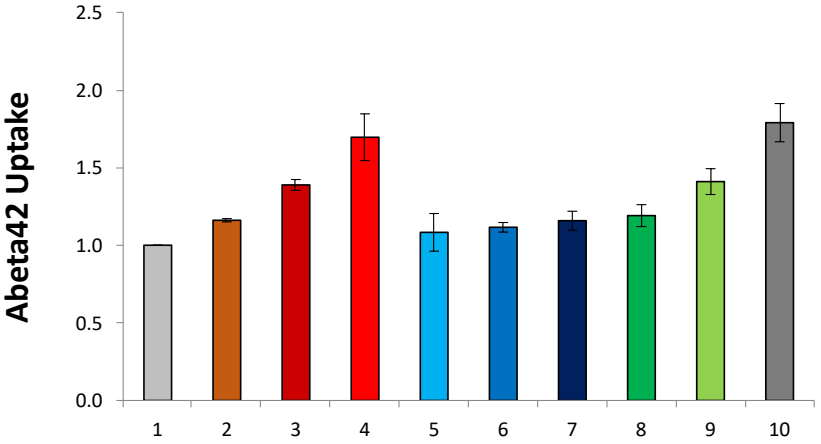
Joseph Park, Dr. Doo Yeon Kim, Luisa Quinti, Alan-Charles Dean

3D Human Mixed Neural-Astocyte-Microglial Culture System: Drug Hits

Compound ID	Activity	Abeta42 uptake	Cytokine reduction (Post LPA)
4	Ca2+ channel blocker	X	X
6	dihydroorotate dehydrogenase inhibitor		X
7	glucocorticoid agonist		X
8	antioxidant; lipoxygenases and glutathione S-transferase inhibitor		X
12	OX1 antagonist		X
15	Aryl hydrocarbon receptor antagonist		X
19	Cdk4/cyclin D1 and CaM kinase II inhibitr; antiviral		X
39	Cdk1 inhibitor	X	
40	Src-family tyrosine kinases inhibitor	N.D.	
41	leucine aminopeptidase inhibitor	N.D.	X
42	aminopeptidase inhibitor	X	X
45	PRAK and MAPKAP-K2 kinase inhibitor	X	

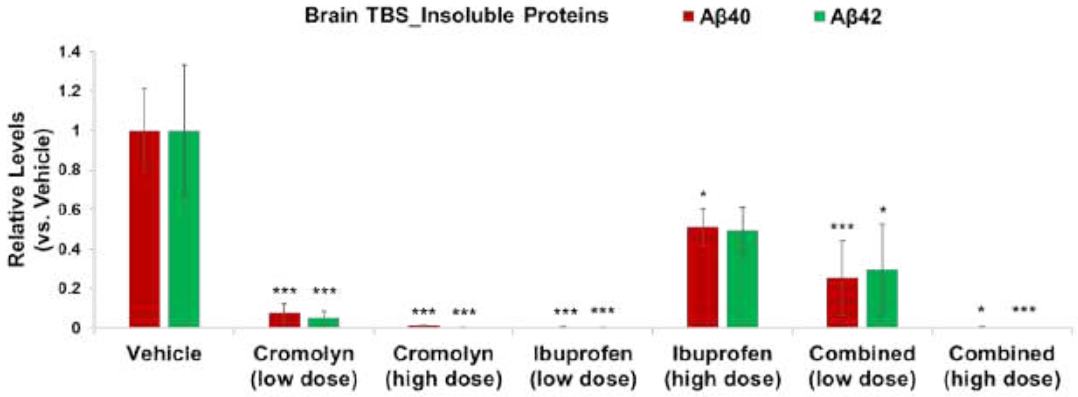
The image part with relationship ID rId2 was

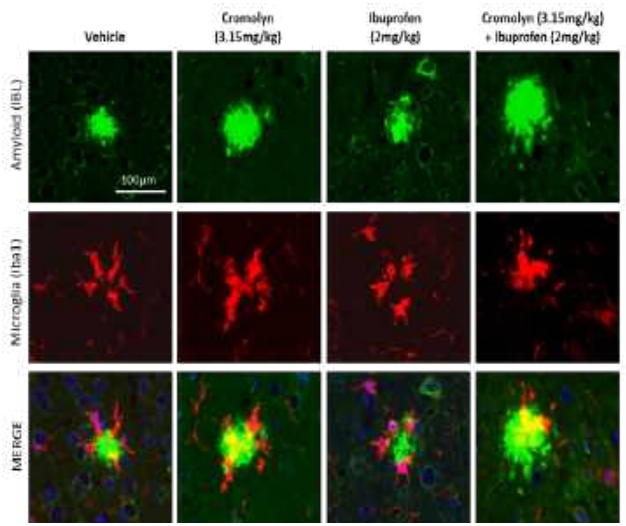
Cromolyn converts microglial cells from a pro-neuroinflammatory (neurotoxic) activation state to a phagocytic (β-amyloid-clearing) activation state in Tg AD mice.

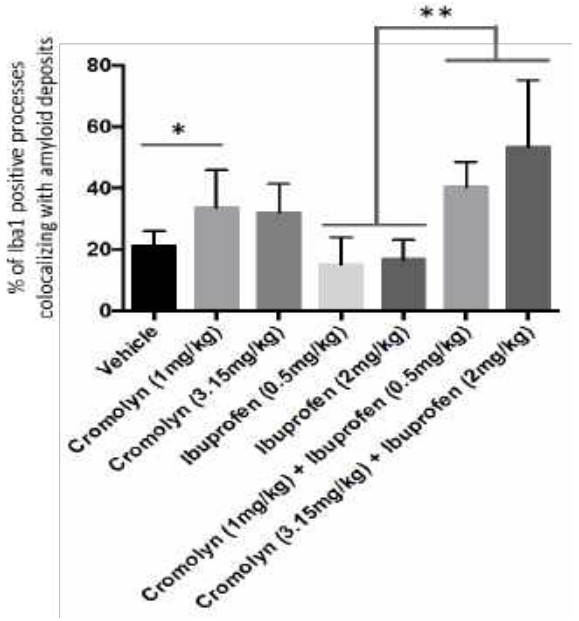


1. Vehicle
2. Cromolyn (10 µM)
3. Cromolyn (100 µM)
4. Cromolyn (1mM)
5. Ibuprofen (10 µM)
6. Ibuprofen (100 µM)
7. Ibuprofen (1 mM)
8. Cromolyn + Ibuprofen (10 µM)
9. Cromolyn + Ibuprofen (100 µM)
10. Cromolyn + Ibuprofen (1 mM)

n=3 experiments, **p<0.01, ***p<0.001







Zhang C et al., Nature Sci. Rep. 2018

Cromolyn sodium delays disease onset and is neuroprotective in the SOD1^{G93A} Mouse Model of amyotrophic lateral sclerosis

Eric J. Granucci[1,5], Ana Griciuc[2,5], Kaly A. Mueller[1,5], Alexandra N. Mills[1], Hoang Le[2], Amanda M. Dios[1], Danielle McGinty[2], Joao Pereira[1], David Elmaleh[3], James D. Berry[1], Sabrina Paganoni[1,4], Merit E. Cudkowicz[1], Rudolph E. Tanzi[2] & Ghazaleh Sadri-Vakili[1*]

Key results - Cromolyn:

- **Delayed disease onset and progression**
- **Reduced motor deficits in the Paw Grip Endurance (PaGE) task**
- **Significant effect on motor symptoms as measured by age at paresis onset**
- **Significantly spared lumbar spinal cord motor neurons**
- **Reduced pro-inflammatory cytokine/chemokine levels in the spinal cord and plasma**
- **Preserves Neuro-Muscular-Junction integrity**

Granucci et al, 2019

Phase 3 Clinical Trial of Brain-Permeable Cromolyn in AD Patients (COGNITE) – AZ Therapies*

- **Cromolyn: Currently in a phase three clinical trial (COGNITE) for the treatment of mild-moderate AD (N=600 patients); Expected to read out late-2020.**

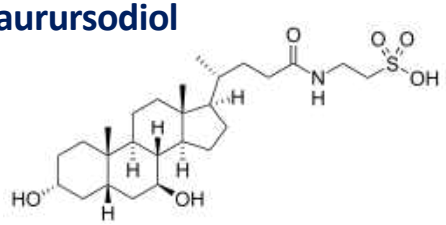
Mechanisms of Action:

1. **Reduces neuroinflammation by converting microglia from pro-inflammatory state to a phagocytic state**
2. **Promotes clearance of Aβ by microglia using Fc-Gamma receptor (similar to MOA of aducanumab)**
3. **Could use combination of brain-permeable cromolyn and a GSM to remove Aβ from the brain, but….**

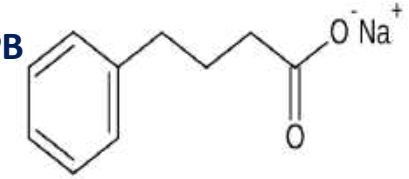
*R. Tanzi is Chair of SAB & Shareholder

Amylyx*: AMX0035

Taurursodiol



PB



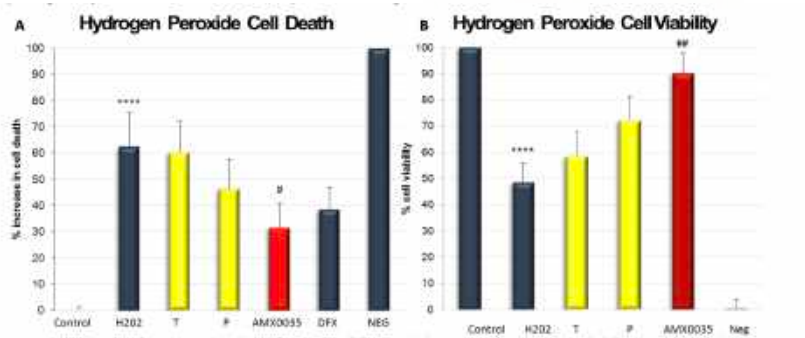
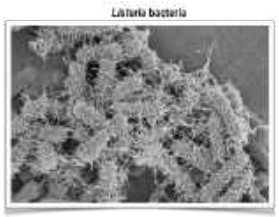


Figure 1: Primary rat cortical neurons were cultured for ten days following which test compounds were supplied (taurursodeoxycholate 300uM, phenylbutyrate 1mM, the combination thereof (AMX0035), deferoxamine 100uM, and negative control 300uM NMDA). After twenty four hours of compound exposure, cultures were exposed to 40uM H_2O_2 for one hour following which compounds were again supplied for twenty four hours. PrestoBlue analysis **(A)** was conducted after compounds exposure for cell viability and LDH analysis **(B)** was used to determine cell death. One way ANOVA followed by Dunnett's post hoc was applied for statistical significance. Error bars represent standard error.

- **Drug Combination Repurposing Two Small Molecules:** Sodium Phenyl Butyrate and Taurursodiol aimed at preventing neuronal cell death due to neuroinflammation by protecting against endoplasmic reticulum and mitochondrial stress.
- **ALS Phase 2 RCT (CENTAUR N=132) –**Statistically significant slowing of functional decline over 24 weeks in ALS patients, the majority of whom were also receiving riluzole, edaravone, or both. Paganoni S. et al. *NEJM*, 2020
- **AD Phase 2 (PEGASUS N=100) – Reads Out in 2020**

*R. Tanzi – Co-founder/SAB Chair & Shareholder

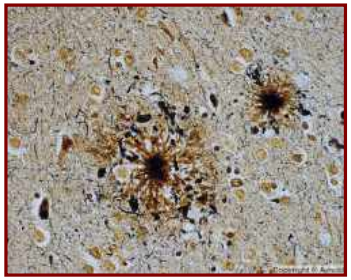
Sub-Clinical Infections: virus, bacteria, fungus



Anti-virals
Antibiotics
Immunization

Primary Prevention

β-Amyloid Deposition



GSM; Aβ-ImmunoRx

Secondary Prevention

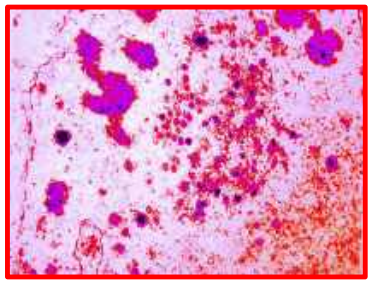
Seeding of Amyloid-β

Tangle Seeding/Spreading

Neuroinflammation

Tangles/Tauopathy

Secondary Prevention & Mild-Moderate AD



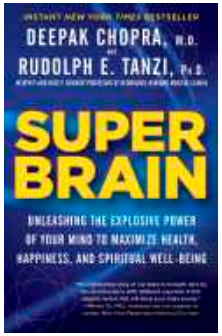
AZT-Cromolyn
Amylyx AMX0035
CD33/TREM2 Rx

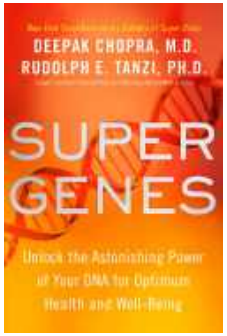
Neurodegeneration

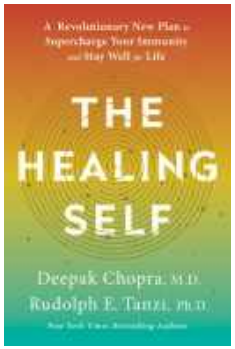
P-Tau-ImmunoRx

Secondary Prevention

Microglial Activation and Astrogliosis







Sleep 8 Hours

During deep night sleep amlyoid production is turned down. In addition to less plaque forming, the brain cleans itself out.

Handle Stress

Take 10 minutes a day to meditate, take a walk, or do something else that relaxes you.

Interact With Others

Loneliness causes stress that can lead to chemical changes in the brain that kills nerve cells. Speaking with people involves nerve activity that strengthens the brain.

Exercise

Walking 8,000-10,000 steps per day reduces pathology leading to Alzheimer's and helps grow new nerve cells.

Learn New Things

Learning something new strengthens the connections between nerve cells called synapses and provides cognitive reserve.

Diet

Nothing is better for the brain than the Mediterranean diet.
Eat less red meat and more fruits, nuts, and vegetables

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

HENRY AND ALLISON MCCANCE CENTER FOR BRAIN HEALTH

Lifestyle Interventions:

Sleep

Handling Stress

Interactions with Others

Exercise

Learn New Things

Diet

Sleep 8 Hours

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Sleep

Handle Stress

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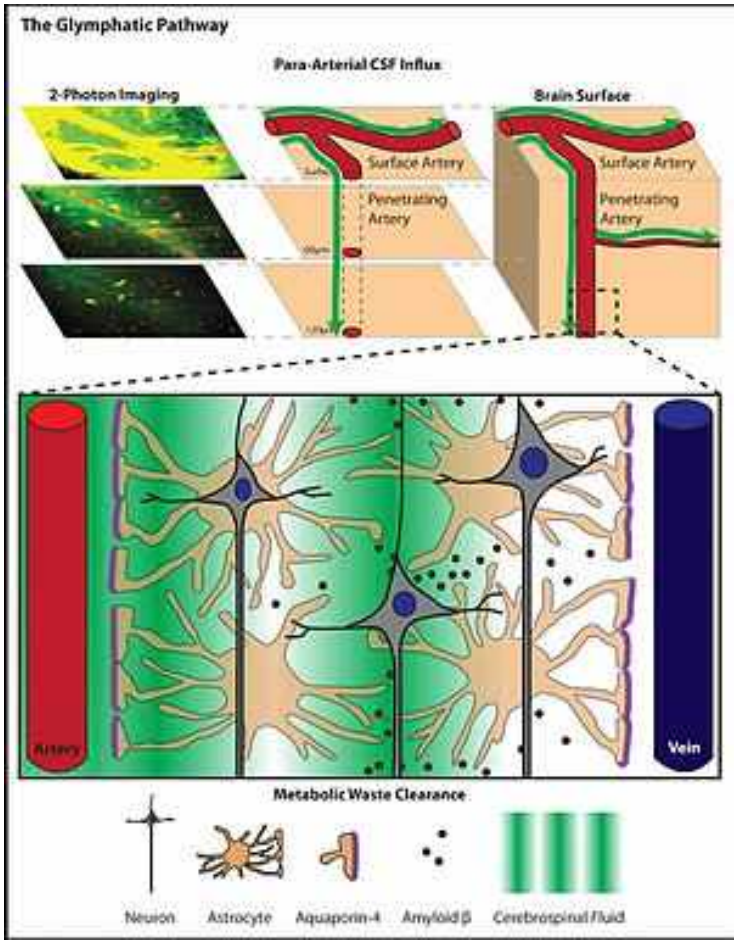
During Deep Sleep: Your Brain is Cleaned of Plaque and Other Neurotoxic Debris



OPEN

Citation: Transl Psychiatry (2016) 6, e880; doi:10.1038/tp.2016.164
www.nature.com/tp

ORIGINAL ARTICLE

Meditation and vacation effects have an impact on disease-associated molecular phenotypes

ES Epel[1], E Puterman[1], J Lin[2], EH Blackburn[2], PY Lum[3], ND Beckmann[4], J Zhu[4], E Lee[4], A Gilbert[1], RA Rissman[5], RE Tanzi[6] and EE Schadt[4]

Handling Stress

Meditation and vacation led to beneficial changes in gene networks involved with stress response and inflammation.

A week of meditation led to increased telomerase activity and beneficial changes in Alzheimer's-related plasma biomarkers.

Deep meditation can turn down default mode network activity, the network that promotes propagation of Alzheimer's pathology.

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Interaction with Others

Loneliness increases risk for AD by 2-fold

Table 3. Relation of Cumulative Loneliness to Incident Alzheimer Disease (Models A and B) and Global Cognitive Decline (Models C and D)*

Model Term	Model A RR (95% CI)	Model B RR (95% CI)	Model C Estimate (SE); *P* Value	Model D Estimate (SE); *P* Value
Cumulative loneliness	2.10 (1.45-3.06)	1.84 (1.11-3.07)		
Cumulative loneliness			-0.20 (0.03); <.01	-0.09 (0.04); .02
Cumulative loneliness × time			-0.03 (0.01); <.01	-0.05 (0.01); <.01

Abbreviation: CI, confidence interval; RR, relative risk; SE, standard error.
*Estimated from proportional hazards (A and B) or mixed-effects (C and D) models adjusted for age, sex, and level of educational achievement (A and C) and for social activity, social network, physical activity, cognitive activity, depressive symptoms, income, race/ethnicity, disability, and vascular risk factors and conditions (B and D).

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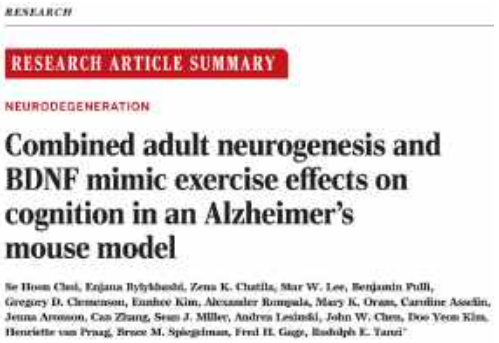

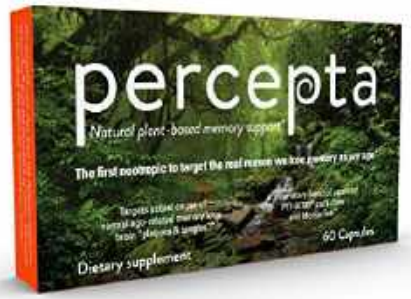

*Finiancial Interest in Chromadex and Cognitive Clarity

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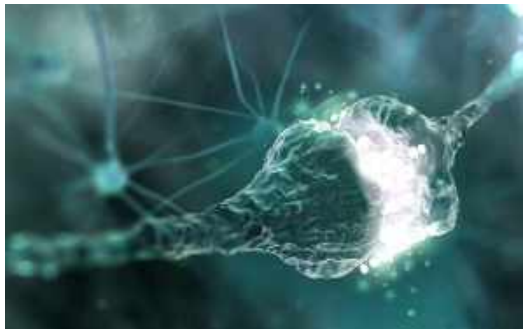
Degree of Dementia in Alzheimer's Disease Correlates Most Closely with Synapse Loss



Build Your Synaptic Reserve Everyday

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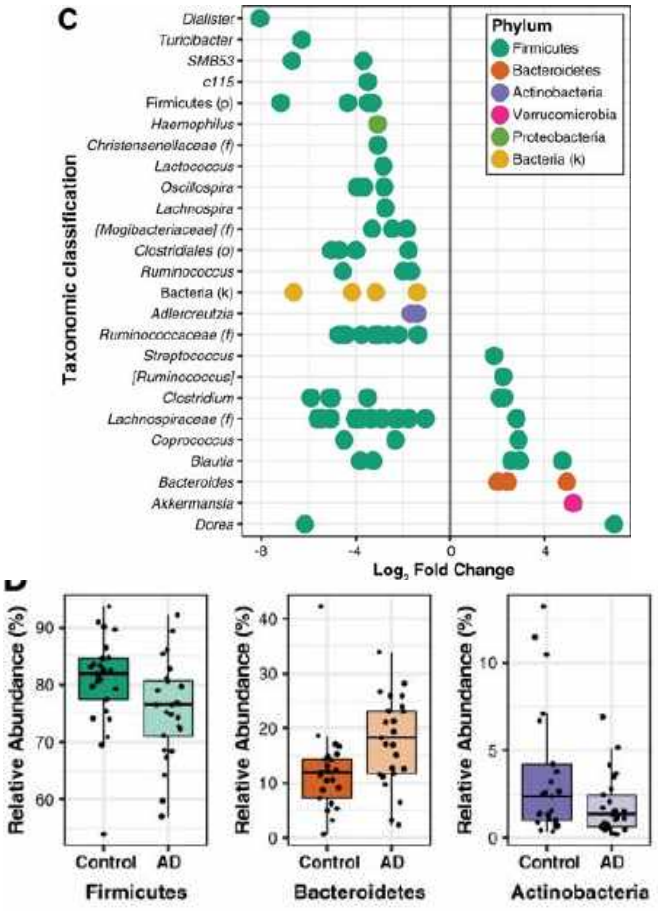
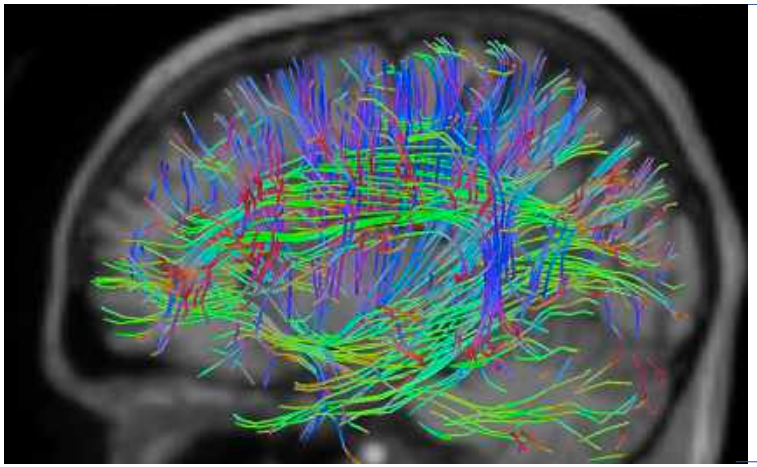
Severe Gut Dysbiosis in AD Patients



Add more organic anti-inflammatory food to your groceries, e.g. fruits, vegetables, leafy greens

Increase plant fiber (whole grains) – prebiotics keep gut microbiome happy

Probiotic supplement or priobiotic foods – yogurt, kefir, etc



McCance Center for Brain Health

1. Identify and study the indicators of brain health

2. Discover and develop lifestyle interventions that prevent brain disease and improve brain function

3. Catalyze a borderless community of knowledge and tools for integrating these indicators and interventions into primary care

To *End* Alzheimer's disease, we need a *cocktail !*

Right Patient, Right Pathology, Right Drug, Right Time
And
The "SHIELD" Lifestyle

- ***Patient Treatment Now (Secondary Prevention):*** **Neuroinflammation**
- ***Secondary Prevention*****: β–Amyloid Deposition and Tangles**
- ***Primary Prevention*****: Lifelong (Sub-Clinical) Brain infections?**

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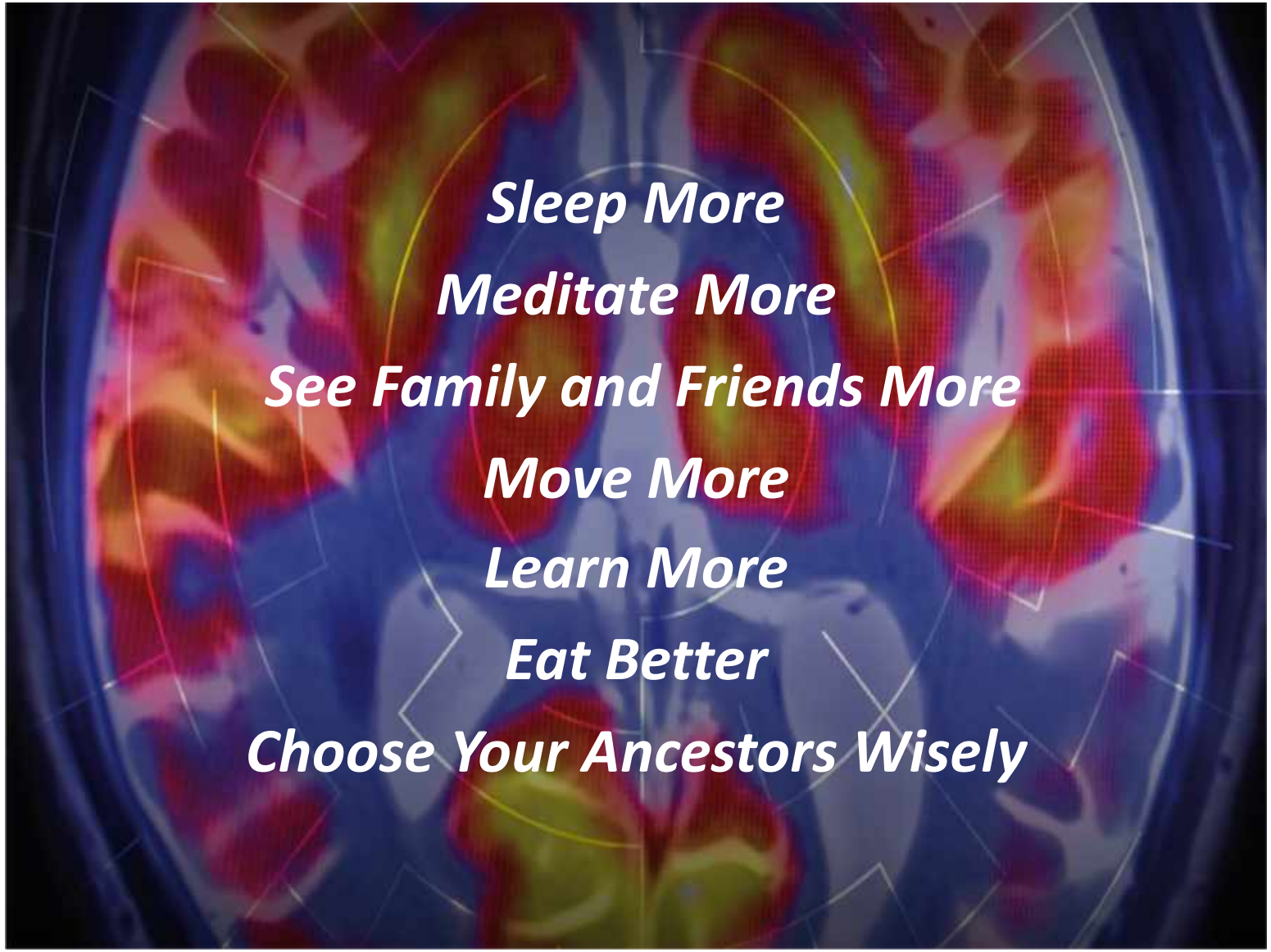
newyorkermag A cartoon by Roz Chast, from this week's issue. Follow @newyorkercartoons for more #TNYcartoons.


Sleep More
Meditate More
See Family and Friends More
Move More
Learn More
Eat Better
Choose Your Ancestors Wisely

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