AlzeCure´s Expert event

Alzheimer's disease and the amyloid hypothesis

PRESENTED BY:

Professor Henrik Zetterberg, MD, PhD,

University of Gothenburg, University College London

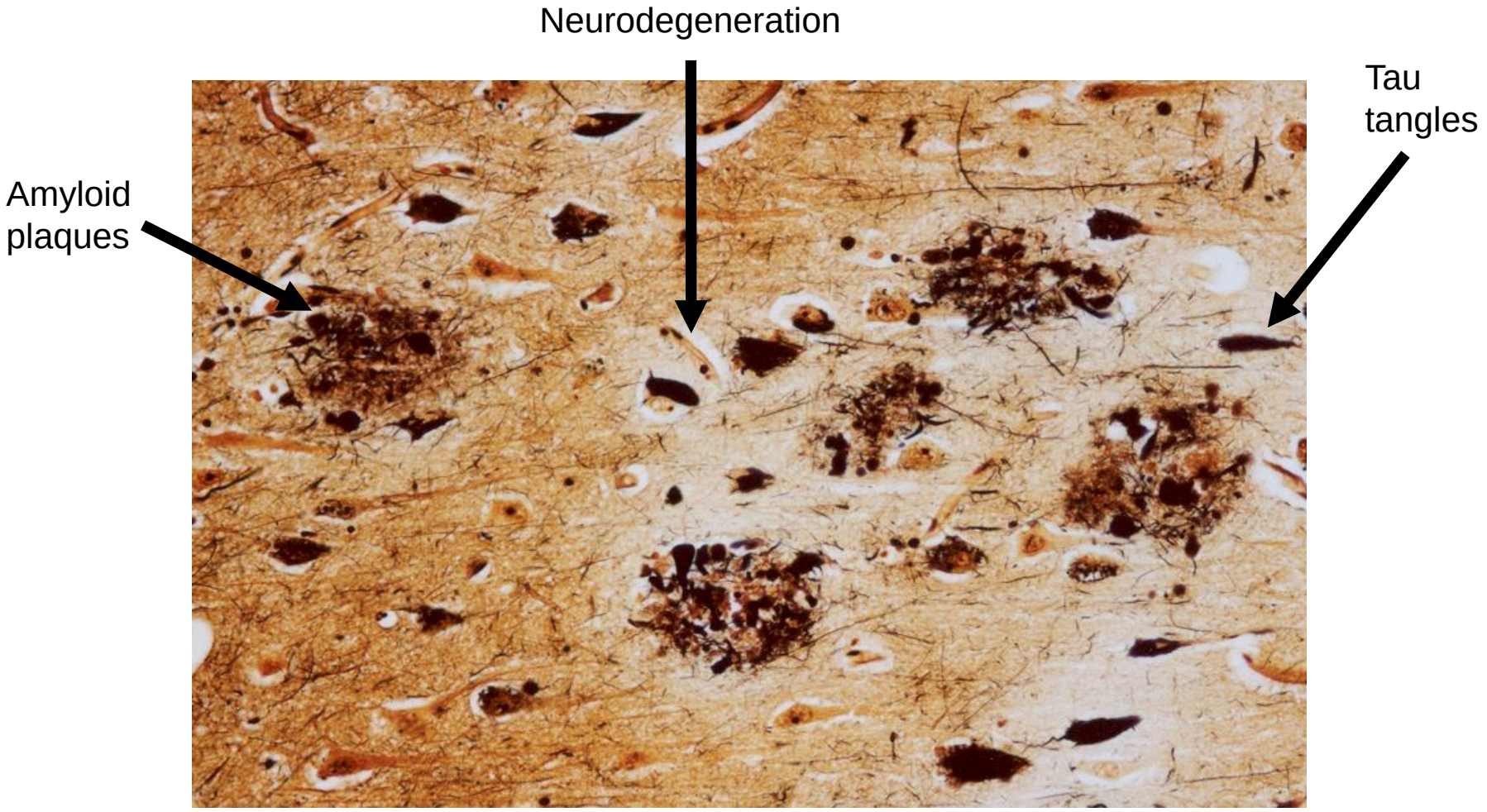
AlzeCure

Alzheimer's and the amyloid cascade hypothesis

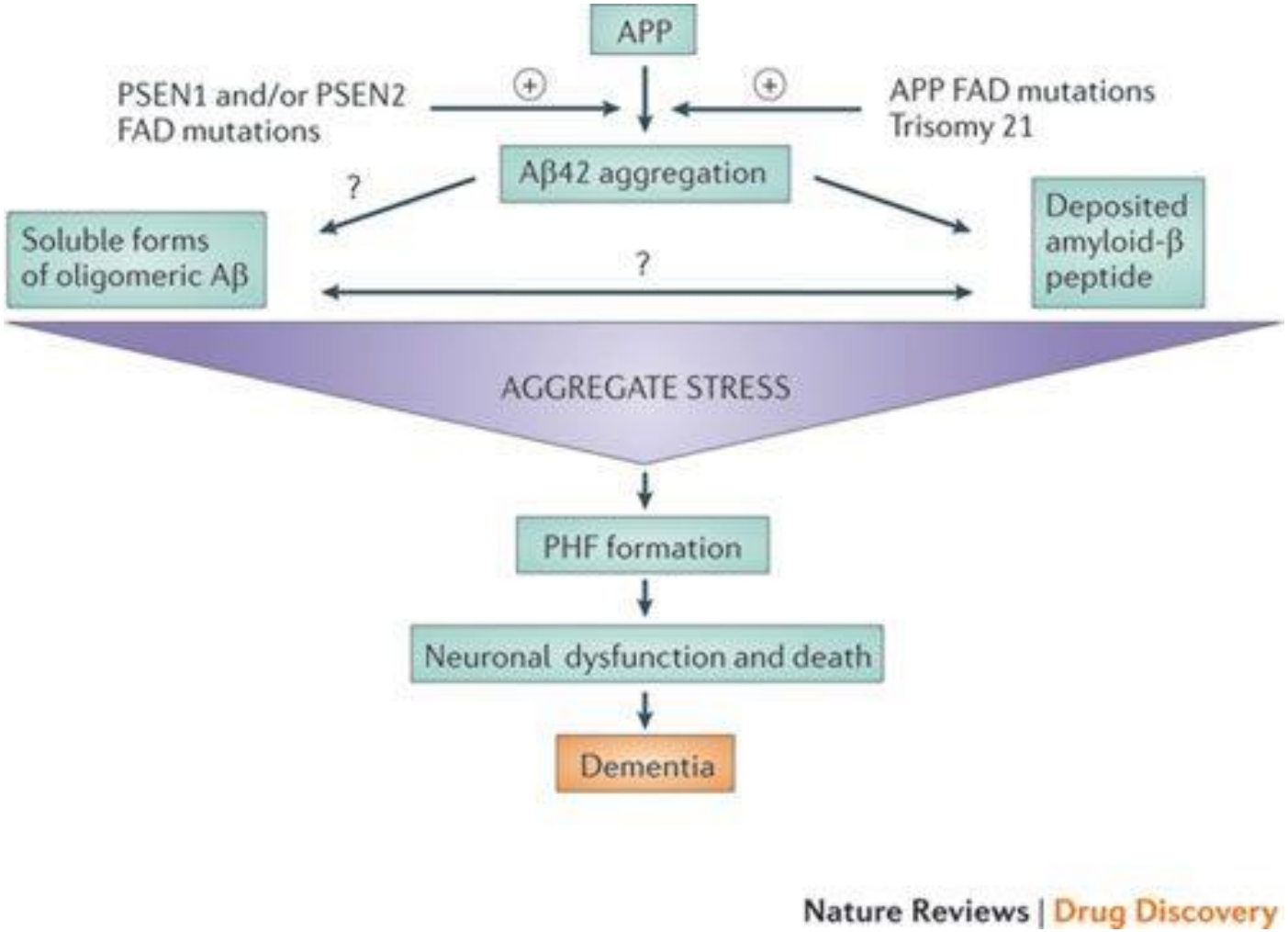
Henrik Zetterberg, MD, PhD
Professor of Neurochemistry
University of Gothenburg and University College London

The Sahlgrenska Academy

The neuropathology of Alzheimer's disease

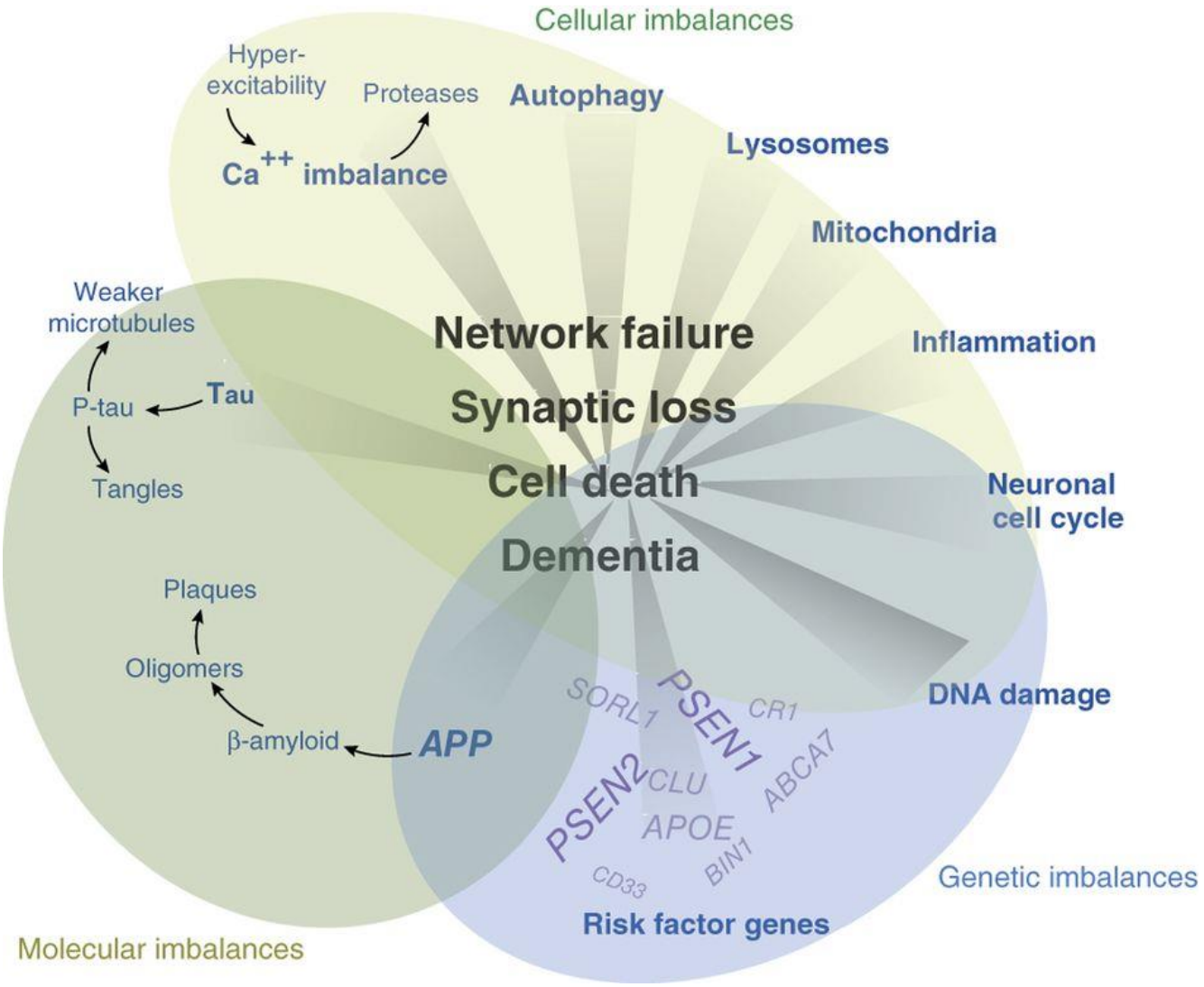


The amyloid cascade hypothesis on Alzheimer's disease – still viable?



Karran et al., 2011

The amyloid cascade hypothesis on Alzheimer's disease – still viable?



Herrup et al., 2015

Risk factors for Alzheimer's disease

High age	**key risk factor**	
***APOE* ε4 allele**	**heterozygote** **homozygote**	**3-4 times increase in risk** **10-12 times increased risk**

Diabetes mellitus	**Relative risk 1.46**	**95% CI 1.20 – 1.77**
Mid-life hypertension	**Relative risk 1.61**	**95% CI 1.16 – 2.24**
Mid-life obesity	**Relative risk 1.60**	**95% CI 1.34 – 1.92**
Physical inactivity	**Relative risk 1.82**	**95% CI 1.19 – 2.78**
Smoking	**Relative risk 1.59**	**95% CI 1.15 – 2.20**

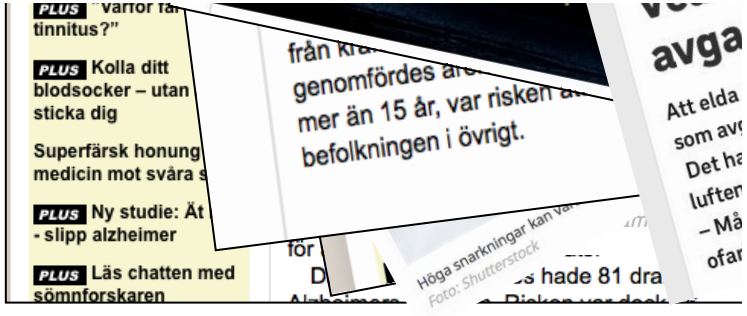
unv.is/ expressen.se/halsoliv/inloggad/daglig-bastu-minskar-risken-for-alzheimers

Daglig bastu minskar risken för Alzheimers

Source: *http://expressen.se/halsoliv/inloggad/daglig-*

Show more from expressen.se

Det är första gången som sambandet mellan bastuba
medelålders män från östra Finland och resultatet är



Stjärnkock: "Nudlar ger alzheimers"

Publicerad 1 okt 2010 kl 10.03, uppdaterad kl 10.06

AD pathology can be identified using biomarkers

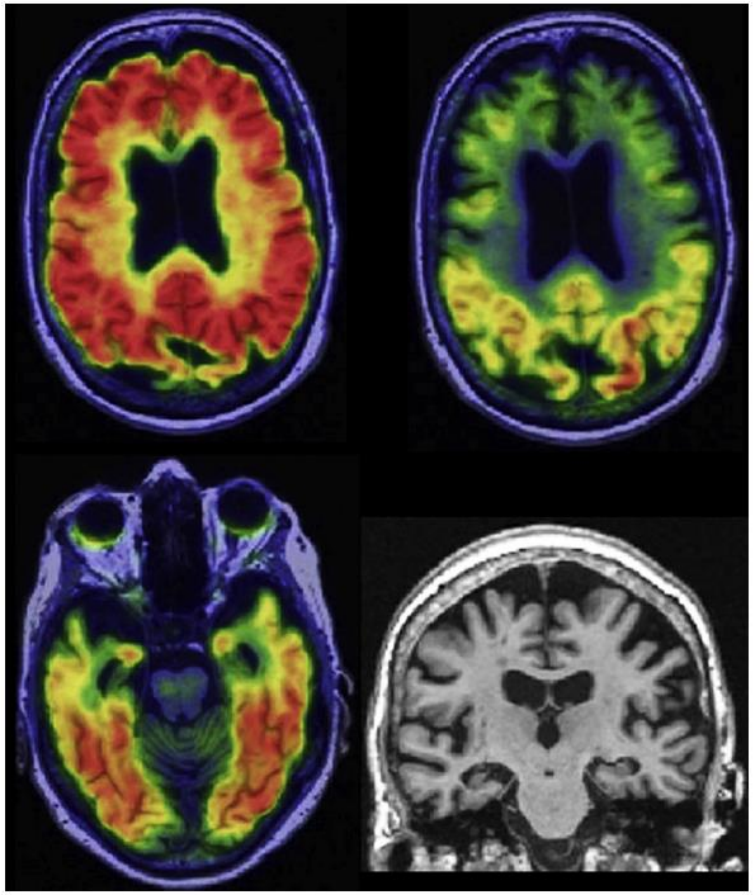
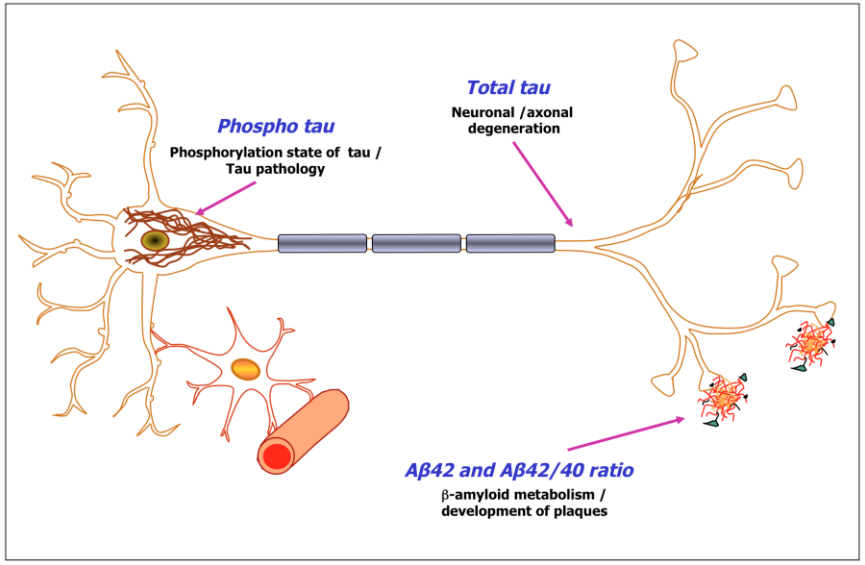


Fig. 1. Alzheimer's disease with dementia. A 75-year-old woman with amnestic multidomain dementia. Participant in the Mayo Alzheimer's Disease Research Center. Abnormal amyloid PET with Pittsburgh compound B (top left), tau PET with flortaucipir (top right and bottom left), and atrophy on MRI (bottom right). Biomarker profile A+T+(N)+.



ELSEVIER

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

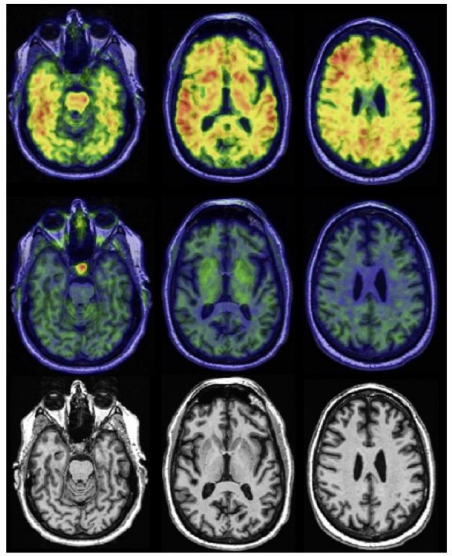
NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Biomarker Profile	Cognitively Unimpaired	Mild Cognitive Impairment	Dementia
$A^-T^-(N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
$A^+T^-(N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
$A^+T^+(N)^-$ $A^+T^+(N)^+$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's disease with dementia
$A^+T^-(N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
$A^-T^+(N)^-$ $A^-T^-(N)^+$ $A^-T^+(N)^+$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia

➔ **Amyloid and tau pathology (+/- neurodegeneration) = Alzheimer's disease**

➔ **Amyloid pathology only = Alzheimer's pathologic change**



Amyloid PET - positive

Tau PET - negative

MRI - normal

>30% of cognitively unimpaired elderly have brain amyloidosis (preclinical Alzheimer's disease)

Late-onset Alzheimer's disease

J Neuropathol Exp Neurol
Copyright © 2012 by the American Association of Neuropathologists, Inc.
Vol. 71, No. 4
April 2012
pp. 266–273

ORIGINAL ARTICLE

Accuracy of the Clinical Diagnosis of Alzheimer Disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010

Thomas G. Beach, MD, PhD, Sarah E. Monsell, PhD, Leslie E. Phillips, PhD, and Walter Kukull, PhD

	No AD pathology	Yes AD pathology	
No probable AD (clinical)	213	180	NPV=54 %
Probable AD (clinical)	88	438	PPV=83 %
	Specificity = 70.8%	Sensitivity = 70.9%	

- Clinical criteria for AD have poor diagnostic accuracy

doi:10.1093/brain/aww224 BRAIN 2016: 139; 2983–2993 | 2983

BRAIN
A JOURNAL OF NEUROLOGY

TDP-43 stage, mixed pathologies, and clinical Alzheimer's-type dementia

Bryan D. James,[1] Robert S. Wilson,[2,3] Patricia A. Boyle,[3] John Q. Trojanowski,[4] David A. Bennett[2] and Julie A. Schneider[2,5]

- Aβ - plaques
- PHF-tau – tangles

- TDP-43 inclusions
- α-synuclein / Lewy bodies
- Neuronal and synaptic degeneration
- Microvascular pathology
- Hippocampal sclerosis

- Late-onset Alzheimer-type dementia show multiple pathologies in different combinations

Risk factors for Alzheimer's disease

High age	key risk factor
APOE ε4 allele	heterozygote 3-4 times increase in risk homozygote 10-12 times increased risk

Diabetes mellitus	Relative risk 1.46	95% CI 1.20 – 1.77
Mid-life hypertension	Relative risk 1.61	95% CI 1.16 – 2.24
Mid-life obesity	Relative risk 1.60	95% CI 1.34 – 1.92
Physical inactivity	Relative risk 1.82	95% CI 1.19 – 2.78
Smoking	Relative risk 1.59	95% CI 1.15 – 2.20

Epidemiological studies are not based on biomarkers

- **preclinical AD is found in 20-30% of cognitively unimpaired elderly**
- **pure clinical diagnosis have poor diagnostic accuracy**
- **late onset AD is heterogeneous with multiple pathologies**

➔Risk factors for Alzheimer's disease (= amyloid and tau pathology) ?
Cerebrovascular pathology lowering threshold for AD-type pathology ?
Neurodegeneration in old-age dementia ?

Risk factors for Alzheimer's disease in biomarker studies

Research

JAMA Neurol. doi:10.1001/jamaneurol.2017.0244

JAMA Neurology | Original Investigation

Evaluation of Amyloid Protective Factors and Alzheimer Disease Neurodegeneration Protective Factors in Elderly Individuals

Prashanthi Vemuri, PhD; David S. Knopman, MD; Timothy G. Lesnick, MS; Scott A. Przybelski, BS; Michelle M. Mielke, PhD; Jonathan Graff-Radford, MD; Melissa E. Murray, PhD; Rosebud O. Roberts, MB, ChB, MS; Maria Vassilaki, MD, MPH, PhD; Val J. Lowe, MD; Mary M. Machulda, PhD; David T. Jones, MD; Ronald C. Petersen, MD, PhD; Clifford R. Jack Jr, MD

DESIGN, SETTING, AND PARTICIPANTS This cohort study conducted a prospective analysis of 942 elderly individuals (70-≥90 years) with magnetic resonance imaging and Pittsburgh compound B–positron emission tomography scans enrolled in the Mayo Clinic Study of Aging, a longitudinal population-based study of cognitive aging in Olmsted County, Minnesota.

Table 2. Characteristics by Amyloid and Neurodegeneration Status for Continuous Variables and Categorical Variables

Characteristic	A−N− (n = 277)	A−N+ (n = 142)	A+N− (n = 274)	A+N+ (n = 249)	*P* Value[a] A− vs A+	*P* Value[a] N− vs N+
Intellectual enrichment, mean (SD)						
Education, y	14.5 (2.9)	14.1 (3.0)	14.5 (2.8)	14.1 (2.8)	.68	.14
Job score	3.2 (1.5)	3.3 (1.4)	3.4 (1.5)	3.1 (1.4)	.75	.19
Midlife cognitive activities	20.6 (9.4)	20.5 (9.5)	21.0 (8.5)	21.1 (9.6)	.68	.49
Midlife risk factors						
Physical inactivity, mean (SD)	11.6 (4.3)	11.8 (4.6)	11.8 (4.5)	12.0 (4.8)	.59	.52
Obesity, No. (%)	92 (33)	45 (32)	80 (29)	94 (38)	.11	<.001
Ever smoked, No. (%)	128 (46)	78 (55)	126 (46)	119 (48)	.49	.02
Diabetes, No. (%)	16 (6)	11 (8)	19 (7)	16 (6)	.64	.12
Hypertension, No. (%)	111 (40)	58 (41)	102 (37)	100 (40)	.96	.07
Dyslipidemia, No. (%)	153 (55)	87 (61)	184 (67)	130 (52)	.07	.10

➔**The "classical" AD risk factors (low education, midlife cardiovascular disease and smoking) do not confer risk of amyloid pathology, and thus not for Alzheimer's disease**

Drug treatment of Alzheimer's disease

➔ **Symptomatic drugs / cognitive enhancers**

– improve symptoms but no effects on progression of pathology or neurodegeneration

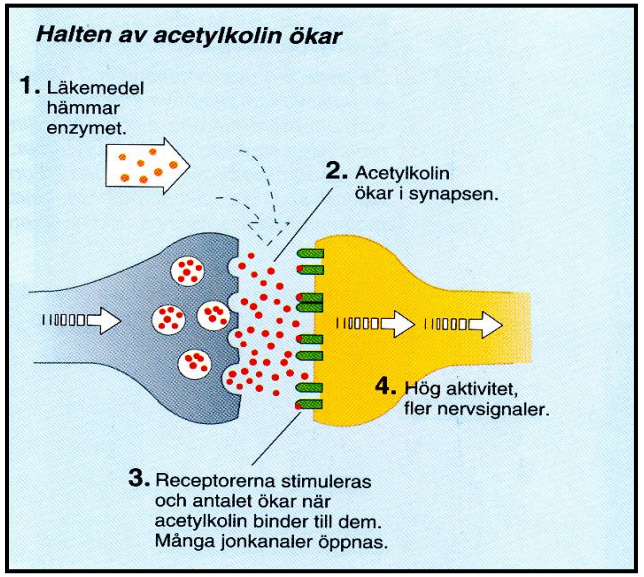
➔ **Disease-modyfing drugs**

- designed to target a specific pathophysiology / pathology
- no short-term symptomatic effect, but slowing of progression
- marked focus on anti-amyloid drugs, but recently also on tau

Symptomatic drugs/cognitive enhancers

Acetylcholinesterase inhibitor

- Improves cognition (no effect on underlying disease)
- Mild to moderate AD dementia
- *E.g.*, donepezil, rivastigmine and galantamine



Partial NMDA receptor antagonist

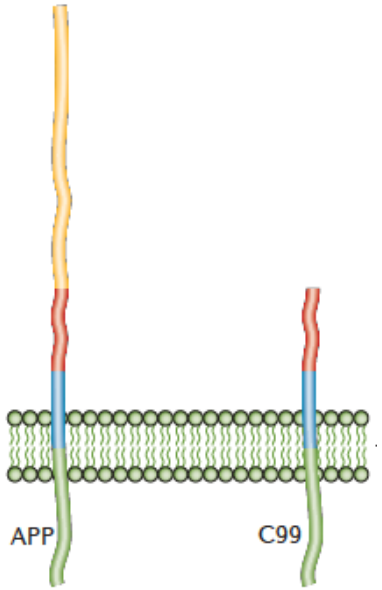
- Moderate to severe AD dementia
- Memantine

Nature Rev Dis Primers 2015:15056

PRIMER

Alzheimer's disease

Colin L. Masters[1], Randall Bateman[2], Kaj Blennow[3], Christopher C. Rowe[4], Reisa A. Sperling[5,6] and Jeffrey L. Cummings[7]



➔ **Several anti-amyloid have been tested and are in late stage clinical trials**

γ-Secretase inhibitor treatment for Alzheimer's mice

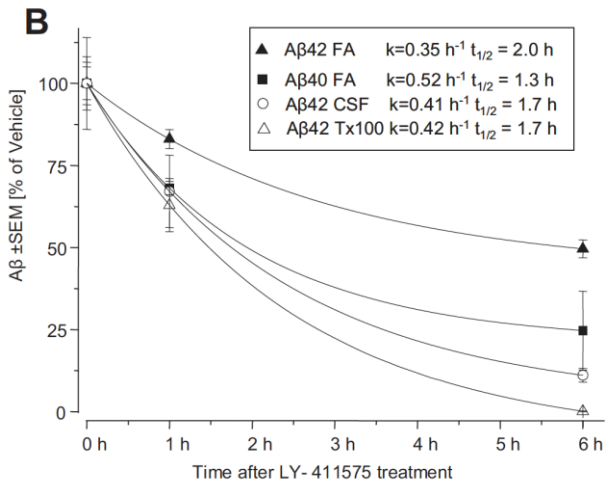
0022-3565/08/3272-411–424$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 2008 by The American Society for Pharmacology and Experimental Therapeutics
JPET 327:411–424, 2008
Vol. 327, No. 2
140327/3395142
Printed in U.S.A.

Dynamics of Aβ Turnover and Deposition in Different β-Amyloid Precursor Protein Transgenic Mouse Models Following γ-Secretase Inhibition[S]

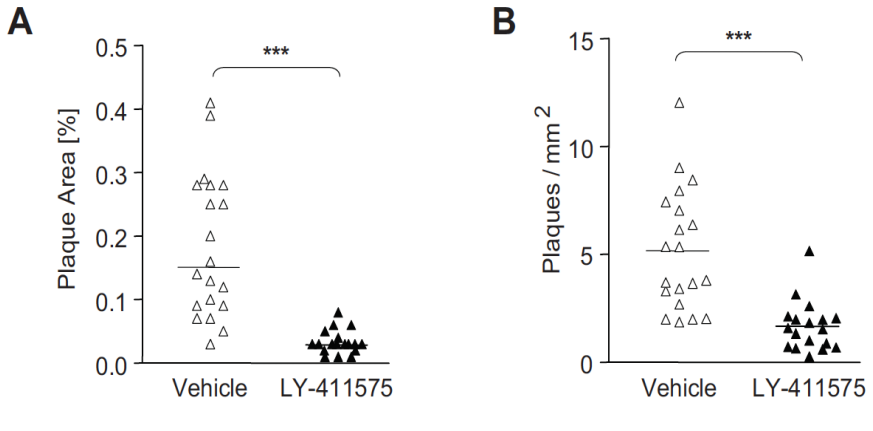
Dorothee Abramowski, Karl-Heinz Wiederhold, Ulrich Furrer, Anne-Lise Jaton, Anton Neuenschwander, Marie-Josephine Runser, Simone Danner, Julia Reichwald, Domenico Ammaturo, Dieter Staab, Markus Stoeckli, Heinrich Rueeger, Ulf Neumann, and Matthias Staufenbiel

APP24 mice (hAPP, Swedish, and London mutations)
LY-411575 = semagacestat

Acute treatment



9 months of treatment



➔ **Dose-dependent reduction in brain and CSF amyloid levels**
➔ **Marked (80%) reductions in amyloid plaque counts**

γ-Secretase inhibitor treatment for Alzheimer patients

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2013;369:341-50.

ORIGINAL ARTICLE

A Phase 3 Trial of Semagacestat for Treatment of Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Rema Raman, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Feng He, M.S., Xiaoying Sun, M.S., Ronald G. Thomas, Ph.D., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Gopalan Sethuraman, Ph.D., and Richard Mohs, Ph.D., for the Semagacestat Study Group

METHODS

We conducted a double-blind, placebo-controlled trial in which 1537 patients with probable Alzheimer's disease underwent randomization to receive 100 mg of semagacestat, 140 mg of semagacestat, or placebo daily. Changes in cognition from baseline to week 76 were assessed with the use of the cognitive subscale of the Alzheimer's Disease Assessment Scale for cognition (ADAS-cog), on which scores range from 0 to 70 and higher scores indicate greater cognitive impairment, and changes in functioning were assessed with the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale, on which scores range from 0 to 78 and higher scores indicate better functioning. A mixed-model repeated-measures analysis was used.

Table 2. Estimated Mean Change from Baseline for the Coprimary and Secondary Outcomes, According to a Mixed-Model Repeated-Measures Analysis.*

Outcome	Placebo	Semagacestat, 100 mg	Semagacestat, 140 mg	P Values	
				Semagacestat, 100 mg, vs. Placebo	Semagacestat, 140 mg, vs. Placebo
ADAS-cog score				0.15	0.07
No. of participants with results	486	483	497		
Mean change in score (95% CI)	6.4 (5.48 to 7.40)	7.5 (6.44 to 8.53)	7.8 (6.72 to 8.85)		
ADCS–ADL†				0.14	<0.001
No. of participants with results	480	481	490		
Mean change in score (95% CI)	−9.0 (−10.37 to −7.67)	−10.5 (−11.94 to −9.07)	−12.6 (−14.1 to −11.2)		
CDR-SB‡				0.06	<0.01
No. of participants with results	485	480	494		
Mean change in score (95% CI)	2.4 (2.06 to 2.67)	2.8 (2.47 to 3.13)	3.1 (2.73 to 3.41)		
NPI§				0.28	0.05
No. of participants with results	473	463	472		
Mean change in score (95% CI)	1.9 (0.69 to 3.12)	2.9 (1.58 to 4.21)	3.7 (2.36 to 5.08)		
MMSE				0.23	0.03
No. of participants with results	400	328	303		
Mean change in score (95% CI)	−3.4 (−3.95 to −2.86)	−3.9 (−4.51 to −3.30)	−4.3 (−4.99 to −3.68)		

CONCLUSIONS

As compared with placebo, semagacestat did not improve cognitive status, and patients receiving the higher dose had significant worsening of functional ability. Semagacestat was associated with more adverse events, including skin cancers and infections. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT00594568.)

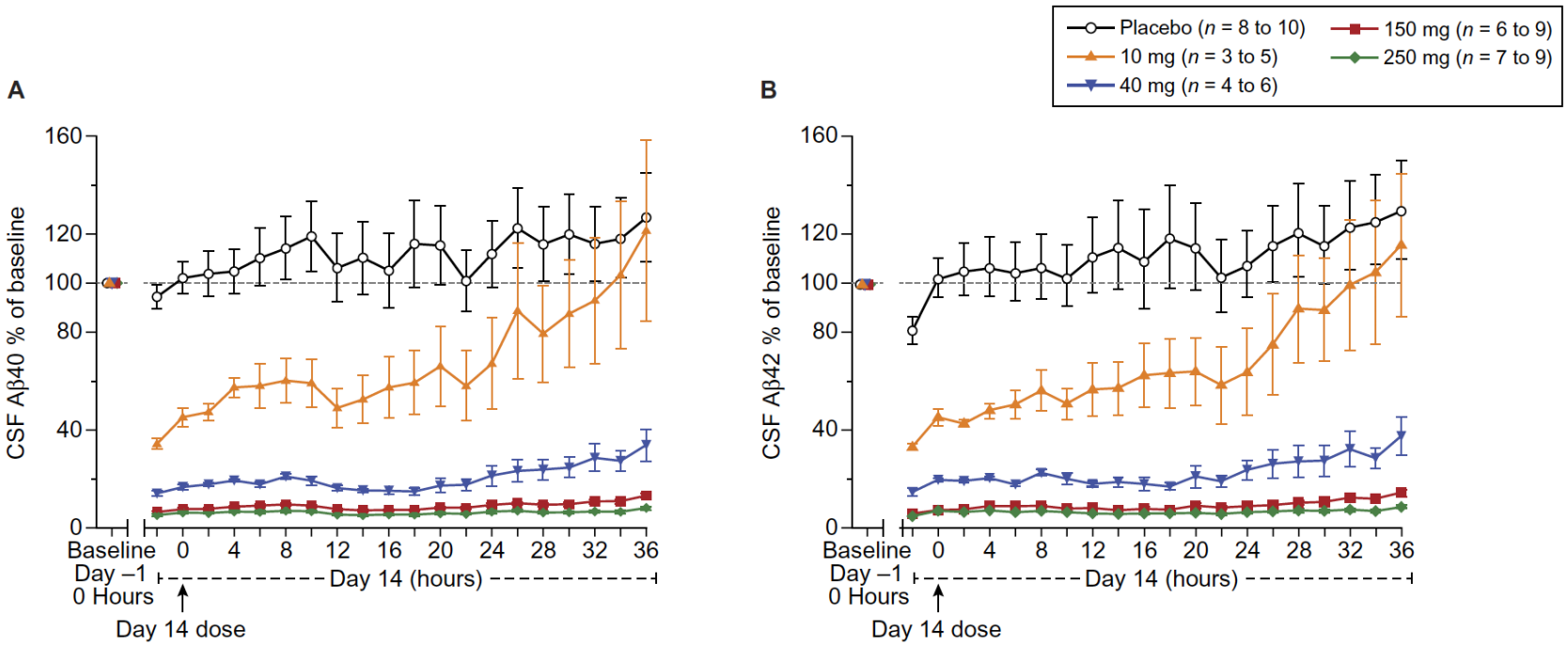
➔ **Evidence of target engagement and amyloid plaque removal in mice**
may not directly translate to disease-modifying effect / clinical benefit in AD patients

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ALZHEIMER'S DISEASE

The BACE1 inhibitor verubecestat (MK-8931) reduces CNS β-amyloid in animal models and in Alzheimer's disease patients

Matthew E. Kennedy,[1]* Andrew W. Stamford,[2]* Xia Chen,[1] Kathleen Cox,[3] Jared N. Cumming,[2] Marissa F. Dockendorf,[3] Michael Egan,[4] Larry Ereshefsky,[5] Robert A. Hodgson,[1†] Lynn A. Hyde,[1] Stanford Jhee,[5] Huub J. Kleijn,[3‡] Reshma Kuvelkar,[1] Wei Li,[2] Britta A. Mattson,[6] Hong Mei,[3] John Palcza,[7] Jack D. Scott,[2] Michael Tanen,[8] Matthew D. Troyer,[9§] Jack L. Tseng,[9¶] Julie A. Stone,[3] Eric M. Parker,[1]* Mark S. Forman[9]*



➔ **Dose-dependent marked reduction in β-amyloid production with BACE1 inhibitor treatment**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer's Disease

Michael F. Egan, M.D., James Kost, Ph.D., Pierre N. Tariot, M.D., Paul S. Aisen, M.D., Jeffrey L. Cummings, M.D., Sc.D., Bruno Vellas, M.D., Ph.D., Cyrille Sur, Ph.D., Yuki Mukai, M.D., Tiffini Voss, M.D., Christine Furtek, B.S., Erin Mahoney, B.A., Lyn Harper Mozley, Ph.D., Rik Vandenberghe, M.D., Ph.D., Yi Mo, Ph.D., and David Michelson, M.D.

METHODS

We conducted a randomized, double-blind, placebo-controlled, 78-week trial to evaluate verubecestat at doses of 12 mg and 40 mg per day, as compared with placebo, in patients who had a clinical diagnosis of mild-to-moderate Alzheimer's disease. The coprimary outcomes were the change from baseline to week 78 in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog; scores range from 0 to 70, with higher scores indicating worse dementia) and in the score on the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory scale (ADCS-ADL; scores range from 0 to 78, with lower scores indicating worse function).

RESULTS

A total of 1958 patients underwent randomization; 653 were randomly assigned to receive verubecestat at a dose of 12 mg per day (the 12-mg group), 652 to receive verubecestat at a dose of 40 mg per day (the 40-mg group), and 653 to receive matching placebo. The trial was terminated early for futility 50 months after onset, which was within 5 months before its scheduled completion, and after enrollment of the planned 1958 patients was complete. The estimated mean change from baseline to week 78 in the ADAS-cog score was 7.9 in the 12-mg group, 8.0 in the 40-mg group, and 7.7 in the placebo group (P=0.63 for the comparison between the 12-mg group and the placebo group and P=0.46 for the comparison between the 40-mg group and the placebo group). The estimated mean change from baseline to week 78 in the ADCS-ADL score was −8.4 in the 12-mg group, −8.2 in the 40-mg group, and −8.9 in the placebo group (P=0.49 for the comparison between the 12-mg group and the placebo group and P=0.32 for the comparison between the 40-mg group and the placebo group). Adverse events, including rash, falls and injuries, sleep disturbance, suicidal ideation, weight loss, and hair-color change, were more common in the verubecestat groups than in the placebo group.

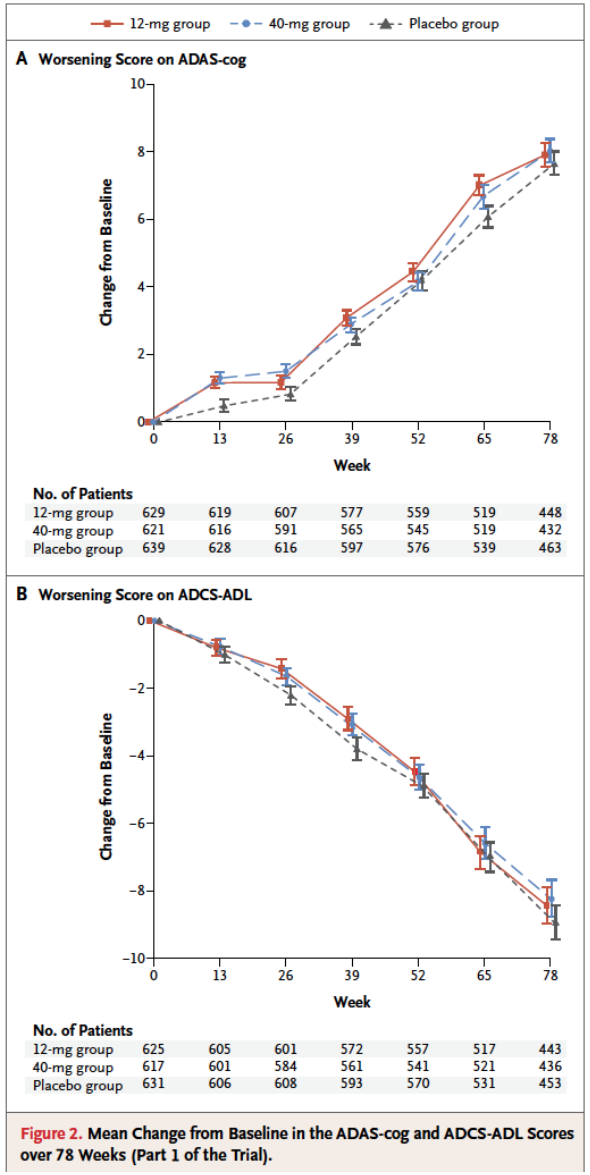


Figure 2. Mean Change from Baseline in the ADAS-cog and ADCS-ADL Scores over 78 Weeks (Part 1 of the Trial).

➔ **Evidence of target engagement may not directly translate to disease-modifying effect / clinical benefit**

Lack of clinical effect and/or side effects (among others, cognitive worsening) have made researchers and companies afraid of gamma- and beta-secretase as drug targets

Two (at least) options remain viable and in need of further study:

1. gamma-Secretase modulation (e.g., reduce Abeta42, increase Abeta38 without influencing overall gamma-secretase activity)

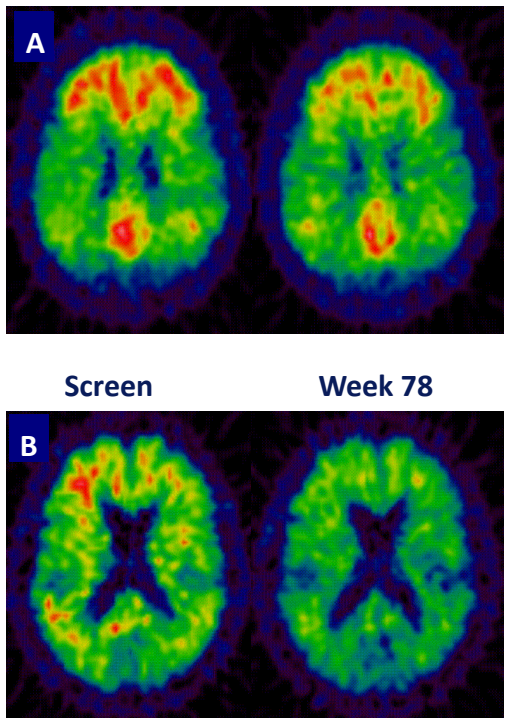
2. Low-dose BACE1 inhibition (not 70-90% inhibition but maybe 20-30%?)

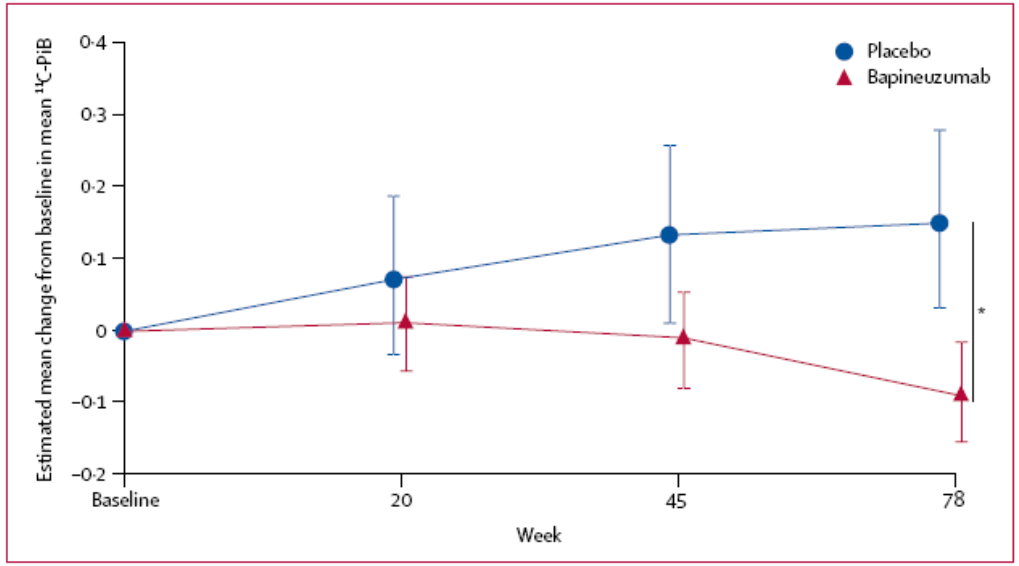
Both have strong support from genetics, as primary prevention strategies against amyloid build-up in the brain and Alzheimer's disease

Lancet Neurol 2010; 9: 363–72

^{11}C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study

Juha O Rinne, David J Brooks, Martin N Rossor, Nick C Fox, Roger Bullock, William E Klunk, Chester A Mathis, Kaj Blennow, Jerome Barakos, Aren A Okello, Sofia Rodriguez Martinez de Llano, Enchi Liu, Martin Koller, Keith M Gregg, Dale Schenk, Ronald Black, Michael Grundman





➔ Treatment with β-amyloid antibodies
may reduce plaque load in Alzheimer patients

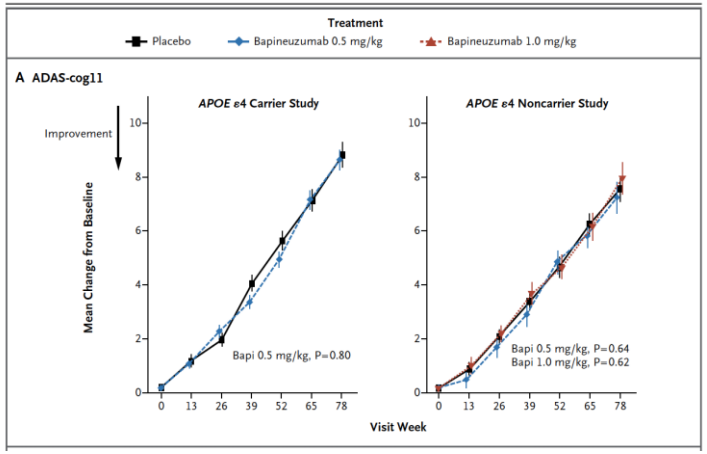
The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2014;370:322-33.
ORIGINAL ARTICLE

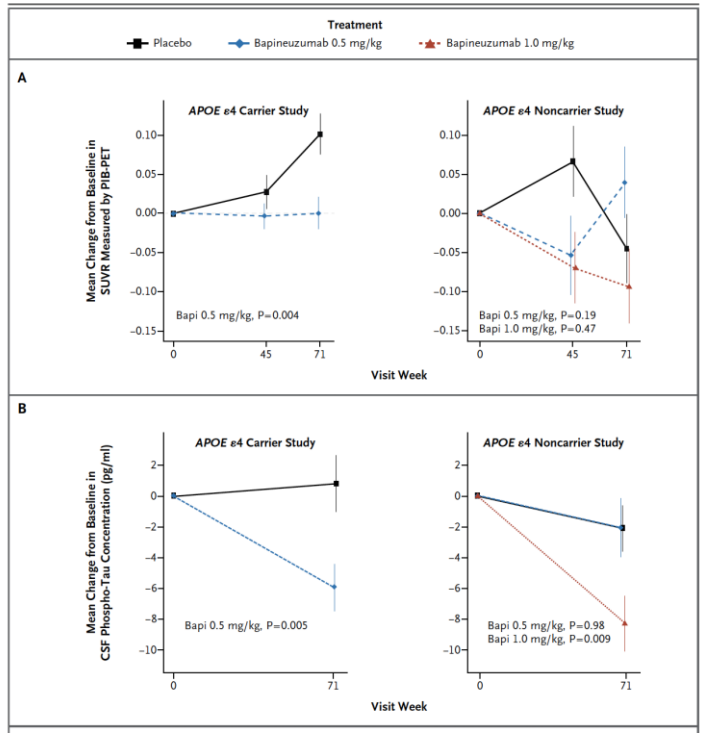
Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

Stephen Salloway, M.D., Reisa Sperling, M.D., Nick C. Fox, M.D., Kaj Blennow, M.D., William Klunk, M.D., Murray Raskind, M.D., Marwan Sabbagh, M.D., Lawrence S. Honig, M.D., Ph.D., Anton P. Porsteinsson, M.D., Steven Ferris, Ph.D., Marcel Reichert, M.D., Nzeera Ketter, M.D., Bijan Nejadnik, M.D., Volkmar Guenzler, M.D., Maja Miloslavsky, Ph.D., Daniel Wang, Ph.D., Yuan Lu, M.S., Julia Lull, M.A., Iulia Cristina Tudor, Ph.D., Enchi Liu, Ph.D., Michael Grundman, M.D., M.P.H., Eric Yuen, M.D., Ronald Black, M.D., and H. Robert Brashear, M.D., for the Bapineuzumab 301 and 302 Clinical Trial Investigators*

METHODS

We conducted two double-blind, randomized, placebo-controlled, phase 3 trials involving patients with mild-to-moderate Alzheimer's disease — one involving 1121 carriers of the apolipoprotein E (*APOE*) ε4 allele and the other involving 1331 noncarriers. Bapineuzumab or placebo, with doses varying by study, was administered by intravenous infusion every 13 weeks for 78 weeks. The primary outcome measures were scores on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11, with scores ranging from 0 to 70 and higher scores indicating greater impairment) and the Disability Assessment for Dementia (DAD, with scores ranging from 0 to 100 and higher scores indicating less impairment). A total of 1090 carriers and 1114 noncarriers were included in the efficacy analysis. Secondary outcome measures included findings on positron-emission tomographic amyloid imaging with the use of Pittsburgh compound B (PIB-PET) and cerebrospinal fluid phosphorylated tau (phospho-tau) concentrations.





➔ Treatment with the β-amyloid antibody bapineuzumab did not improve cognition, but effects on amyloid load and CSF P-tau suggest minor disease-modifying effect

ARTICLE

doi:10.1038/nature19323

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

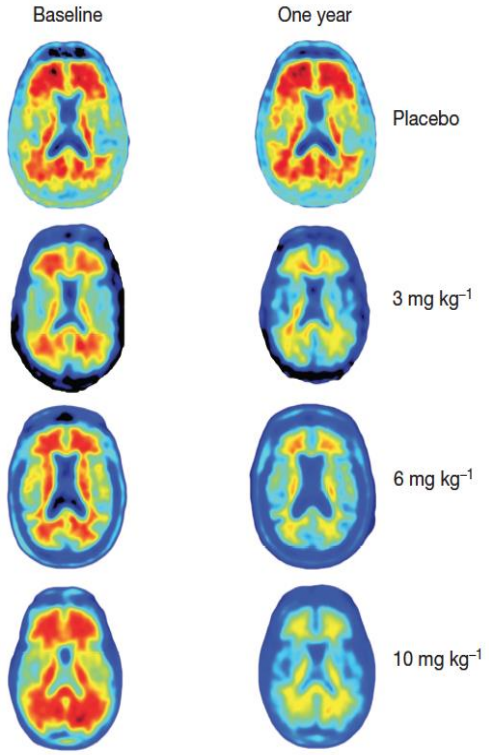
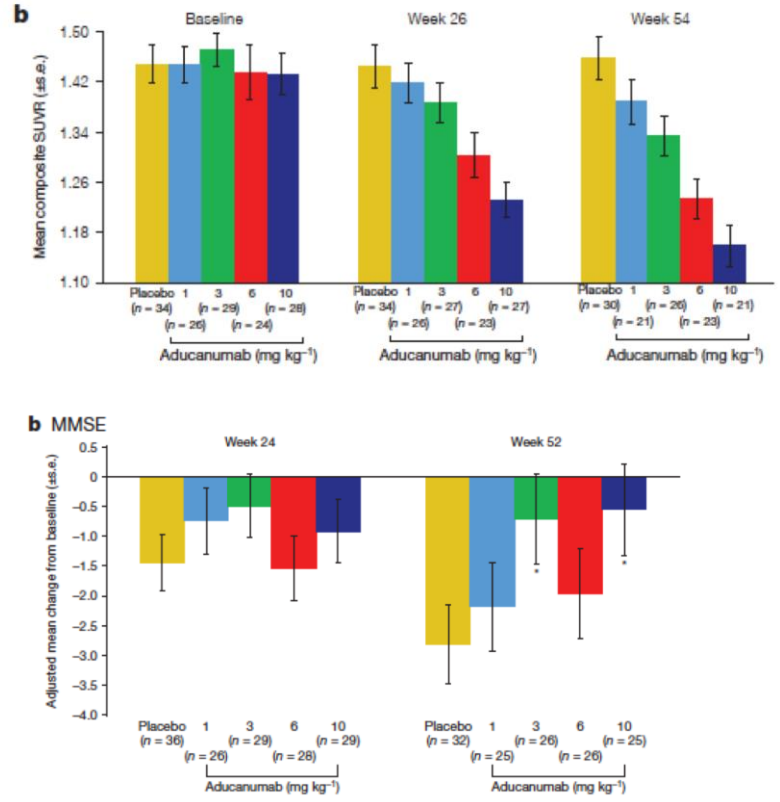


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54.



- ➔ **Reduction in amyloid PET clearly indicates target engagement**
- ➔ **Reduction in neurodegeneration biomarkers needed to support disease-modification**

Biogen Plans Regulatory Filing for Aducanumab in Alzheimer's Disease Based on New Analysis of Larger Dataset from Phase 3 Studies

October 22, 2019 06:30 ET | **Source:** Biogen Inc.

New analysis of larger dataset showed that aducanumab reduced clinical decline in patients with early Alzheimer's disease as measured by the pre-specified primary and secondary endpoints

Based on discussions with the FDA, the Company plans to submit a Biologics License Application in early 2020

Biogen aims to offer aducanumab to eligible patients previously enrolled in clinical studies

The positive results of this new analysis were driven primarily by greater exposure to high dose aducanumab in the larger dataset as compared to data available at the time of the futility analysis

FDA ACCEPTS BIOGEN'S ADUCANUMAB BIOLOGICS LICENSE APPLICATION FOR ALZHEIMER'S DISEASE WITH PRIORITY REVIEW

August 7, 2020 at 7:30 AM EDT

- *Priority Review accelerates FDA review time, with a Prescription Drug User Fee Act (PDUFA) target action on March 7, 2021*
- *If approved, aducanumab would be the first treatment to meaningfully change the course of Alzheimer's disease*

July 6, 2018

BioArctic announces positive topline results of BAN2401 Phase 2b at 18 months in early Alzheimer's Disease

The full 18 month analysis of the 856 patient BAN2401 Phase 2b clinical study in early Alzheimer's disease demonstrated statistically significant and dose-dependent slowing in clinical decline and reduction of amyloid beta accumulated in the brain.

First late-stage study successfully demonstrating potential disease-modifying effects on both clinical function and amyloid beta accumulation in the brain.

Stockholm, Sweden, July 6, 2018 – BioArctic AB (publ) (Nasdaq Stockholm: BIOA B) today announced positive topline results from the Phase 2b study with BAN2401, an anti-amyloid beta protofibril antibody, in 856 patients with early Alzheimer's disease. The study achieved statistical significance on key efficacy endpoints at 18 months on slowing progression in Alzheimer's Disease Composite Score (ADCOMS) and on reduction of amyloid accumulated in the brain as measured by using amyloid-PET (Positron Emission Tomography).

New global Phase 3 program of BAN2401 initiated in preclinical (asymptomatic) Alzheimer's disease

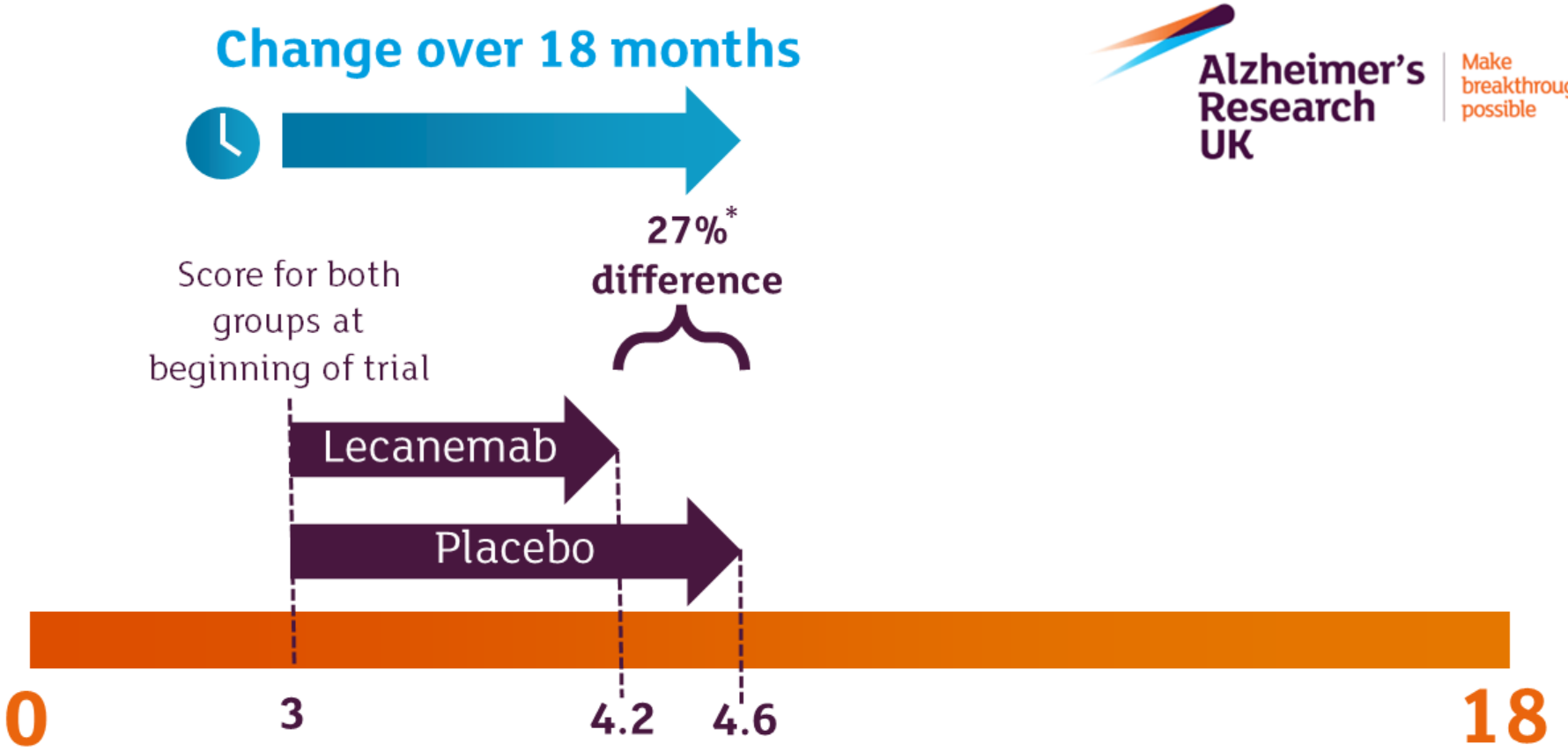
July 14, 2020 - Other press release

Stockholm, July 14, 2020 – BioArctic AB (publ) (Nasdaq Stockholm: BIOA B) announced today that its business partner Eisai, in collaboration with Alzheimer's Clinical Trials Consortium ...

Many other anti-Aβ antibody trials are moving forward

Promising results on biomarkers, less clear on cognition

Lecanemab removes amyloid and shows clinically meaningful benefit



CDR-SB score used to measure cognitive decline – greater score means greater cognitive impairment

**diagram not to scale*

FDA NEWS RELEASE

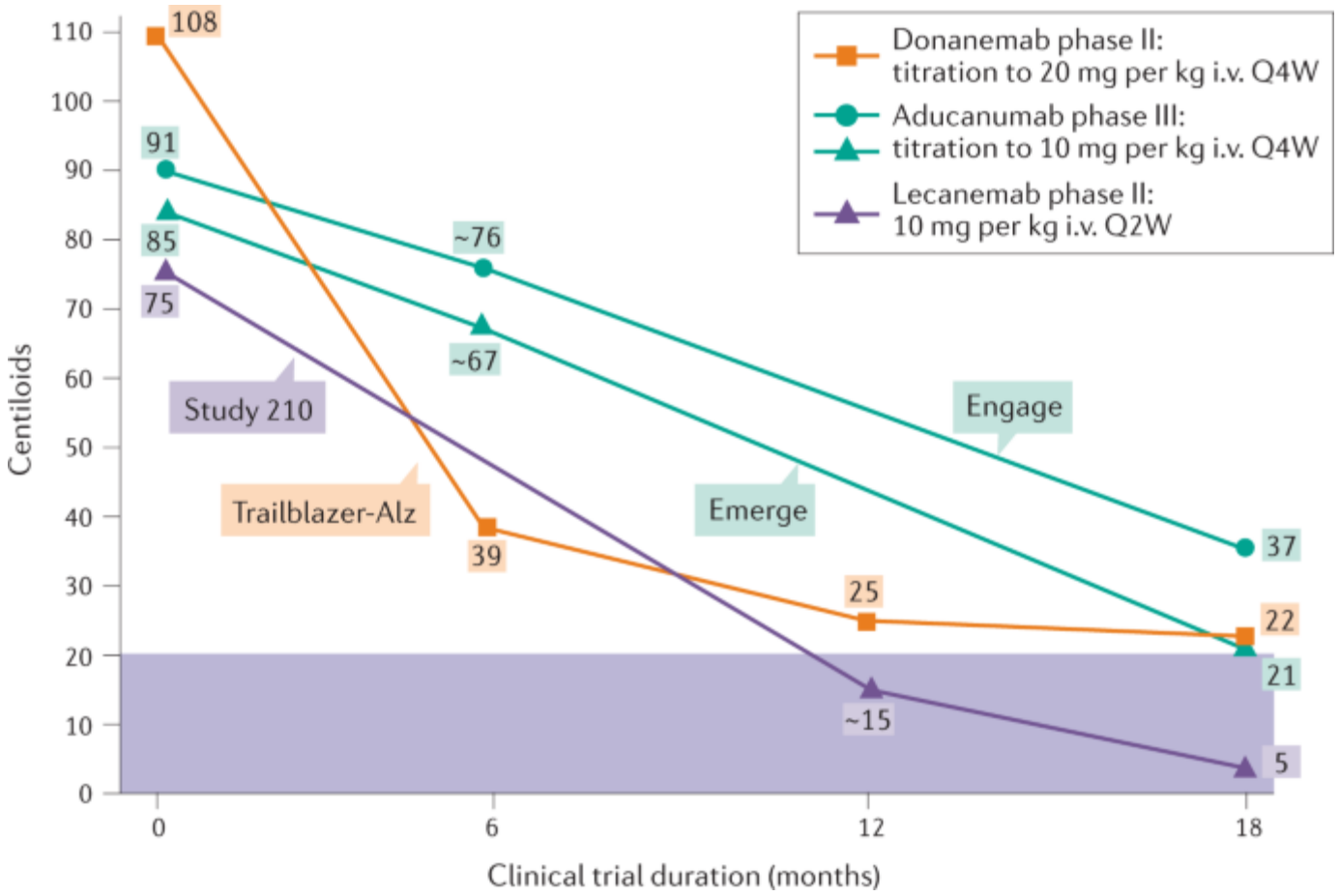
FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval

Action Follows Confirmatory Trial to Verify Clinical Benefit

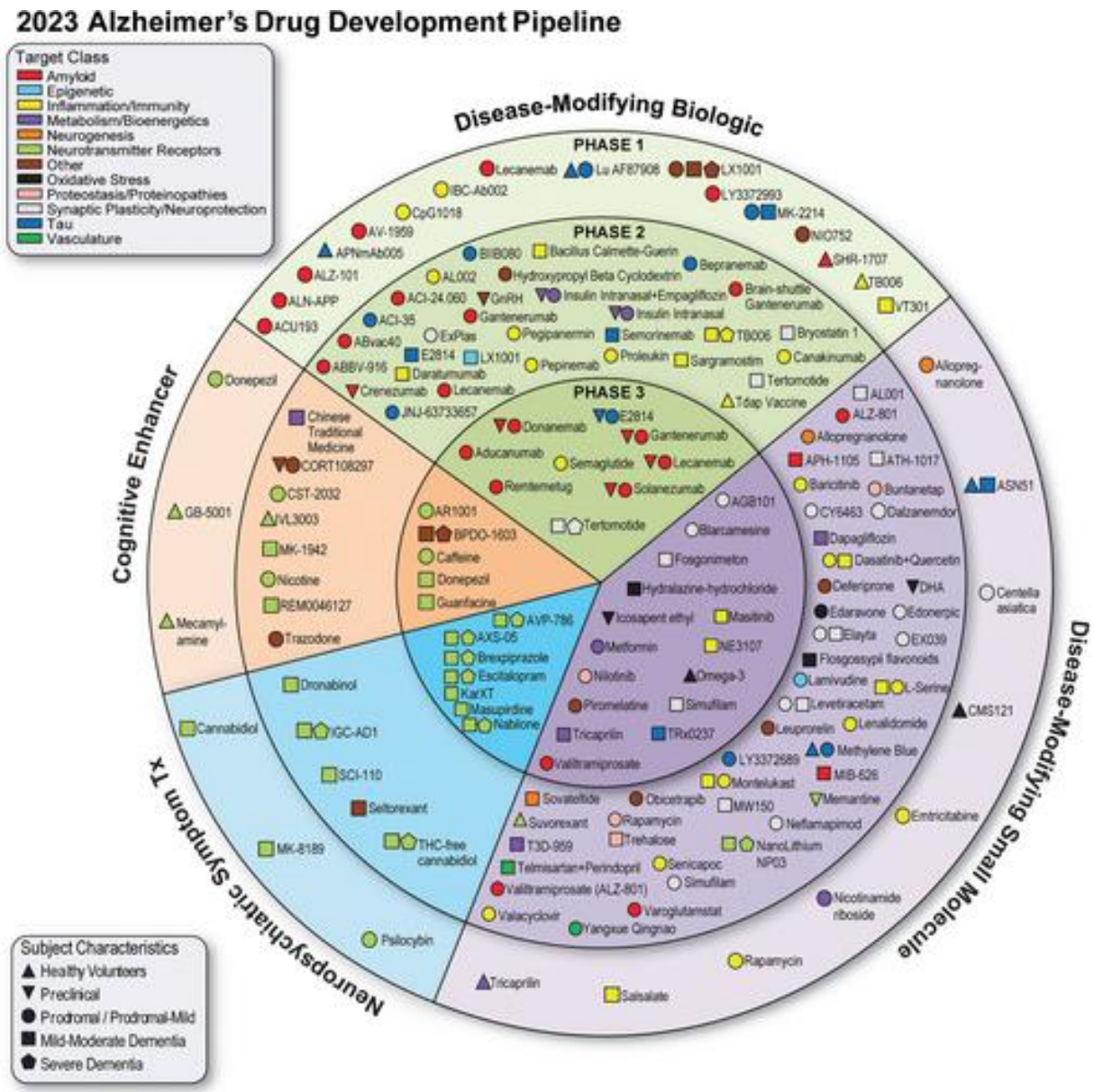
For Immediate Release:

July 06, 2023

Time to significant amyloid removal determines if a drug can show a clinically meaningful effect



Karran & de Strooper 2022



Cummings J: https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.12385

Problems with antibody-based removal of established amyloid pathology:

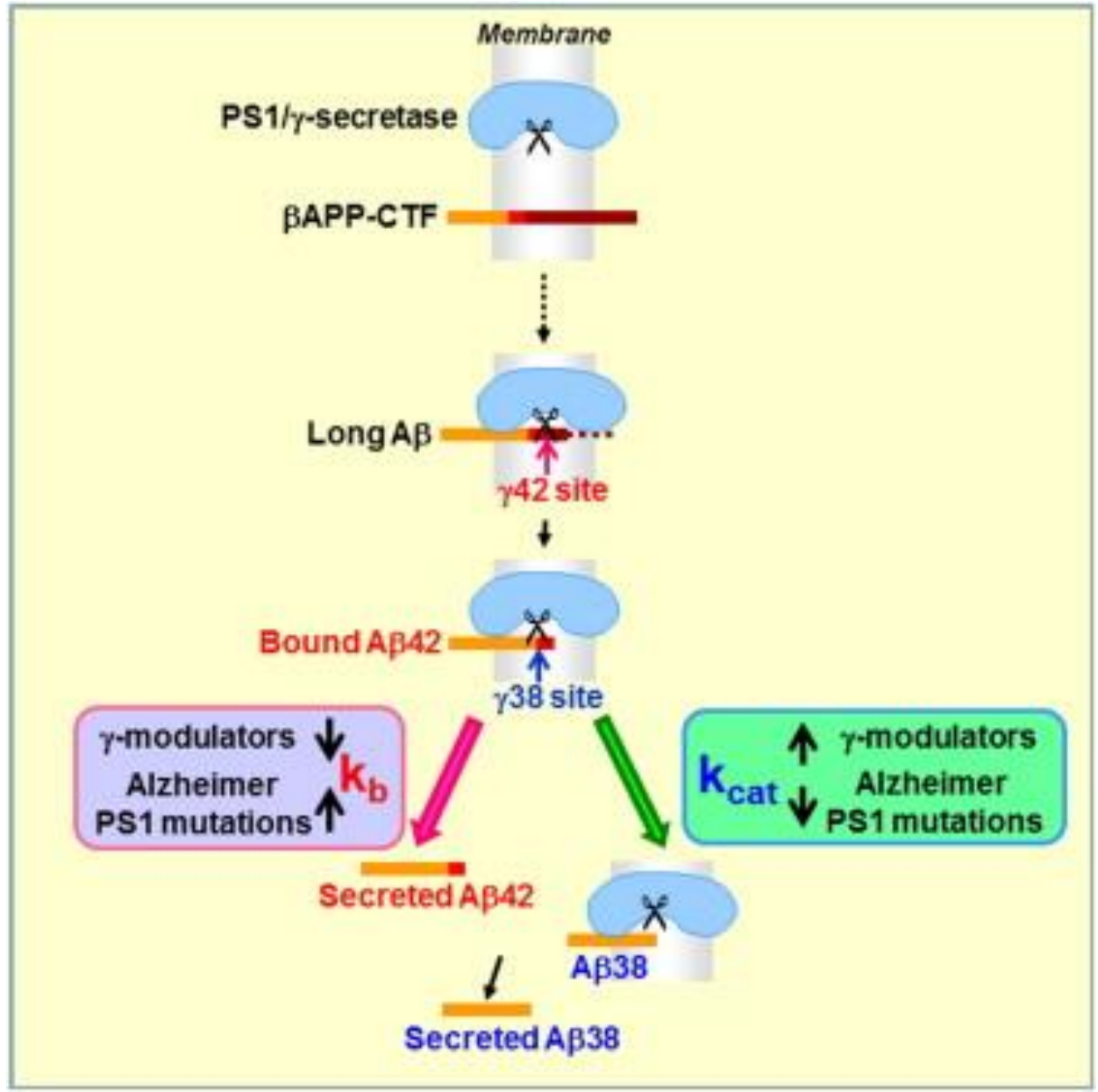
Amyloid-related imaging abnormalities

Expensive

Neuronal network damage may have already occurred

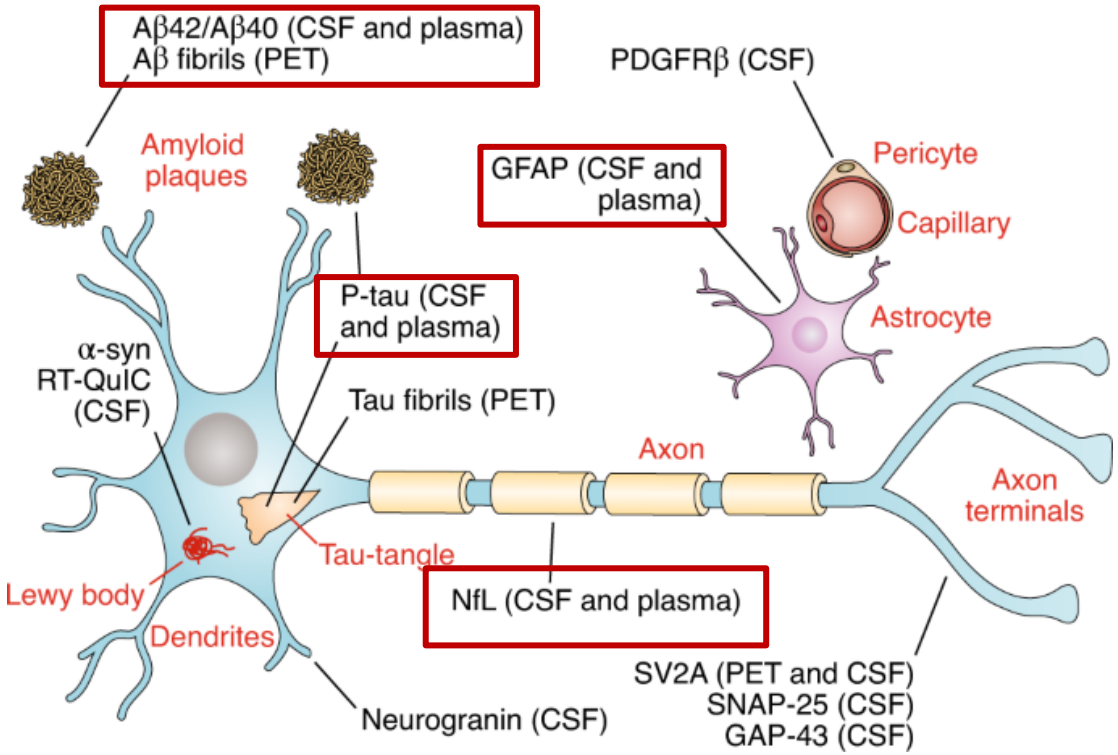
Tau pathology may have taken off

The case for gamma-secretase modulation



Okochi *et al*., 2013

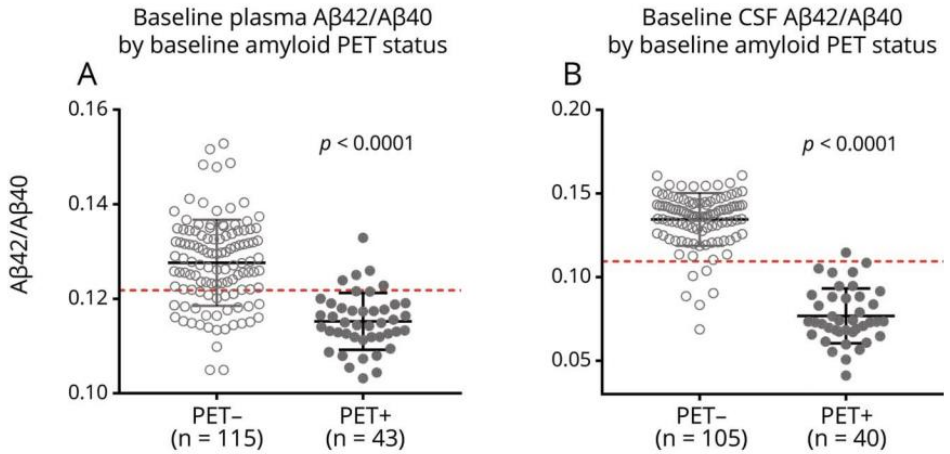
Available targeted protein biomarkers for dementias



Hansson 2022 Nature Medicine (PMID: 34083813)

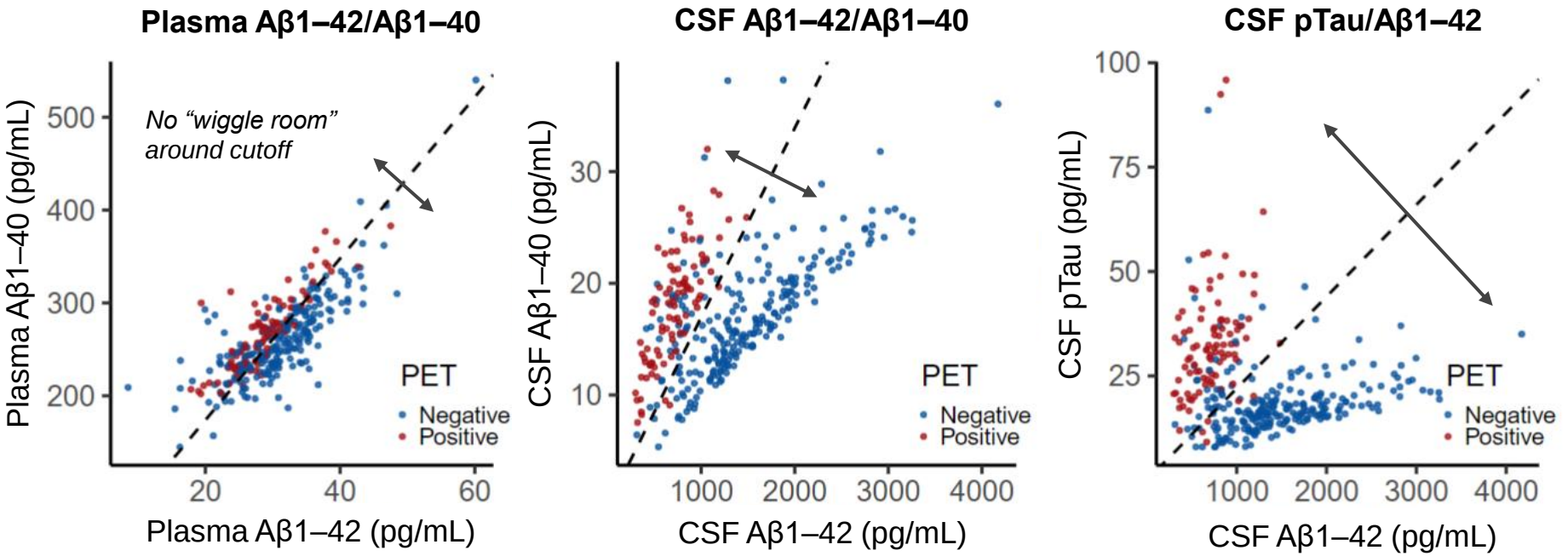
Plasma amyloid β

- The fold changes of plasma Aβ42/40 between PET Aβ+ and PET Aβ- are not large



Karikari, Ashton et al., 2022 Nature Reviews Neurology (PMID: 35585226) / Schindler et al., 2019 Neurology (PMID: 31371569)

Plasma amyloid β

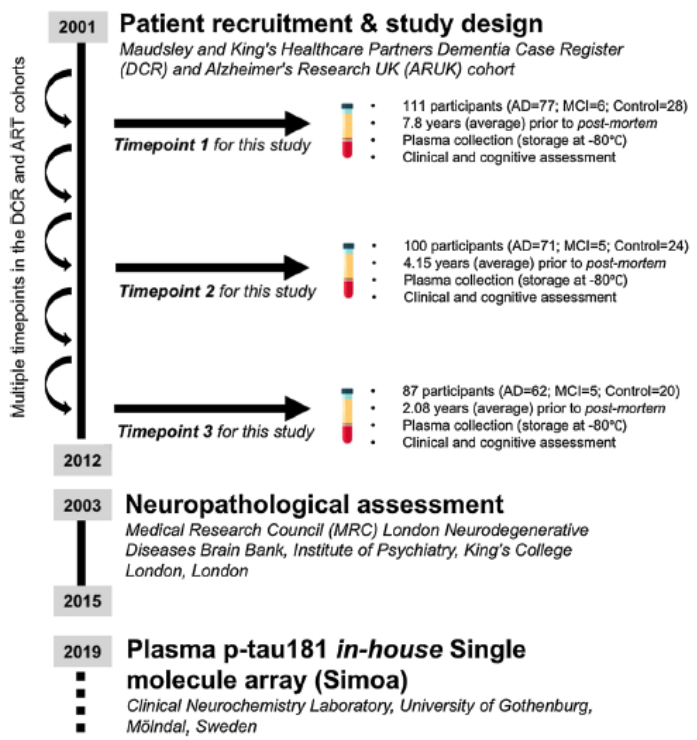


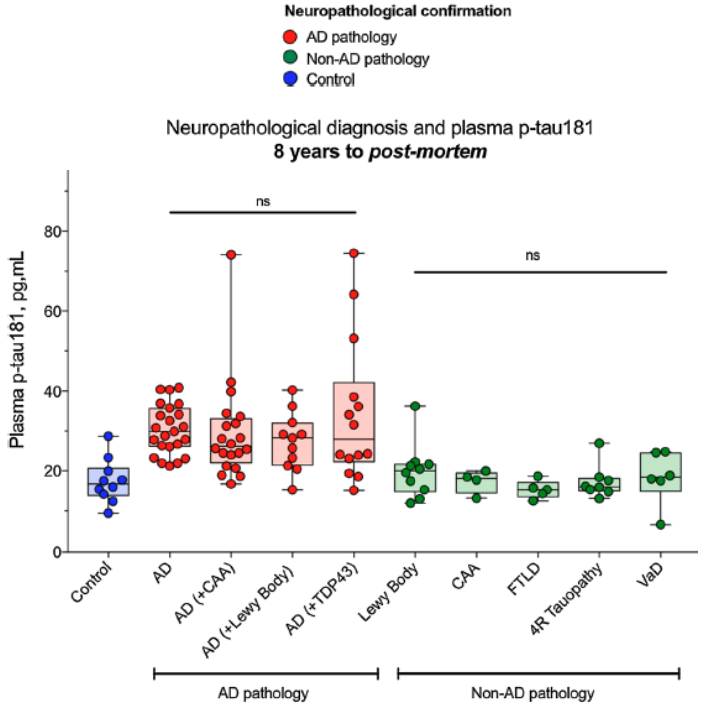
Rabe C *et al*., 2022

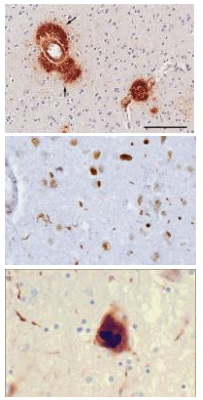
Plasma p-tau indicates AD pathology (including amyloid)

Lantero-Rodriguez et al., 2020 Acta Neuropathologica (PMID: 32720099)

Plasma p-tau indicates AD pathology (including amyloid)





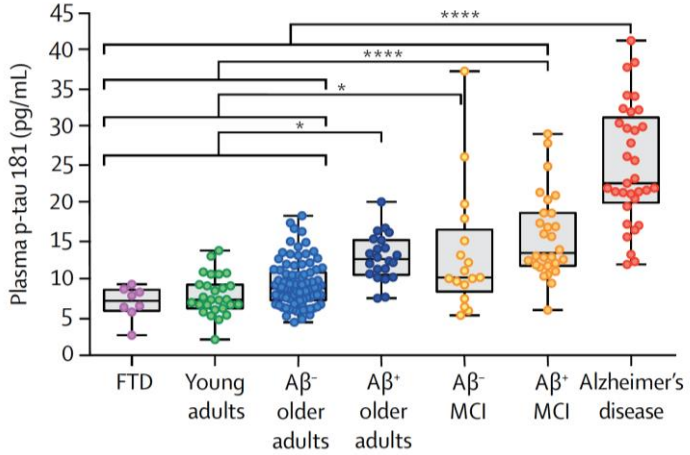


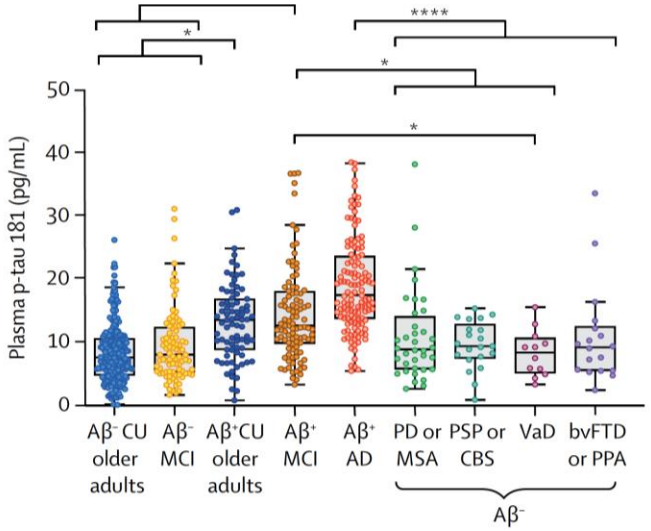
Lantero-Rodriguez et al., 2020 Acta Neuropathologica (PMID: 32720099)

Plasma p-tau in the Alzheimer's disease continuum

Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts

Thomas K Karikari*, Tharick A Pascoal*, Nicholas J Ashton, Shorena Janelidze, Andréa Lessa Benedet, Juan Lantero Rodriguez, Mira Chamoun, Melissa Savard, Min Su Kang, Joseph Therriault, Michael Schöll, Gassan Massarweh, Jean-Paul Soucy, Kina Höglund, Gunnar Brinkmalm, Niklas Mattsson, Sebastian Palmqvist, Serge Gauthier, Erik Stomrud, Henrik Zetterberg, Oskar Hansson†, Pedro Rosa-Neto†, Kaj Blennow†





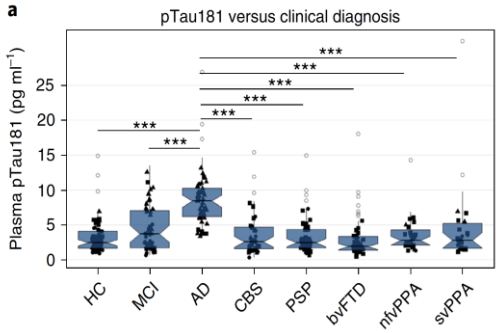
Karikari, Pascoal et al., 2020 Lancet Neurology (PMID: 32333900)

Plasma p-tau in the Alzheimer's disease continuum

nature medicine ARTICLES
https://doi.org/10.1038/s41591-020-0762-2

Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration

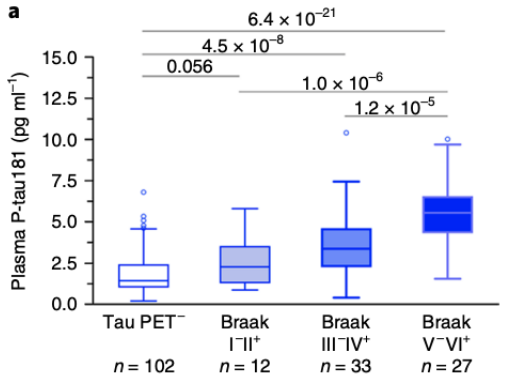
Elisabeth H. Thijssen[1,2], Renaud La Joie[1], Amy Wolf[1], Amelia Strom[1], Ping Wang[1], Leonardo Iaccarino[1], Viktoriya Bourakova[1], Yann Cobigo[1], Hilary Heuer[1], Salvatore Spina[1], Lawren VandeVrede[1], Xiyun Chai[3], Nicholas K. Proctor[3], David C. Airey[3], Sergey Shcherbinin[3], Cynthia Duggan Evans[3], John R. Sims[3], Henrik Zetterberg[4,5,6,7], Kaj Blennow[4,5], Anna M. Karydas[1], Charlotte E. Teunissen[2], Joel H. Kramer[1], Lea T. Grinberg[1,8], William W. Seeley[1,8], Howie Rosen[1], Bradley F. Boeve[9], Bruce L. Miller[1], Gil D. Rabinovici[1,10], Jeffrey L. Dage[3], Julio C. Rojas[1], Adam L. Boxer[1] and Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) investigators*



nature medicine ARTICLES
https://doi.org/10.1038/s41591-020-0755-1

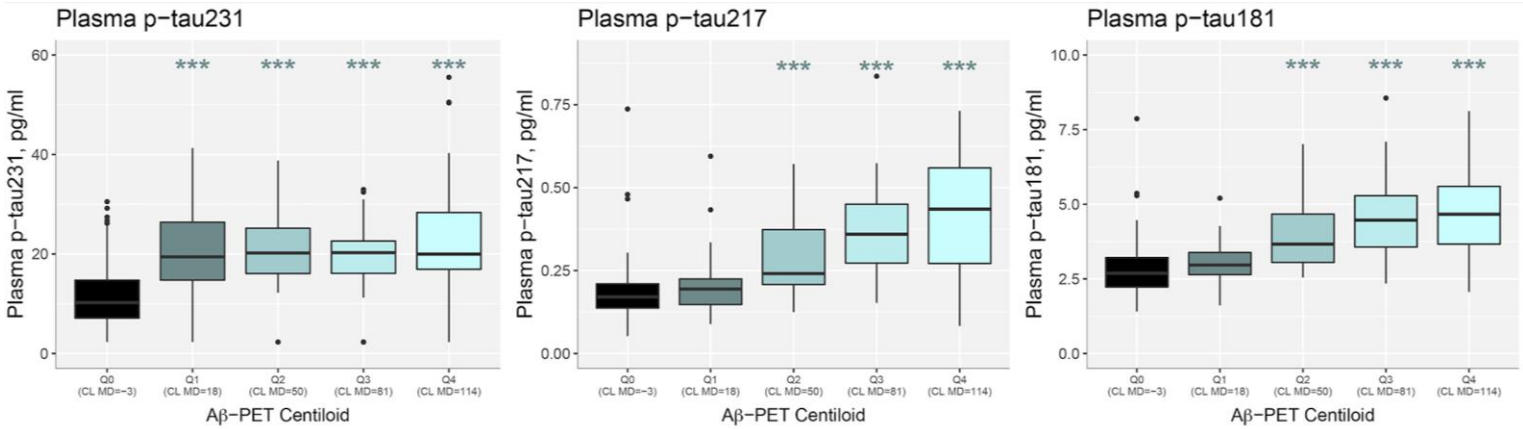
Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia

Shorena Janelidze[1,13]*, Niklas Mattsson[1,2,3,13], Sebastian Palmqvist[1,2], Ruben Smith[1,2], Thomas G. Beach[4], Geidy E. Serrano[4], Xiyun Chai[5], Nicholas K. Proctor[5], Udo Eichenlaub[6], Henrik Zetterberg[7,8,9,10], Kaj Blennow[7,8], Eric M. Reiman[11], Erik Stomrud[1,12], Jeffrey L. Dage[5] and Oskar Hansson[1,12]*



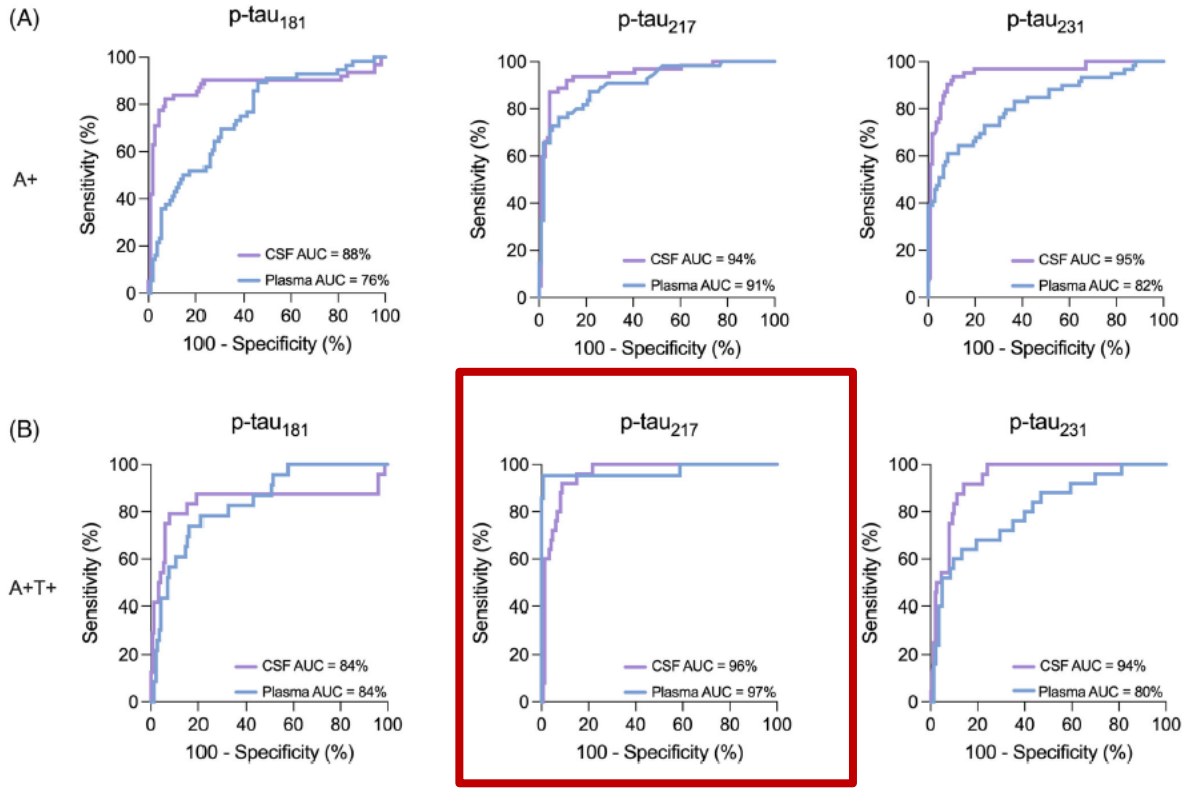
Thijssen et al., 2020 Nature Medicine (PMID: 32123386) / Janelidze et al., 2020 Nature Medicine (PMID: 32123385) / Mielke et al., 2018 Alzheimer's & Dementia (PMID: 29626426)

Different phospho-forms of tau can be measured in plasma



Ashton *et al*., Nature Med. 2022

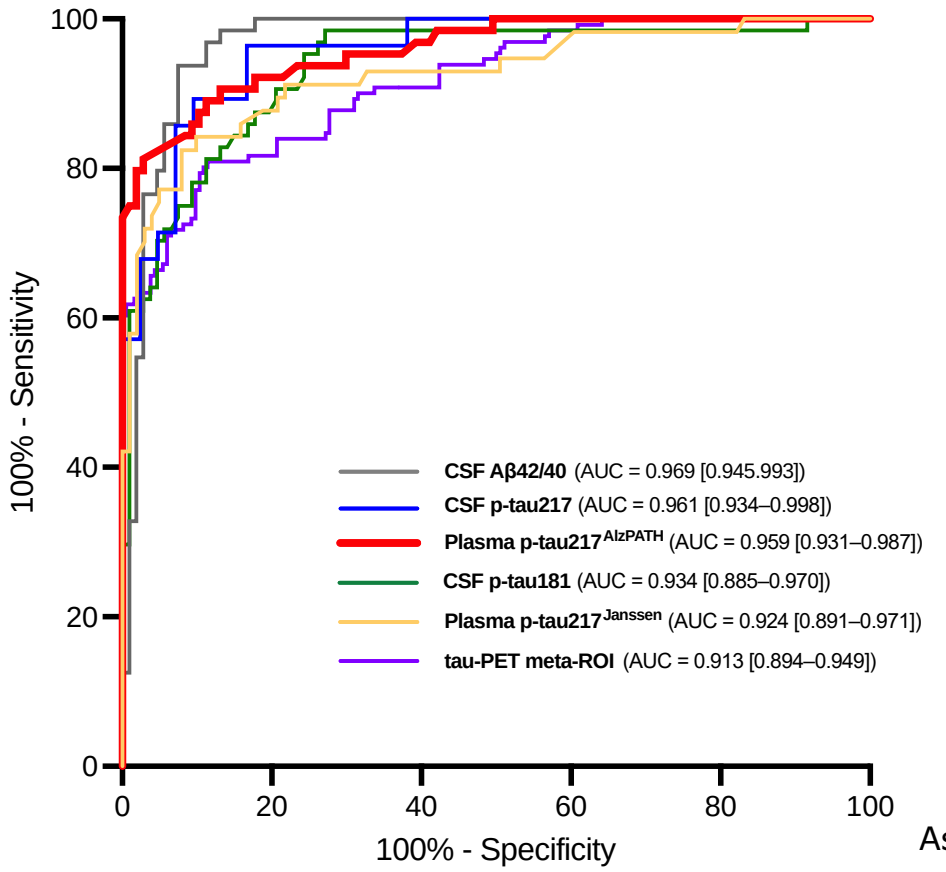
Equivalence of plasma p-tau217 with cerebrospinal fluid in the diagnosis of Alzheimer's disease



Therriault *et al*., A&D, 2023

Plasma p-tau217 to screen for Aβ pathology – results from TRIAD and WRAP

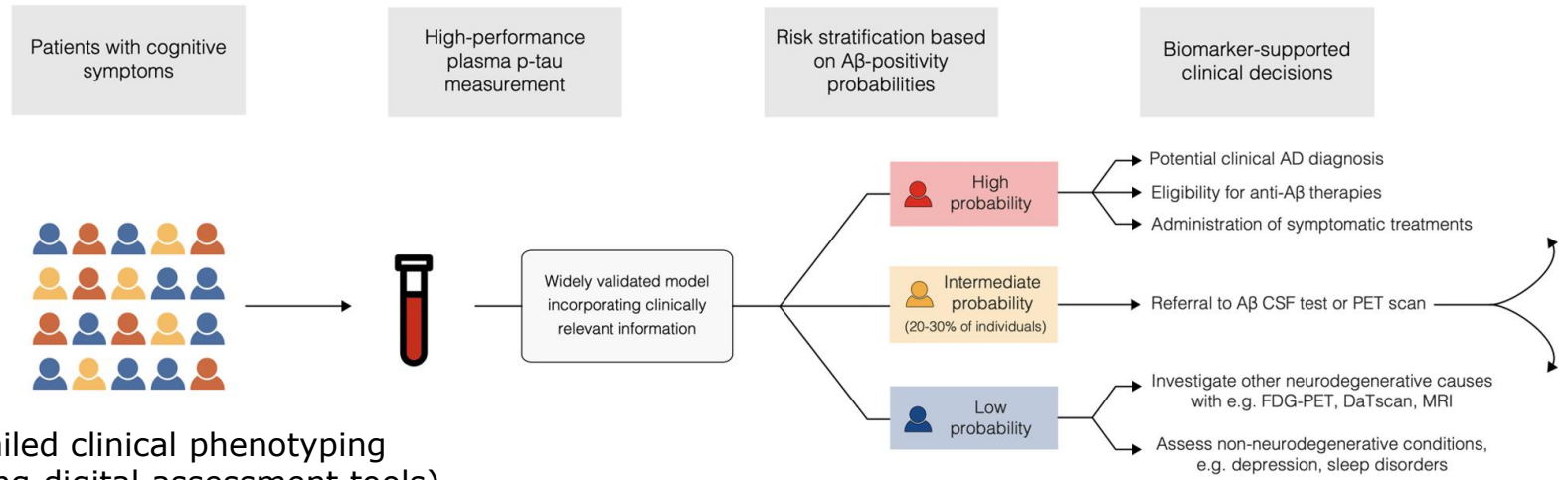
Figure 1A – predicting amyloid PET positivity



Ashton *et al*., JAMA Neurol 2024

A two-step workflow based on plasma p-tau to screen for Aβ pathology

THE SWEDISH BIOFINDER STUDY – a case study in Mild Cognitive Impairment (MCI)

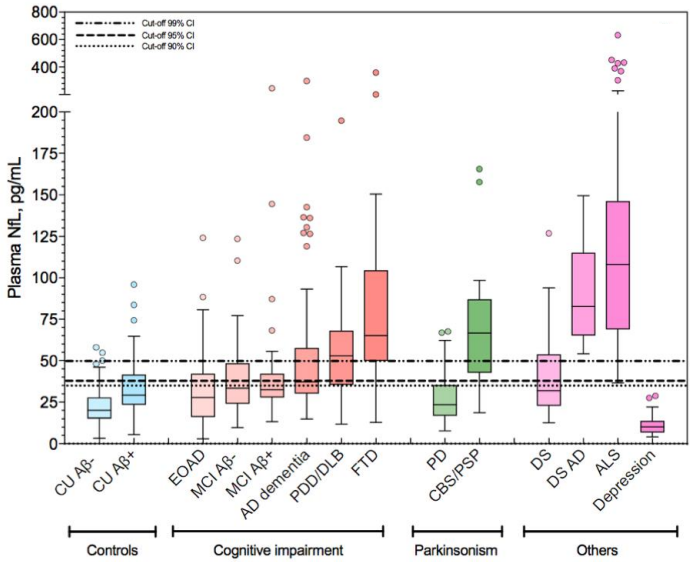


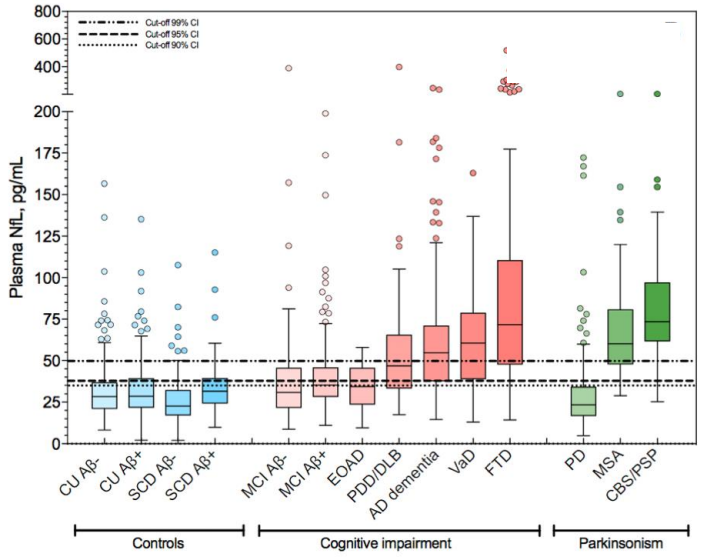
Detailed clinical phenotyping
(including digital assessment tools)

Brum, Cullen et al., *2023*

Plasma neurofilament light

Blood **neurofilament light (NfL)** is a measure of axonal injury irrespective of cause

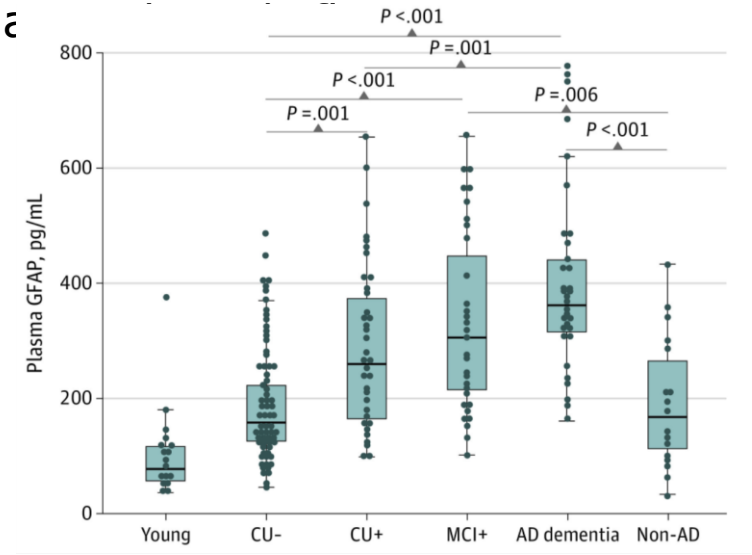


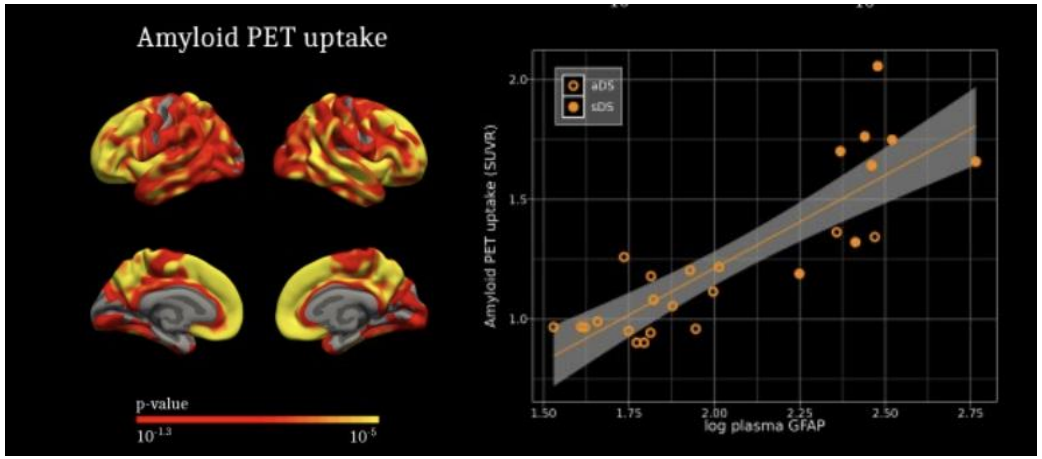


Ashton et al., 2020 Nature Communications (PMID: 34099648)

Plasma glial fibrillary acidic protein

Blood **glial fibrillary acidic protein (GFAP)** is a marker for reactive a





Representative, preliminary results, pending publication in a peer-reviewed journal

Benedet, Milà-Alomà, Vrillon et al., 2021 JAMA Neurology (PMID: 34661615) / Montoliu-Gaya, Alcolea et al., *in review*

Blood spot collection

Nick Ashton
Haley Weninger
Lara Grötschel
Joel Simrén
Hanna Huber
Laia Montoliu-Gaya

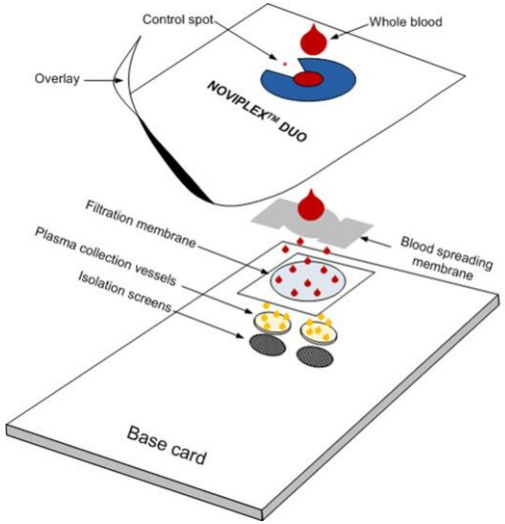
Advantages

- 65uL of whole blood
(no need for centrifugation for plasma).

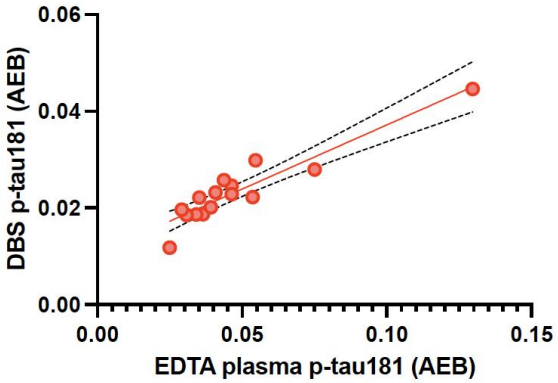
- Stable at room temperature >1-month
(Transferrable by normal post or stored without cooling/freezing)

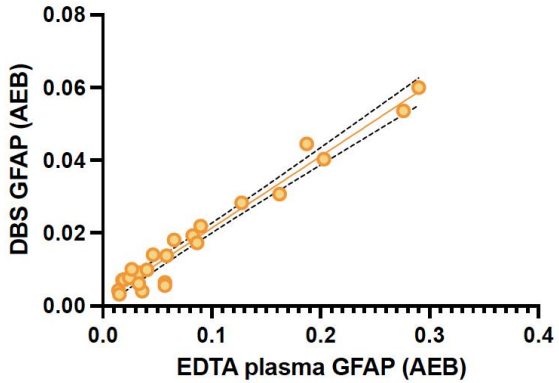
- Capillary blood is possible
(Remote self-collection, paediatric neurology, onset sports injuries, field clinicis)

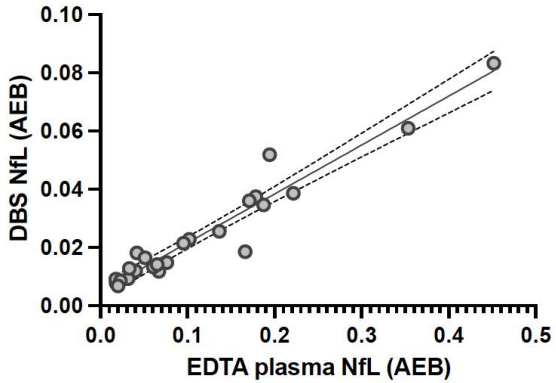
- Dementia biomarkers are measurable by Simoa with a modified extraction protocol



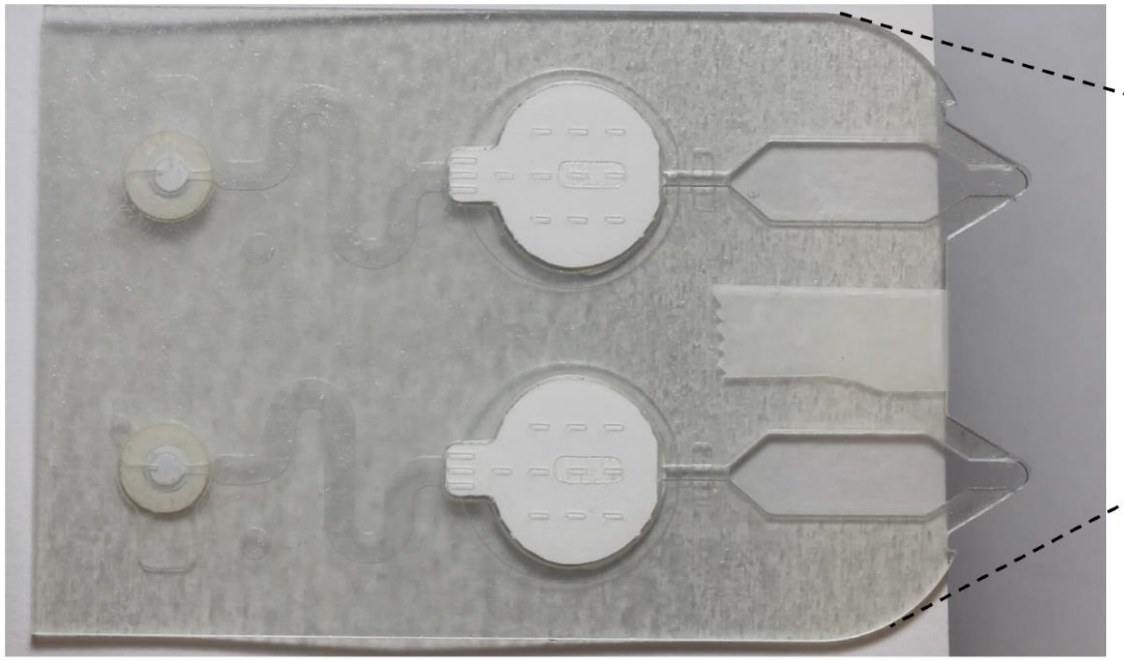
Blood spot collection – venous blood







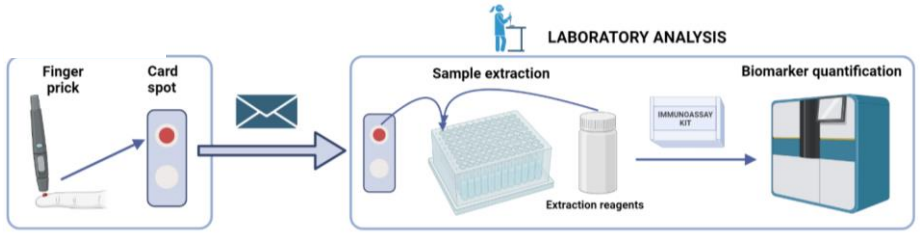
Capitainer®CF

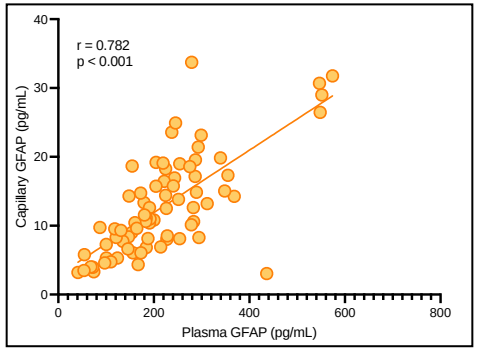


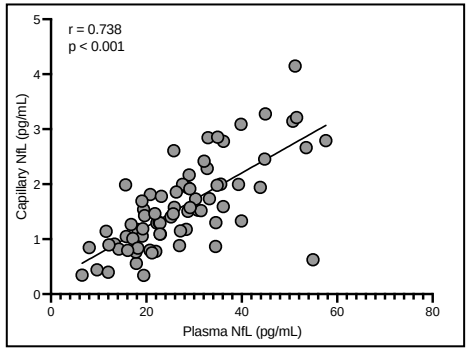
Storage | Metering | Filtration | Pre metering 70 µl

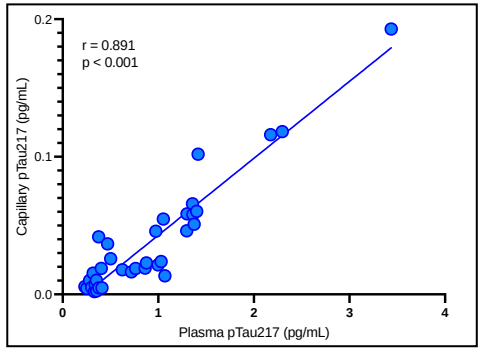
DROP-AD: detecting AD blood biomarkers using a finger-prick

- Current blood processing protocol require a strict procedures – useful in primary care?
- How do we monitor people overtime (including those on DMT) for personalised management?
- Detecting pre-clinical changes – if/when that it is required?









Summary – blood biomarkers for diagnosis

ATN biomarkers in blood:

A = plasma Aβ42/Aβ40 and P-tau
T = plasma P-tau
N = plasma NfL

G/I = plasma GFAP and other inflammatory proteins
V = placental growth factor (?)

Summary – the therapeutic landscape

Antibody-based removal of existing amyloid pathology is clinically meaningful

Side effects

When should one stop?

Gamma-secretase modulation could be a safe primary prevention strategy in high-risk individuals

Gamma-secretase modulation could prevent amyloid pathology from returning following antibody-mediated amyloid removal

Accessible biomarkers exist for all of the Alzheimer’s continuum

Thanks!!

henrik.zetterberg@gu.se
h.zetterberg@ucl.ac.uk

To all patients, relatives, team members, collaborators and funders