Expert Event

Advances in the treatment of Alzheimer's disease

– Small molecule **Gamma-Secretase Modulators** (GSMs) as promising disease-modifying treatments

PRESENTED BY

Henrik Zetterberg

Professor
University of Gothenburg
University College London

Martin Jönsson

CEO
AlzeCure Pharma

Johan Sandin

CSO
AlzeCure Pharma

Professor Zetterberg will provide an overview of cutting-edge science in the Alzheimer's space & comment on the recent developments

Together with AlzeCure's CEO & CSO Prof. Zetterberg will also discuss the potential impact on the sector including AlzeCure

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Today's presenters

Professor
Henrik Zetterberg
MD, PhD,

EXPERIENCES

› Professor of Neurochemistry and has a research background in molecular biology and clinical chemistry
› Professorship both in Gothenburg, Sweden & at University College London, UK
› Education: MD, PhD from Sahlgrenska Academy, Gothenburg University

CEO
Martin Jönsson

› Extensive experience in various senior management positions with >25 years of international experience in the pharma & biotech industry
› Education: MSc in BA from Lund University, Ottawa, Canada & Freiburg, Germany

CSO
Johan Sandin
PhD &
co-founder

› Expert in in vivo Pharmacology with >20 years experience from the drug discovery industry within Neurology
› Education: Ph.D. in Neuropharmacology, Karolinska Institutet

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Agenda

Advances in the treatment of Alzheimer's disease

– Small molecule **Gamma-Secretase Modulators** (GSMs) as promising disease-modifying treatments

- 15:00 **Welcome address, agenda & company overview**
  - Martin Jönsson, CEO, AlzeCure
- 15:10 **Alzheimer's disease and the amyloid hypothesis**
  - Professor Henrik Zetterberg[1], MD, PhD, Gothenburg University & University College London
- 15:50 **Alzstatin: a small molecule disease-modifying therapy against Alzheimer's disease**
  - Dr Johan Sandin, PhD, CSO, AlzeCure
- 16:05 **Q&A**
- 16:25 **Concluding remarks**
  - Martin Jönsson, CEO, AlzeCure

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AlzeCure Pharma
February 19, 2024

AlzeCure Pharma
Company Overview

Martin Jönsson, CEO

AlzeCure

AlzeCure Pharma – in brief

- Working in **Alzheimer's Disease** (AD) and **Pain** – Hugh unmet medical need & multi-billion sales potential
- Spin-out from **AstraZeneca** – as a result of their exit from the CNS area
- Founded in **2016** out of a research foundation sponsored by **Alzheimerfonden**
- Based at Novum Science Park, **Karolinska Institute**, Stockholm, Sweden

- Three project platforms with multiple **small molecule** candidates with **first-in-class properties**
  - **Alzstatin®** – An innovative preventive & disease-modifying treatment against Alzheimer's (AD)
  - **NeuroRestore®** – A novel symptomatic treatment for cognitive disorders, e.g. AD with neuroprotective & disease modifying potential
  - **Painless** – Innovative projects for osteoarthritic & neuropathic pain
- Listed on **Nasdaq First North Premier** Growth Market, **Sweden**, since Nov. 2018 (Ticker: ALZCUR)

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A pipeline of small-molecule programs

– Multiple candidates increase chance of success

Platform	Candidate	Target	Indication	Research phase	Preclinical phase	Phase I	Phase II	Phase III
NeuroRestore®	ACD856	Positive allosteric modulator (PAM) of Trk-receptors)	Alzheimer's Disease, TBI - Traumatic brain injuries Parkinson's disease, Sleep disorders, Depression					
Alzstatin®	ACD679	Gamma secretase modulator (GSM)	Alzheimer's Disease					
	ACD680	Gamma secretase modulator (GSM)	Alzheimer's Disease					
PainLess	ACD440	TRPV1 antagonist	Neuropathic Pain					
	ACD137	Negative allosteric modulator (NAM) of TrkA-receptors	Osteoarthritic Pain & other severe pain conditions					

Positive read-out Phase I trial
Safety, Tolerability & Target engagement

Selected new additional CD
ACD680

Positive read-out Phase IIa
Safety, Tolerability & Pain

Selected new CD
ACD137

Phase completed

Phase ongoing

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Progress & Increased Activity in the Alzheimer's field

Scientific validation & de-risking

- Validation of treatment approach: - Amyloid protein targeting
- Positive out-comes in clinical trials: - incl in phase III + approvals
- Vastly improved biomarkers & diagnostics identifying patients
  => *Increased probability of success in future studies*

Increased investments

- Additional Big Pharma companies entering & re-enteringthe field
- More funds and private equity investment in Alzheimer's companies & projects

However …

Still No Curative or Cognitive Enhancing Treatments against Alzheimer's have so far not been developed

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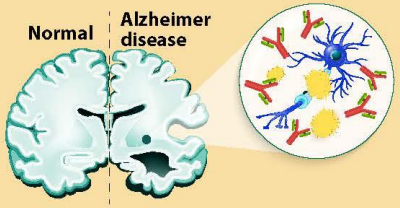
Only 5-8% of Alzheimer's patients* are estimated to be eligible for anti-bodies treatment

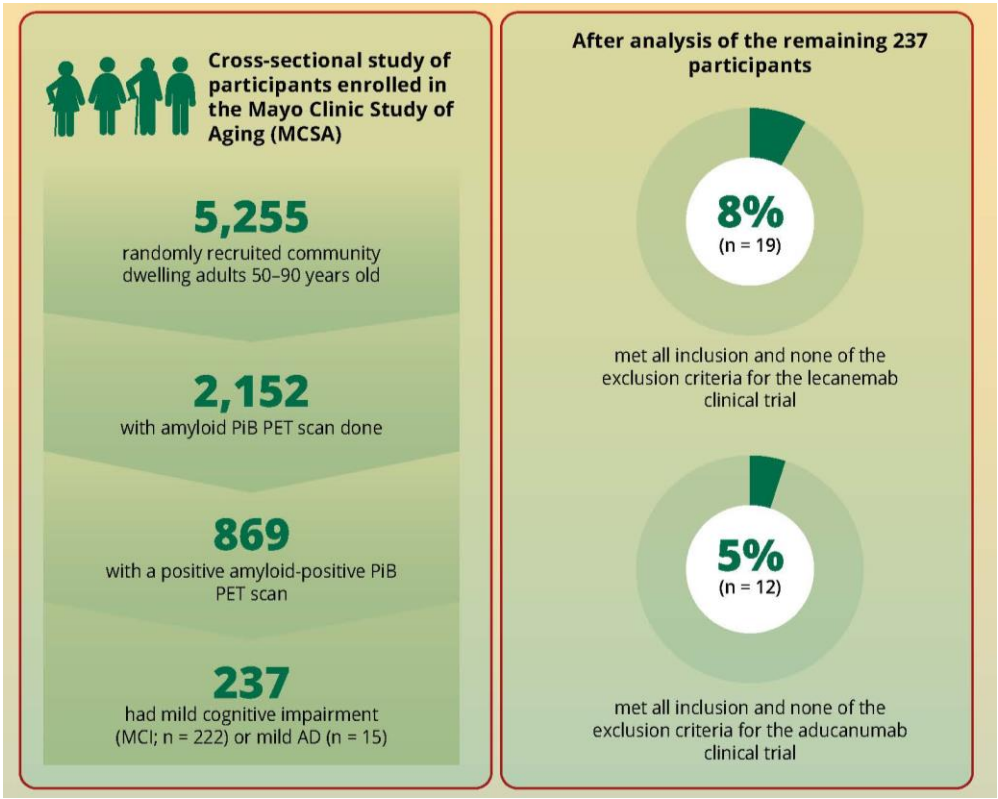
Determining Eligibility for Anti-Beta Amyloid Antibody Treatment in Adults with Mild Cognitive Impairment or Dementia



The anti-beta amyloid monoclonal antibodies (mAbs) lecanemab and aducanumab were recently approved by the FDA for use in the treatment of early symptomatic Alzheimer disease (AD)

What proportion of patients with mild cognitive impairment(MCI) or mild AD seen in a memory clinic would meet the inclusion criteria used in the clinical trials of aducanumab and lecanemab?

Only a small proportion of participants in the MCSA would be eligible for anti-amyloid mABS if the criteria used in the clinical trials of lecanemab and aducanumab were applied in routine practice



- **Huge unmet medical need remains** for alternative Alzheimer's treatments

*) Eligibility for Anti-Amyloid Treatment in a Population-Based Study of Cognitive Aging; Rioghna R. Pittock et al; **Neurology, 2023**;101:e1837-e1849. https://doi.org/10.1212/WNL.0000000000207770

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Two Alzheimer's platforms - 1st-in-class properties & potential game-changers

MEETING NEEDS OF AD PATIENTS – ADRESSING SHORT TERM NEEDS WITH LONG-TERM BENEFITS

Preventive Disease-modifying therapy

Alzstatin®

Gamma-secretase modulator

Targeting Amyloid Production

- *Novel Oral Small Molecule*

Symptomatic & pot. Disease-modifying therapy

NeuroRestore®

Trk-PAM

Improving Neuronal & Cognitive Function

- *Novel Oral Small Molecule*

Two fast followers to **Roche**, **Eisai** respectively → Provides Concept **Validation**

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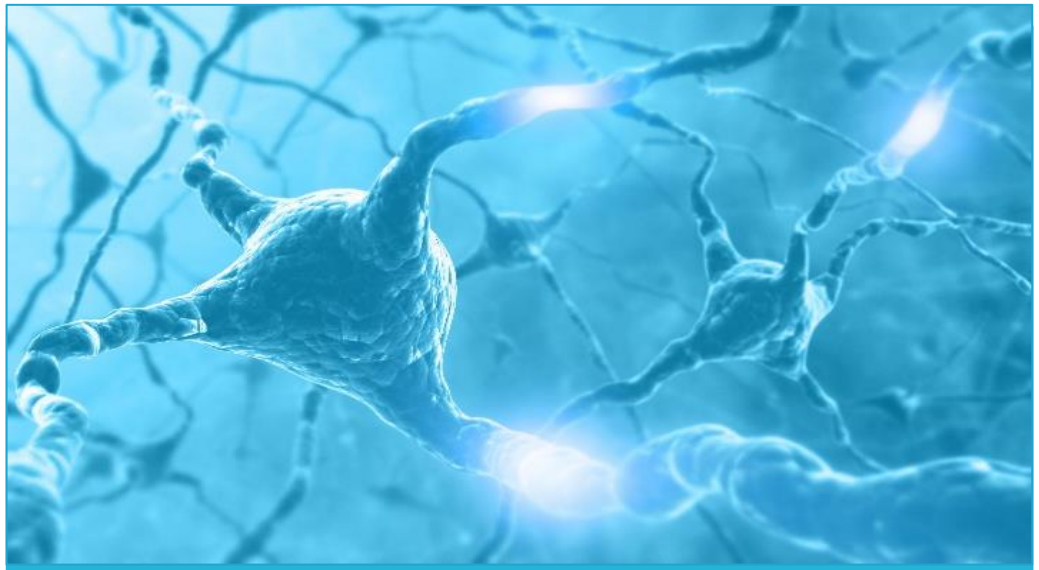
Improving Learning & Memory Capabilities



NeuroRestore®

Trk-PAM

Improving Neuronal Function & Cognition

- *Novel Oral Small Molecule*

Shown safety, tolerability & target engagement in clinical trial phase 1

=> *Prepation for phase 2*

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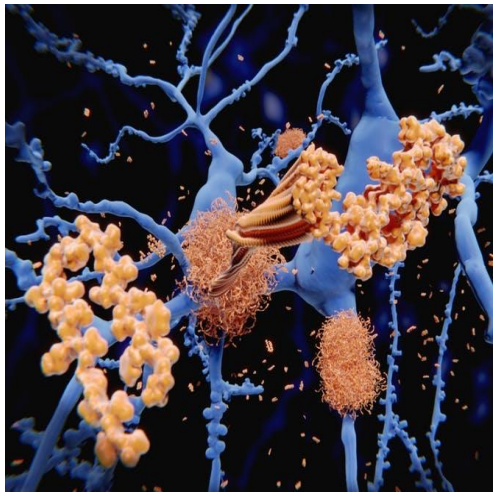
The Relevance of BDNF & NGF Signaling in Alzheimer's

- The neurotrophins Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) are **key for brain health and cognition**
- BDNF& NGF bind to their respective receptors, TrkB and TrkA
- BDNF& NGF signaling are implicated in several key neuronal functions, including **cholinergic function**, hippocampal neurogenesis and **synaptic plasticity**
- **Loss of NGF-dependent cholinergic neurons** in the basal forebrain and hippocampal atrophy are early hallmarks of Alzheimer's disease and **correlates with cognitive decline**
- **Certain genetics** in man, like the BDNF-Val66Met polymorphism, leads to **lower levels of BDNF**, and is associated with **more rapid cognitive impairment** and **increased disease progression** in Alzheimer's



Reduced BDNF and/or NGF-levels could limit the brain's ability to withstand pathological conditions

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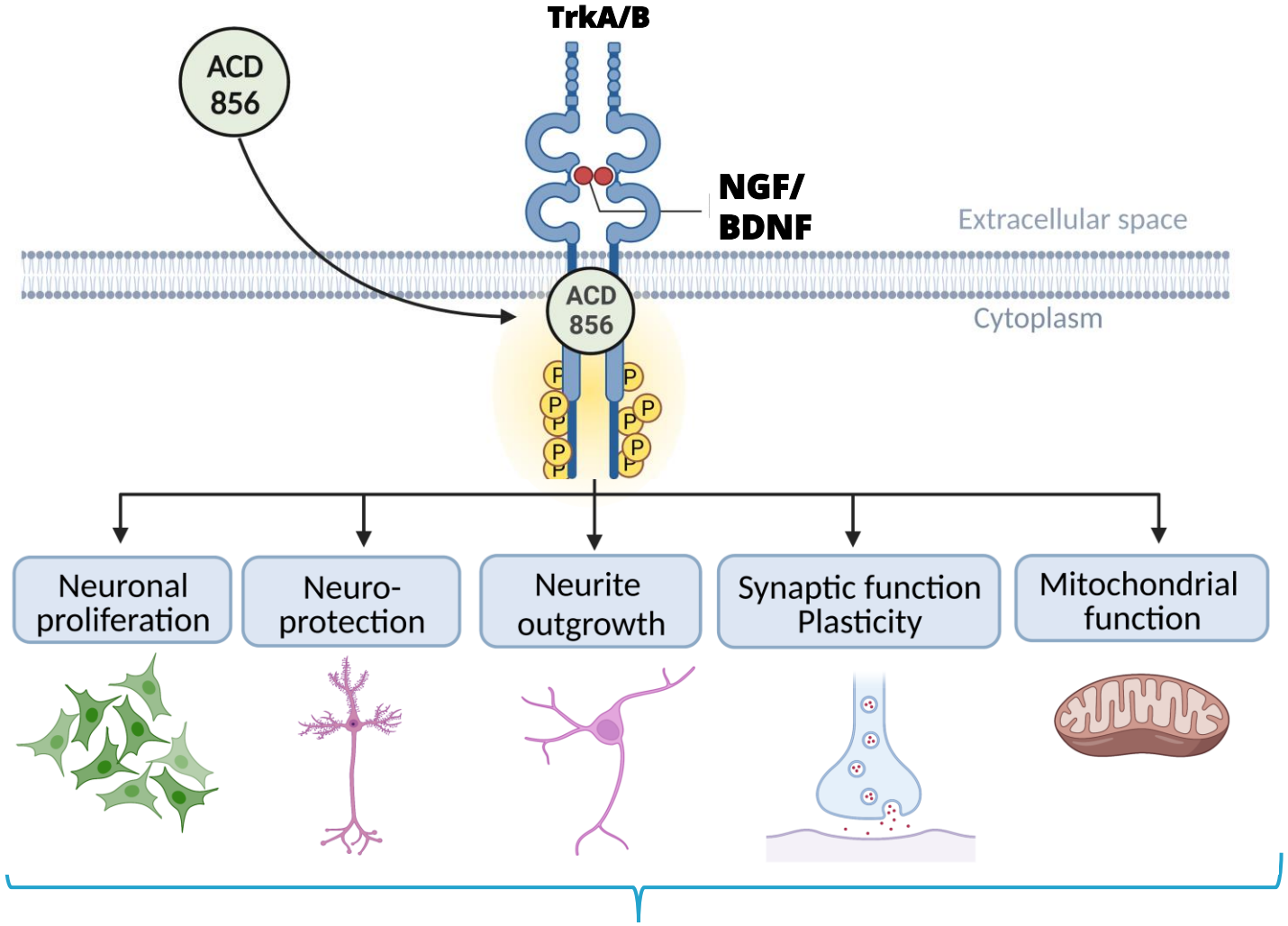
ACD856 - MoA & data supports Disease Modifying Potential

- ACD856 is a novel small molecule positive modulator of Trk-receptors **enhancing the signaling** of neurotrophins such as **NGF** & **BDNF**
- The enhanced signaling leads to immediate **symptomatic effects** & with potential **long-term benefits**
- The long-term effects of ACD856 could include **improved neuronal function, increased mitochondrial function & enhanced cognition, etc**



Potential for Disease Modifying Effect +

Improved Learning, Memory & Depression

Parrado Fernandez C et al. Int J Mol Sci. 2023 Jul 6;24(13):11159. https://doi.org/10.3390/ijms241311159

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ACD856 – Preclinical Data Suggests Disease Modification Effects

ACD856:

- Induces **neurite outgrowth** in PC12 cells at concentrations similar to what is found in CSF in the MAD study
- **Increases levels of synaptic markers** in PC12 cells
- Leads to **increased phosphorylation** of Trk-receptors
- **Improves mitochondrial function** and is **neuroprotective** in an energy-deprived neurotoxicity assay
- **Enhances synaptic plasticity** in the hippocampus – an area critically involved in cognitive function
- Demonstrates **long-term plasticity effects** after repeated dosing

Data Suggest a Disease Modifying Effect, Mediated by Increased Plasticity that Could Explain the Pro-Cognitive & Anti-Depressant Effects

Parrado Fernandez C et al. Int J Mol Sci. 2023 Jul 6;24(13):11159.
https://doi.org/10.3390/ijms241311159

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TrkA-PAM by Eisai: Disease-Modifying Therapy for Neurodegenerative Diseases

FIRST-IN-HUMAN (FIH), SINGLE- AND MULTIPLE-ASCENDING-DOSE (SAD/MAD) STUDIES IN HEALTHY SUBJECTS OF E2511, A NOVEL TROPOMYOSIN RECEPTOR KINASE A (TrkA) POSITIVE ALLOSTERIC MODULATOR (PAM)

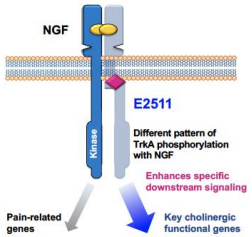
Pau Aceves[1], Nancy Hall[2], Cuiyuan Cai[3], Jagadeesh Aluri[2], Satish Dayal[1], Takuya Yagi[2], Julia Chang[2], Masaki Mikamoto[3], Garth E. Ringheim[2], Tomioka Takesuya[3], Naoki Hiramatsu[3], Robert Gordon[1], Luigi Giorgi[1]

1. Eisai Ltd., Hatfield, United Kingdom. 2. Eisai Inc., Nutley, NJ, USA. 3. Eisai Co, Ltd., Tsukuba, Japan.

Introduction

- Cholinergic innervation is affected early in multiple neurodegenerative diseases and correlates with cognitive dysfunction[1-3]
  - The progressive senescence and eventual loss of cholinergic neurons in Alzheimer's disease (AD) is correlated with cognitive impairment
- Nerve growth factor (NGF) plays a major role in the maintenance and function of cholinergic neurons[4] (see Figure 1)

Figure 1. Activation of specific trophic signaling of TrkA



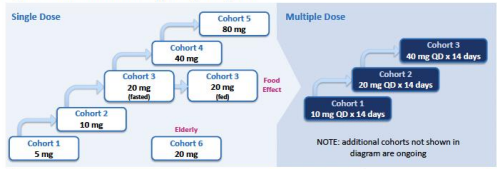
- Activation of NGF-induced trophic signaling via TrkA has potential as a disease modifying therapy to restore cholinergic innervation in neurodegenerative diseases, including AD[5-8]
- E2511 is a novel orally bioavailable small molecule TrkA biased PAM that has shown reinnervative effects on cholinergic neurons in nonclinical studies without NGF-associated hyperalgesia

Methods

- The main objectives of the E2511 FIH Phase 1 studies (SAD [completed] and MAD [ongoing]) are to evaluate the safety, tolerability and pharmacokinetics (PK) in healthy subjects
- Both SAD and MAD are randomized, double-blind and placebo-controlled studies
- The SAD evaluated 5 cohorts in adults and one cohort in elderly subjects (Figure 2); food effect was also evaluated in Cohort 3
- Repeat dosing with E2511 (once daily for 14 days) is currently under evaluation in the MAD study (3 cohorts completed; Figure 2)
- Safety was evaluated through the review of adverse events, physical examinations, clinical laboratory tests, vital signs, electrocardiogram and electroencephalograms
- Serial blood samples were collected for determination of plasma E2511 concentrations
- In MAD Cohorts 1 to 4, CSF was collected via lumbar puncture (LP) for PK/PD assessments in two occasions (1 predose and 1 postdose)

Methods *(continued)*

Figure 2. SAD and MAD Study Design Diagram



Results

Subjects

- A total of 40 and 24 healthy adult subjects have been dosed in the SAD and MAD studies, respectively (Table 1); and 5 Elderly subjects (3 E2511: 2 placebo) in the SAD

Table 1. SAD and MAD Baseline Subject Characteristics

	Single Dose								Multiple Dose					
		E2511								E2511				
	Placebo N=10	5 mg N=6	10 mg N=6	20 mg N=6	40 mg N=6	80 mg N=6	E2511 Total N=30	Total N=40	Placebo N=6	10 mg N=6	20 mg N=6	40 mg N=6	E2511 Total N=18	Total N=24
Age, mean years (SD)	34 (9)	38 (13)	40 (13)	34 (8)	35 (9)	36 (9)	36 (10)	36 (10)	45 (5.8)	27 (4)	36 (9)	32 (5)	32 (7)	35 (8)
Female, %	40	50	33	17	33	33	33	35	0	33	50	33	39	29
Race, %														
White	70	67	67	33	67	100	67	68	33	50	67	17	44	42
Black or African American	20	33	33	50	17	0	27	25	67	17	0	67	28	38
Asian	10	0	0	0	17	0	3	5	0	33	17	17	22	17
American Indian or Alaska Native	0	0	0	17	0	0	3	3	0	0	17	0	6	4
Weight, mean kg (SD)	71 (12)	73 (14)	75 (14)	71 (13)	76 (14)	72 (9)	73 (12)	72 (12)	84 (13)	76 (16)	74 (12)	73 (10)	74 (13)	77 (13)
BMI, mean kg/m², (SD)	25 (3)	25 (2)	25 (3)	24 (4)	26 (1)	25 (4)	25 (3)	25 (3)	26 (3)	25 (4)	25 (4)	25 (3)	25 (14)	25 (14)

Safety

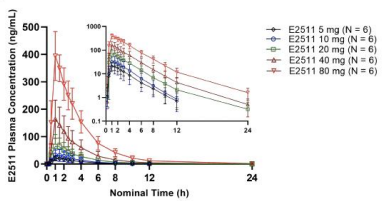
- Single and multiple oral (PO) doses of E2511 were safe and well-tolerated across the investigated doses in adult and elderly healthy subjects
- Most common (≥2) treatment-emergent adverse event (TEAE) in the SAD was contact dermatitis (same incidence in active and placebo-treated subjects [10%])
- Most common (≥2) TEAEs in the MAD were post-LP syndrome, headache, back pain and nausea; generally thought to be related to the LP procedures
- No subjects were withdrawn due to drug-related safety events
- There were no dose dependent, serious or severe TEAEs
- There were no clinically significant changes in the evaluated safety parameters (safety laboratory, vital signs, ECG, EEG and physical exam) on E2511 compared to placebo
- SAD exposure-response analyses confirmed no effects on the Holter ECG parameters, including HR, cardiac repolarization (QTcF), and cardiac conduction (PR, QRS)

Results *(continued)*

SAD: E2511 Clinical Pharmacokinetic Results

- Rapidly absorbed (t_{max}: 1 hour); with a plasma half-life of 3.19 hours (Figure 3)
- Plasma exposures (C_{max} and AUC) increased dose proportionally over the dose range of 5 to 80 mg (power model exponent [90% CI]: 1.09 [0.92, 1.25] for C_{max} and 1.08 [0.91, 1.25] for $AUC_{(0\text{-inf})}$)

Figure 3. SAD: E2511 Plasma Concentration-Time Profiles and PK Parameters



Parameter (SD)	5 mg/kg (n=6)	10 mg/kg (n=6)	20 mg/kg (n=6)	40 mg/kg (n=6)	80 mg (n=6)
C_{max}, ng/mL	21.5 (40.8)	29.1 (98.0)	63.7 (51.8)	156 (50.8)	402 (18.2)
t_{max}, hours[1]	1.0 (1.0, 1.5)	1.0 (1.0, 2.0)	1.3 (1.0, 3.1)	1.0 (0.6, 1.5)	1.1 (1.0, 1.5)
$AUC_{(0\text{-}24h)}$, h·ng/mL	75.6 (43.9)	97.5 (91.8)	222 (55.7)	497 (55.1)	1400 (23.5)
$AUC_{(0\text{-inf})}$, h·ng/mL	75.9 (44.1)	97.8 (92.2)	223 (55.9)	500 (55.2)	1410 (23.6)
CL/F, L/h	65.9 (44.0)	102 (92.2)	89.7 (55.9)	80.2 (55.2)	56.8 (23.7)
V_z/F, L	248 (42.9)	401 (57.2)	420 (37.1)	407 (52.4)	314 (26.5)
$t_{1/2}$, hours	2.61 (39.6)	2.72 (40.5)	3.25 (29.4)	3.52 (8.38)	3.83 (8.79)

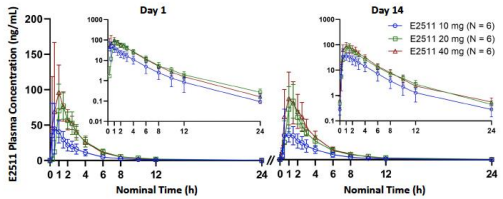
Geometric mean (%CV) values shown unless otherwise noted.
1: Median (range)

- Food (standardized high-fat, high calorie meal) led to a decrease of 19% in C_{max} and 15% in AUC compared to fasted conditions (at a dose of 20 mg)
- Plasma exposures in elderly and younger adult subjects were deemed comparable (at a dose of 20 mg), as Elderly plasma PK exposures (N=3) were fully contained within the observed range of younger adults (N=6, at same dose)

MAD: E2511 Clinical Pharmacokinetic Results

- There was little or no accumulation observed following 14 days of dosing (Figure 4)
- There was no evidence of time dependent-kinetics

Figure 4. MAD: E2511 Plasma Concentration-Time Profiles and PK Parameters



Parameter (SD)	10 mg QD		20 mg QD		40 mg QD	
	Day 1 (n=6)	Day 14 (n=6)	Day 1 (n=6)	Day 14 (n=5)	Day 1 (n=6)	Day 14 (n=6)
C_{max}, ng/mL	47.4 (88)	81.7 (50.2)	86.1 (32.3)	91.8 (22.3)	110 (59.9)	95.0 (35.9)
t_{max}, hours[1]	1.0 (0.3, 1.5)	1.0 (0.5, 2.5)	1.3 (1.0, 1.5)	1.0 (0.5, 1.5)	1.0 (0.5, 2.0)	1.0 (0.5, 2.0)
$AUC_{(0\text{-}24h)}$, ng·h/mL	116 (57.1)	140 (24.6)	247 (22.7)	271 (16.2)	276 (34.6)	309 (30.8)
CL/F, L/h	85.7 (57.4)	71.7 (24.6)	80.4 (22.8)	73.7 (16.2)	145 (34.7)	129 (30.8)
V_z/F, L	355 (43.3)	478 (26.7)	431 (20.7)	448 (20.9)	682 (25.4)	792 (39.0)
$t_{1/2}$, hours	2.87 (46.9)	4.63 (19.2)	3.72 (20.8)	4.21 (12.7)	3.27 (31.0)	4.25 (17.8)
R_{ac}, C_{max}[2]	N/A	1.06 (132)	N/A	0.997 (48.3)	N/A	0.863 (34.9)
R_{ac}, AUC[3]	N/A	1.2 (37.8)	N/A	1.03 (25.2)	N/A	1.12 (19.1)
Rss[4]	N/A	1.2 (38.1)	N/A	1.02 (25.1)	N/A	1.12 (19.2)

Geometric mean (%CV) values shown unless otherwise noted. N/A: not applicable.
1: Median (range);
2: R_{ac}, C_{max}: Accumulation ratio determined based on C_{max} [Day 14]/ C_{max} [Day 1];
3: R_{ac} AUC: Accumulation ratio determined based on $AUC_{(0\text{-}24h)}$ [Day 14]/ $AUC_{(0\text{-}24h)}$ [Day 1];
4: R_{ss}: Time dependency ratio was determined based on $AUC_{(0\text{-}24h)}$ [Day 14]/ / $AUC_{(0\text{-inf})}$ [Day 1]

Conclusions

- E2511 presents an adequate single and multiple dose safety profile in healthy adults up to the currently highest evaluated doses (80 mg PO in SAD; 40 mg QD PO in MAD)
- E2511 has shown predictable single and multiple dose PK with a short plasma half-life that is consistent with human PK projections based on non-clinical data
  - Dose-proportional plasma PK over the dose range of 5 to 80 mg (in the SAD) and time-invariant PK (up to at least 40 mg QD in the MAD)
  - Mild effect of food on rate and extent of plasma E2511 exposure supports dosing without regards to food
  - Plasma E2511 exposures (C_{max}, AUC) in a small group of elderly subjects suggest there is no need for dose adjustment in the target population
- These results support further development of E2511 as a disease-modifying therapy for neurodegenerative diseases

References

1. Ferreira-Vieira TH, et al. Curr Neuropharmacol. 2016;14(1):101-15. 2. Hampel H, et al. Brain. 2018;141(7):1917-33. 3. Mufson EJ, et al. Expert Rev Neurother. 2008;8(11):1703-18. 4. Ginsberg SD, et al. J Neurochem. 2006;97(2):475-87. 5. Hefti F. J Neurosci. 1986;6(8):2155-62. 6. Hagg T, et al. Exp. Neurol. 1988;101:303-12. 7. Hilgert M, et al. Neurochem.Res. 2003;28:467-72. 8. Wu K, et al. Brain Res.2005;1061:107-13.

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If you have any questions about this poster, please email or call Eisai Medical Information at ESI_MedInfo@eisai.com or 888-274-2378

The data is **validating & increasing interest in NeuroRestore**

” These results support further development of E2511 as a disease-modifying therapy for neurodegenerative diseases”

AlzeCure's ACD856 in Comparison to Eisai's E2511

	Eisai E2511	AlzeCure NeuroRestore ACD856
Mechanism of Action	Positive allosteric modulator	Positive allosteric modulator
Target	TrkA	TrkA, TrkB and TrkC
Type	Novel small molecule (<400 Da)	Novel small molecule (<400 Da)
IP	Patent granted	Granted patent in US, Japan, EU, and several other territories are processing applications
Stage of dev.	Phase I: SAD/MAD, half-life = 3.2 h	Phase I: SAD/MAD, half-life = 19 h
Effect on neurite outgrowth	No, not reported	Yes, in two different in vitro models
Neuroprotective	Yes, in two in vivo models	Yes, in two in vitro models
Effect on neuro-transmitters	Yes ACh	Yes Serotonin, noradrenaline and dopamine
Effect on cognition	Not reported	**Yes, cognitive enhancement** in several models
Effect on depression	Not reported	**Yes, anti-depressant & long-term effects + additive to SSRI**

Alzecure: Cells. 2021; Drug Discov Today 2022; Psychopharmacology, 2023, International J. Mol. Sciences 2023
Eisai: AAIC, P51985, 2021; ADPD, P186, 2022; AAIC, P62590 and P66208, 2022

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ACD856 – Evidence of Improvements to Learning & Memory

Stages of memory formation

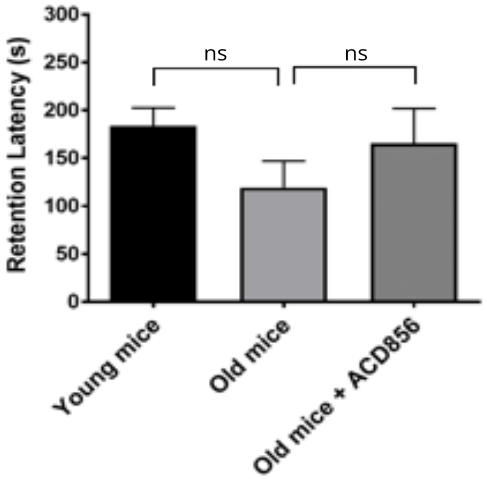
LEARN → STORE → REMEMBER

ACD856 has shown in preclinical models the capacity to improve the ability to learn and remember information

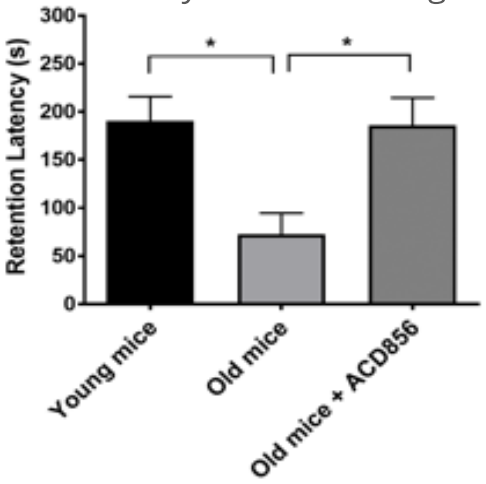
Single dose ACD856 (-30 min) → Learning (t=0 min) → Test #1 (t=1 day) → Test #2 (t=11 days)

ACD856 **improves age-induced memory impairment** in 18-month-old animals to the level of young animals

Memory test #1,
1 day after learning



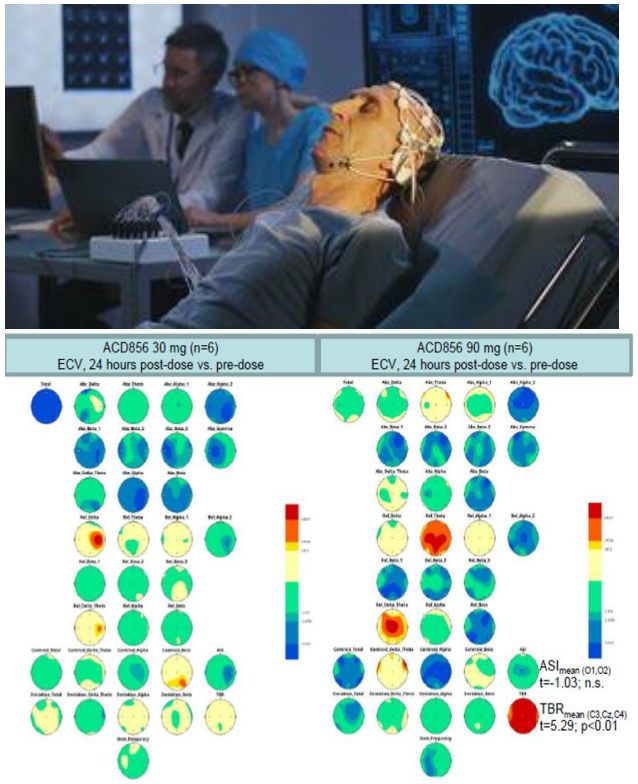
Memory test #2,
11 days after learning



Dahlström M et al. Cells. 2021 Jul 23;10(8):1871.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8391421/pdf/

Phase I Study Summary

- ACD856 is **safe & well tolerated**
  - Single and repeated dosing with ACD856 did not result in any serious adverse events in healthy volunteers at the tested dose levels
- ACD856 has an **excellent PK profile** suitable for **once daily** oral dosing
  - ACD856 has a rapid absorption, a long half-life of ~ 20 hours, high bioavailability and a linear dose-dependent exposure
- ACD856 **present in CSF** with a ratio of ACD856 in CSF to unbound average ACD856 levels in plasma at **> 37%**
  - **ACD856 pass the BBB** and measured concentrations in CSF confirms a **high exposure** at the level of the brain
- ACD856 MAD qEEG results shows clear **CNS target engagement**
  - EEG pattern supports pro-cognitive as well as antidepressant effects of ACD856



Vigilance control brain maps for 30 and 90 mg cohorts

=> Being prepared for ph 2

Önnestam, K et al. J Prev Alzheimers Dis (2023).
https://link.springer.com/article/10.14283/jpad.2023.89

AlzeCure

AlzeCure Pharma
Karolinska Institutet Novum Science Park
Hälsovägen 7, 141 57 Stockholm
SWEDEN

www.alzecurepharma.com - info@alzecurepharma.com

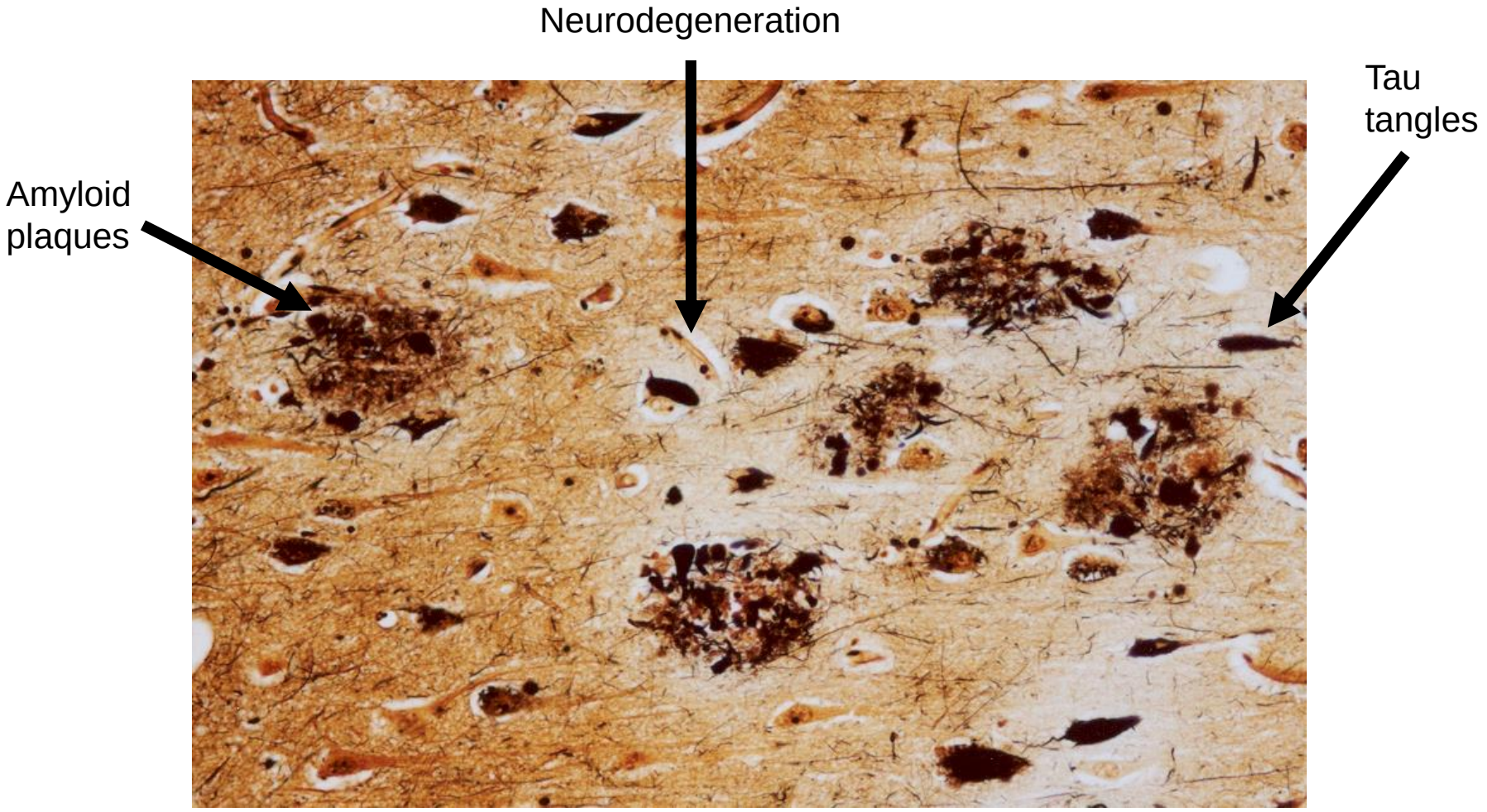
AlzeCure

Alzheimer's and the amyloid cascade hypothesis

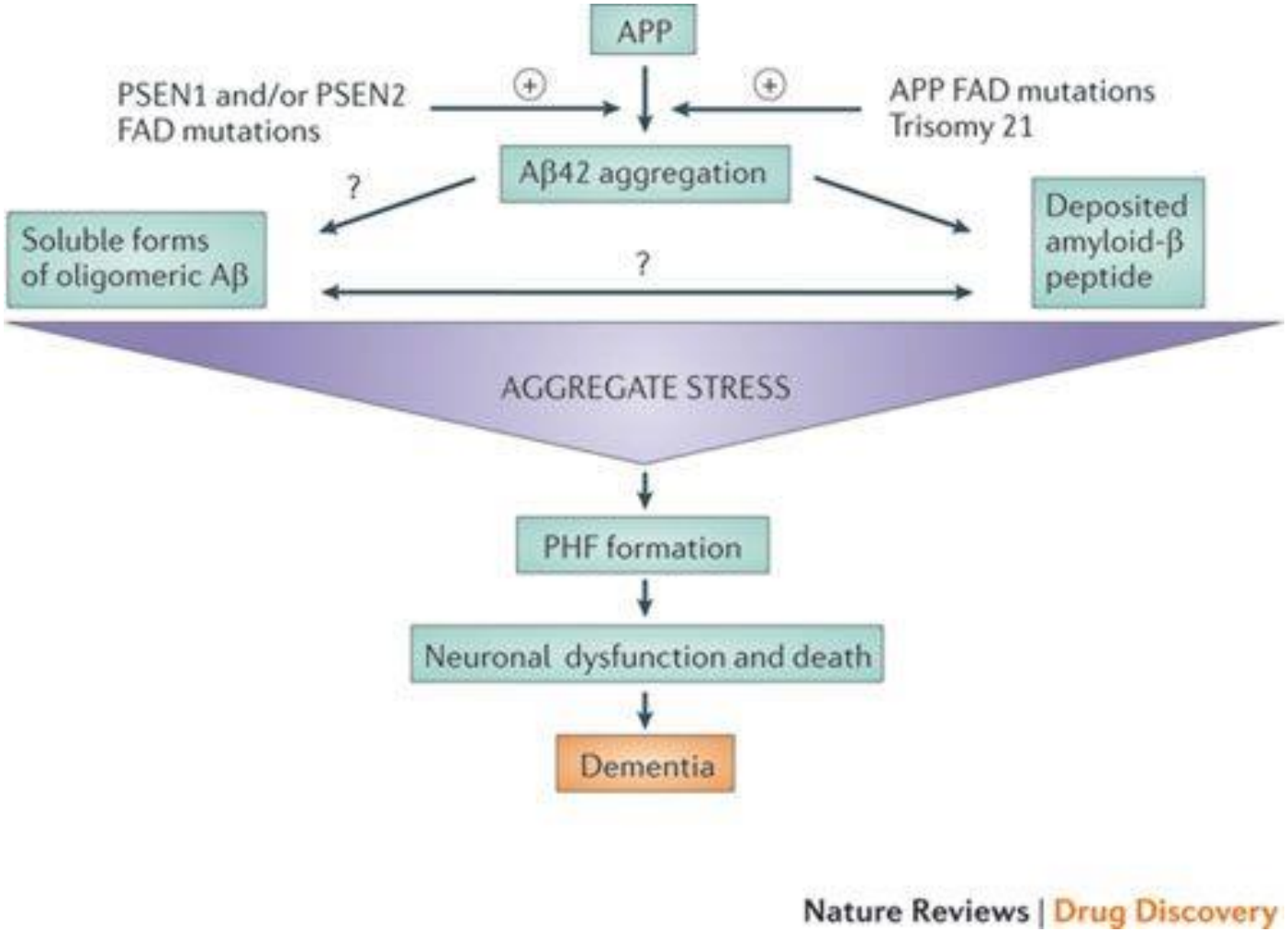
Henrik Zetterberg, MD, PhD
Professor of Neurochemistry
University of Gothenburg and University College London

The Sahlgrenska Academy

The neuropathology of Alzheimer's disease

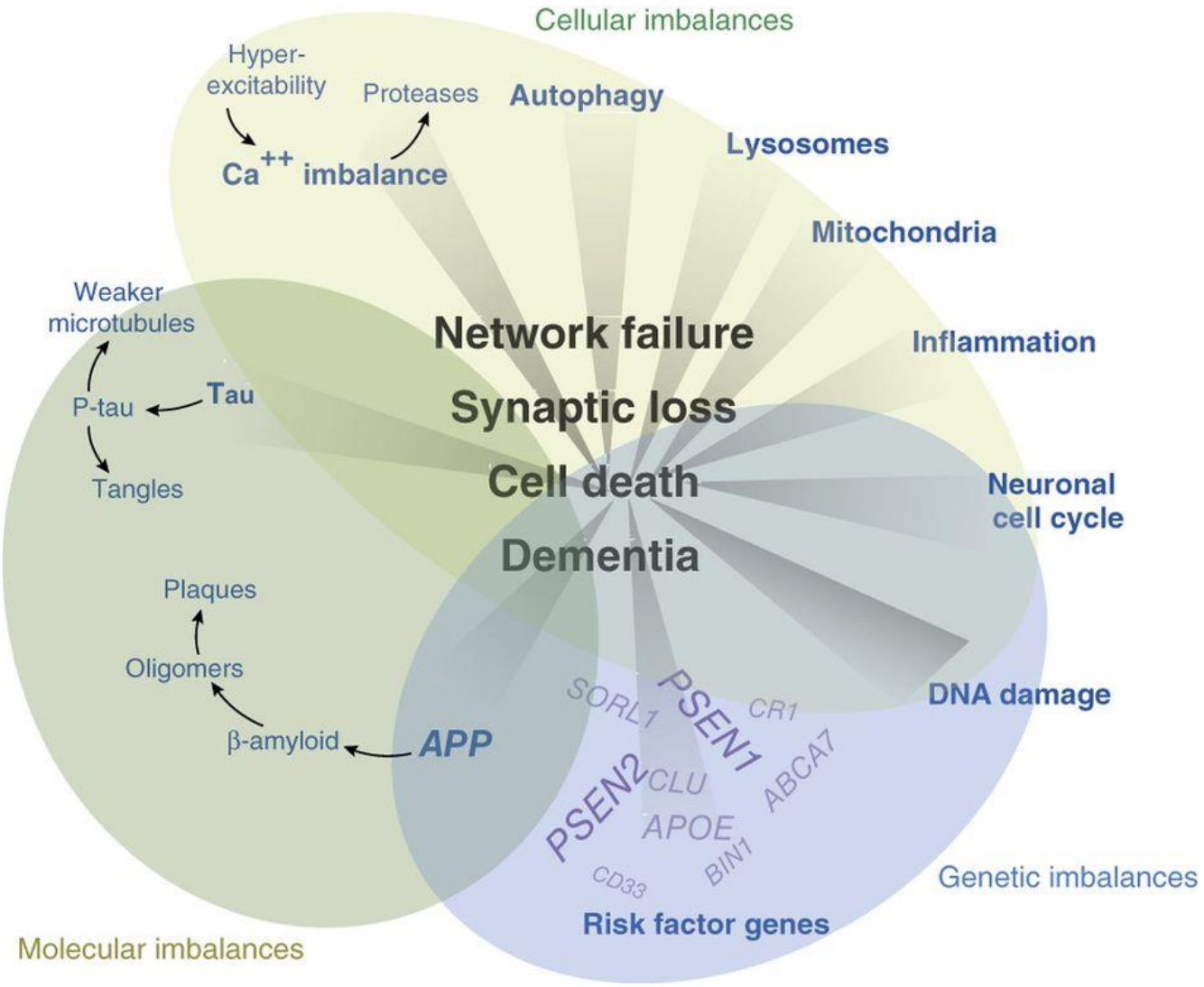


The amyloid cascade hypothesis on Alzheimer's disease – still viable?



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**

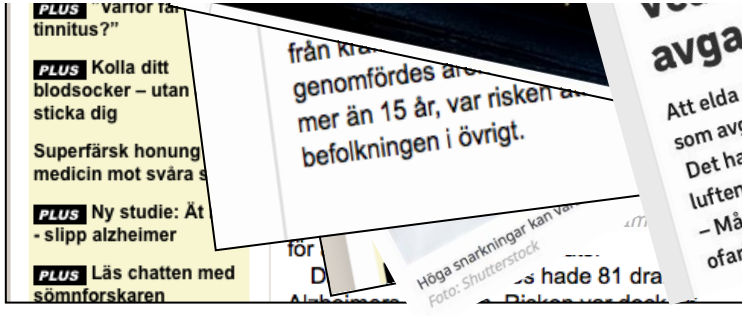
unv.is/ expressen.se/halsoliv/inloggad/daglig-bastu-minskar-risken-for-alzheimers

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

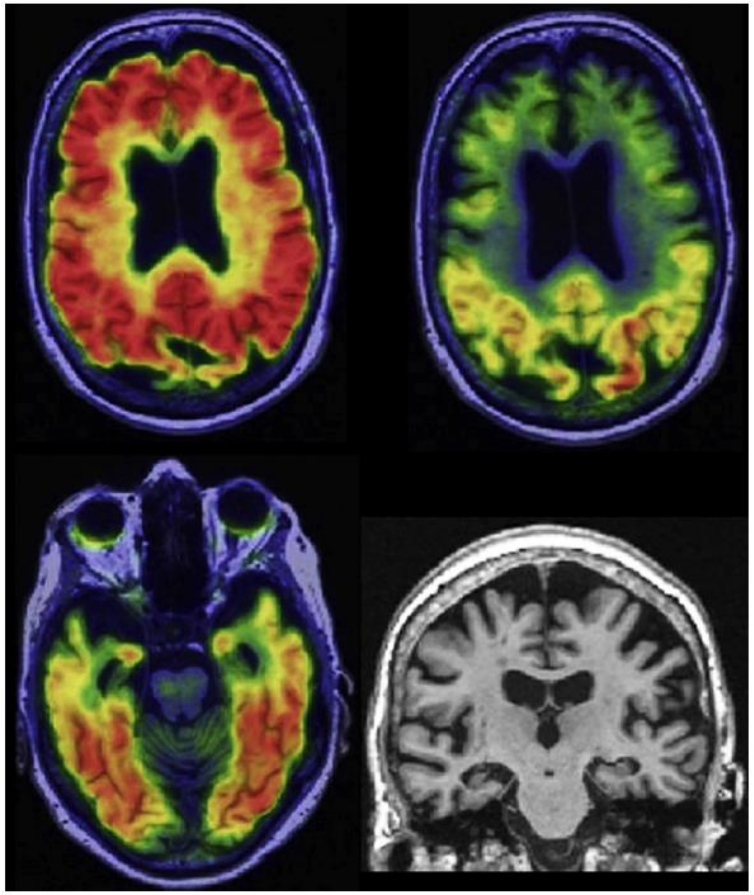
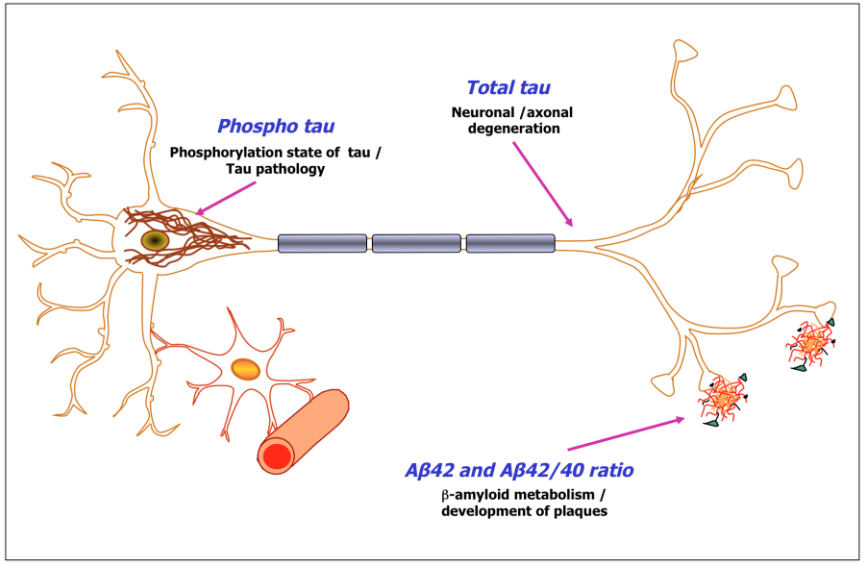


Fig. 1. Alzheimer's disease with dementia. A 75-year-old woman with amnestic multidomain dementia. Participant in the Mayo Alzheimer's Disease Research Center. Abnormal amyloid PET with Pittsburgh compound B (top left), tau PET with flortaucipir (top right and bottom left), and atrophy on MRI (bottom 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

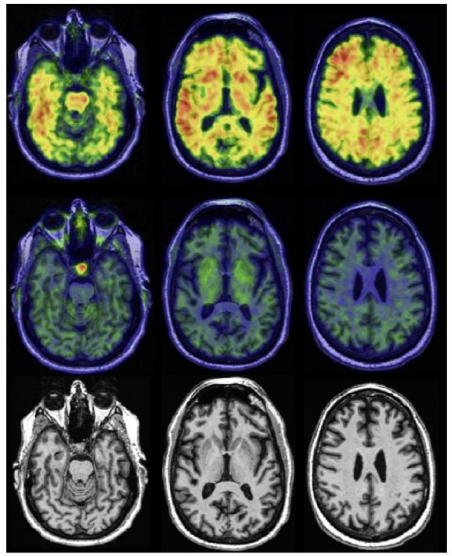
NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

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

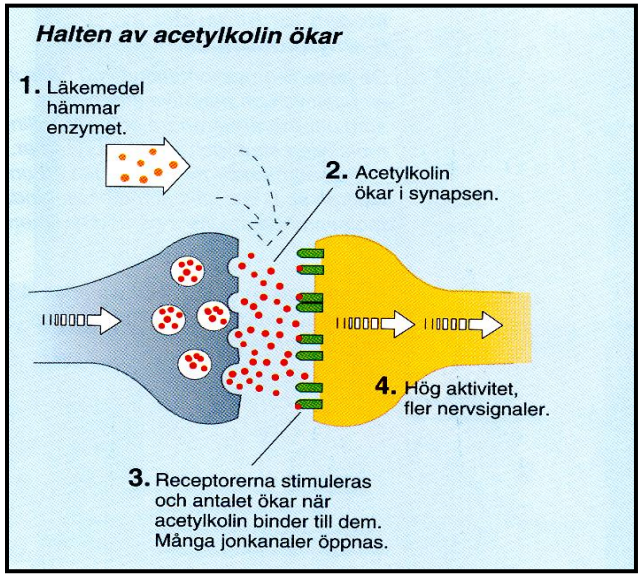
➔ **Disease-modyfing drugs**

- 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

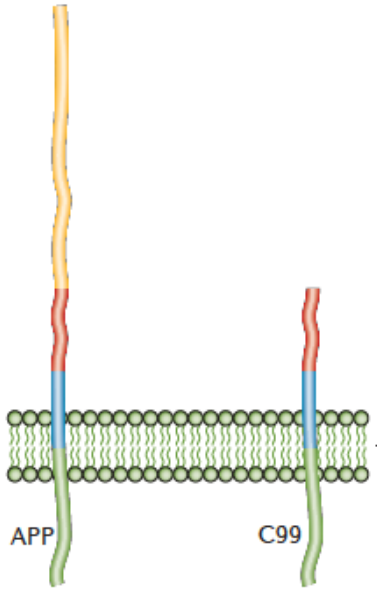
- Moderate to severe AD dementia
- Memantine

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

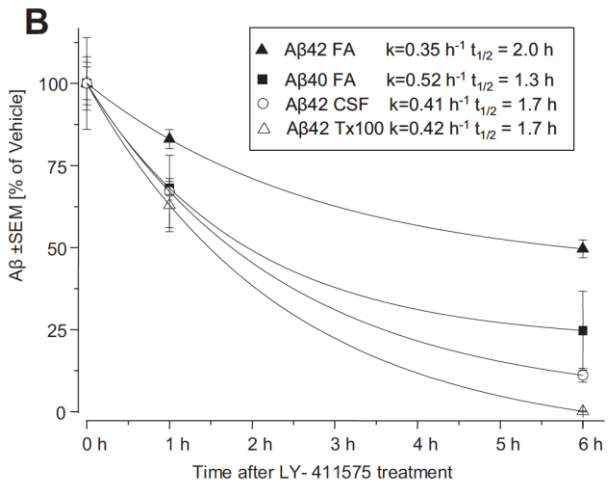
0022-3565/08/3272-411–424$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 2008 by The American Society for Pharmacology and Experimental Therapeutics
JPET 327:411–424, 2008
Vol. 327, No. 2
140327/3395142
Printed in U.S.A.

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

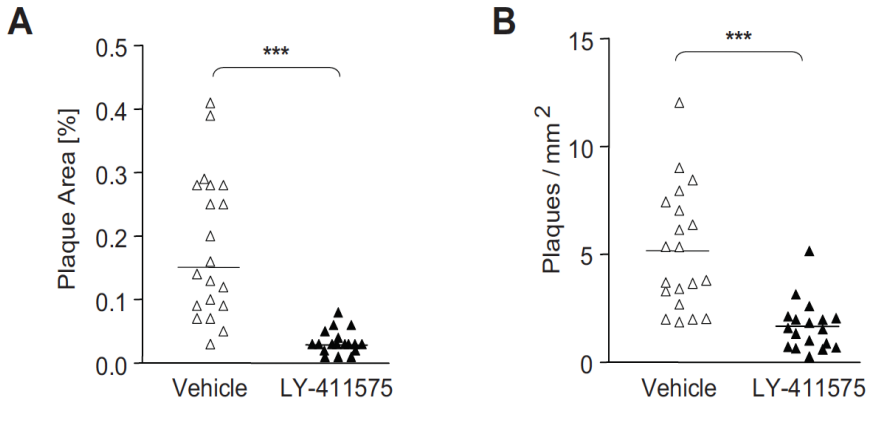
Dorothee Abramowski, Karl-Heinz Wiederhold, Ulrich Furrer, Anne-Lise Jaton, Anton Neuenschwander, Marie-Josephine Runser, Simone Danner, Julia Reichwald, Domenico Ammaturo, Dieter Staab, Markus Stoeckli, Heinrich Rueeger, Ulf Neumann, and Matthias Staufenbiel

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.)

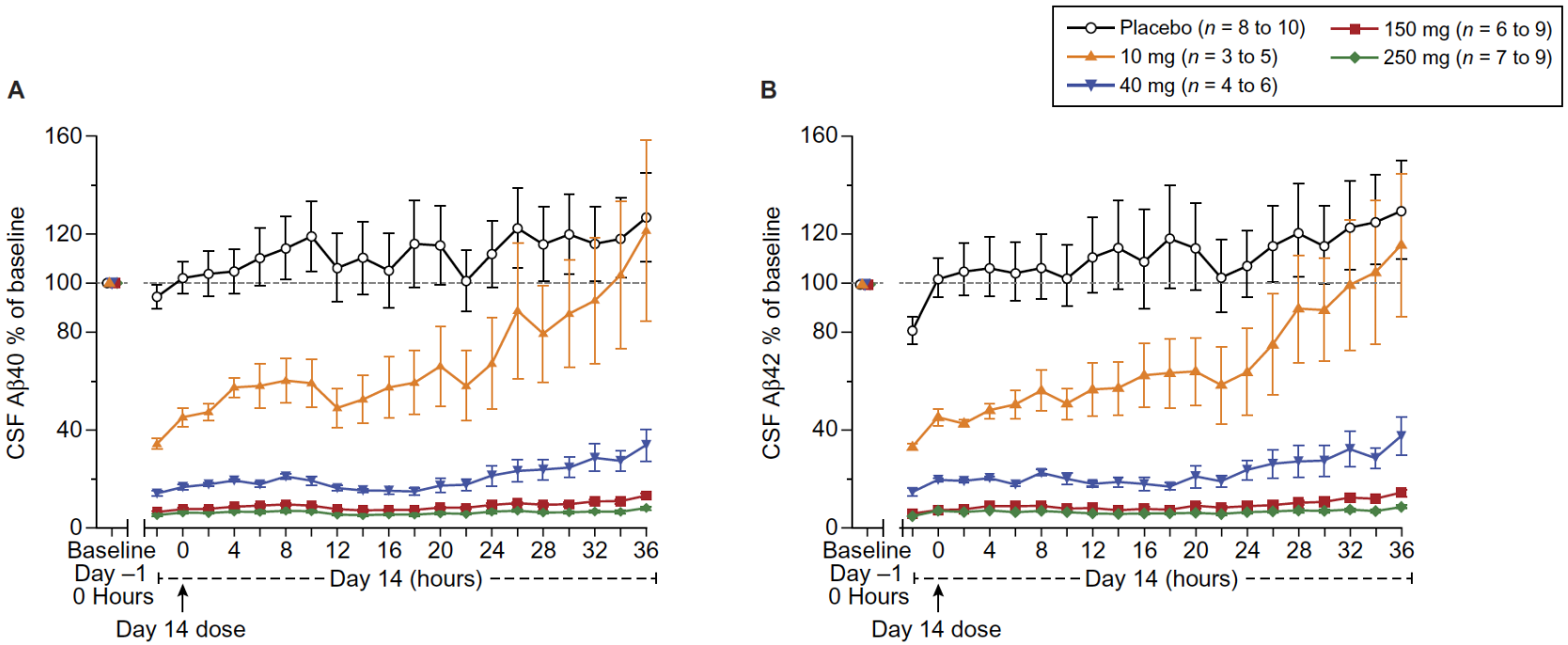
➔ **Evidence of target engagement and amyloid plaque removal in mice**
may not directly translate to disease-modifying effect / clinical benefit in AD patients

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.

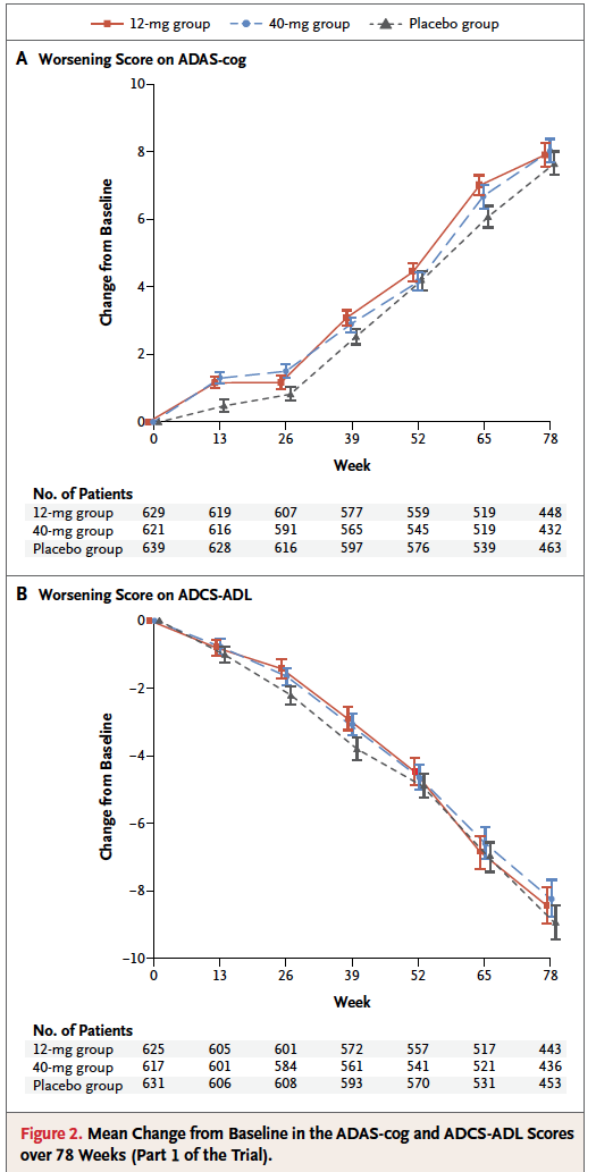


Figure 2. Mean Change from Baseline in the ADAS-cog and ADCS-ADL Scores over 78 Weeks (Part 1 of the Trial).

➔ **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)

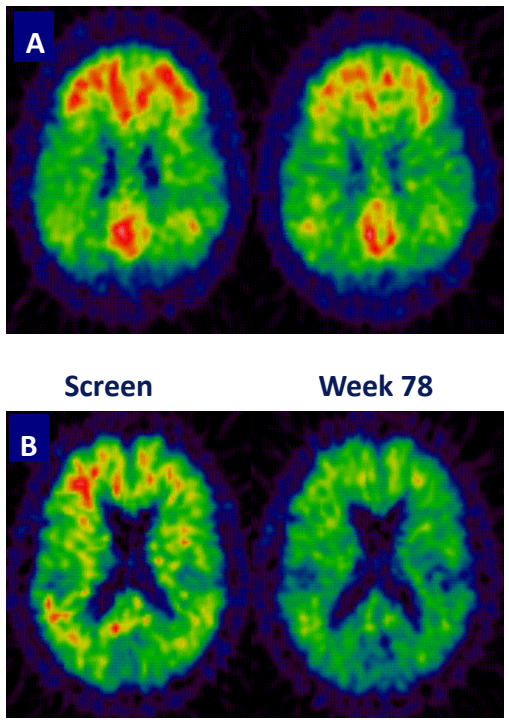
2. Low-dose BACE1 inhibition (not 70-90% inhibition but maybe 20-30%?)

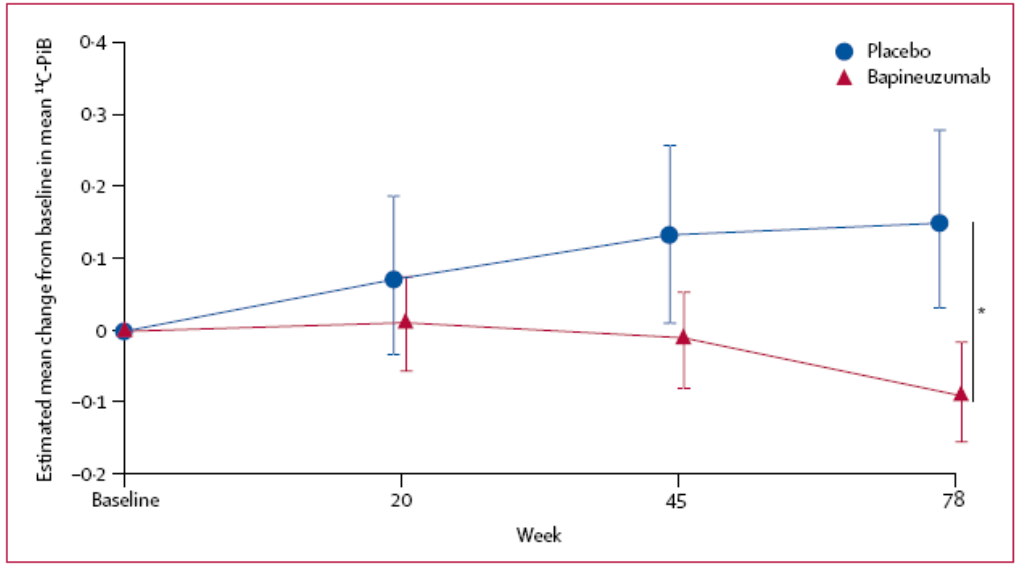
Both have strong support from genetics, as primary prevention strategies against amyloid build-up in the brain and Alzheimer's disease

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

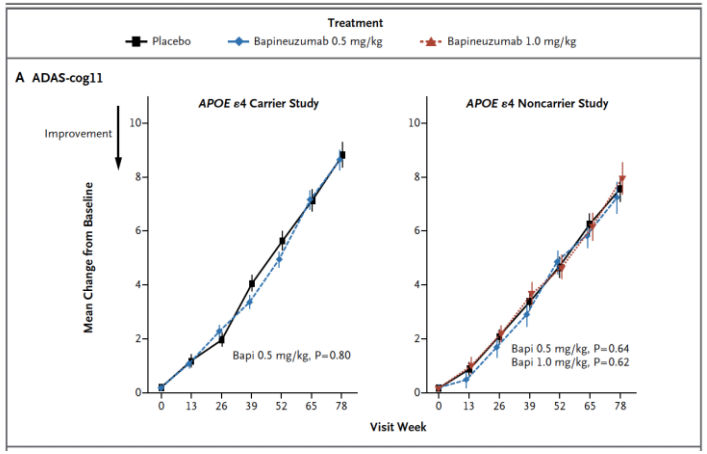
The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2014;370:322-33.
ORIGINAL ARTICLE

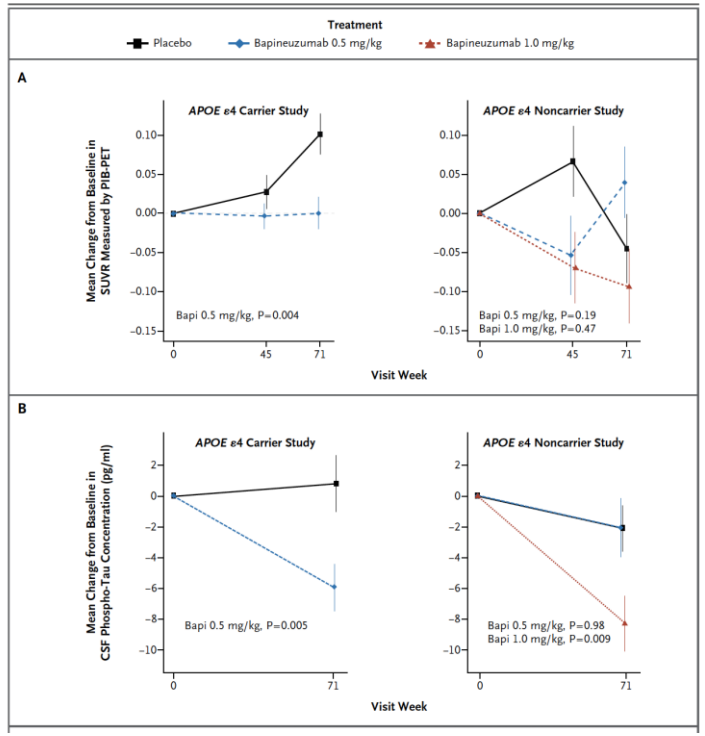
Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

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]§

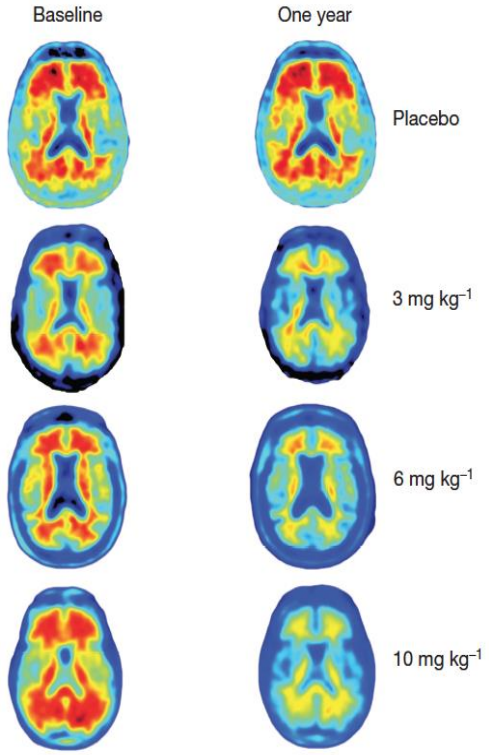
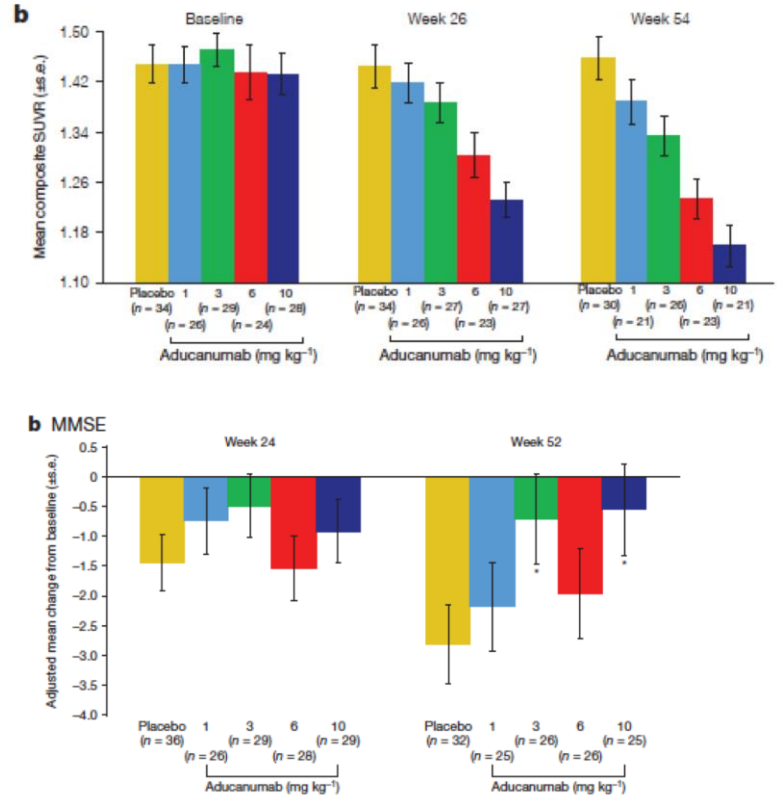


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54.



- ➔ **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

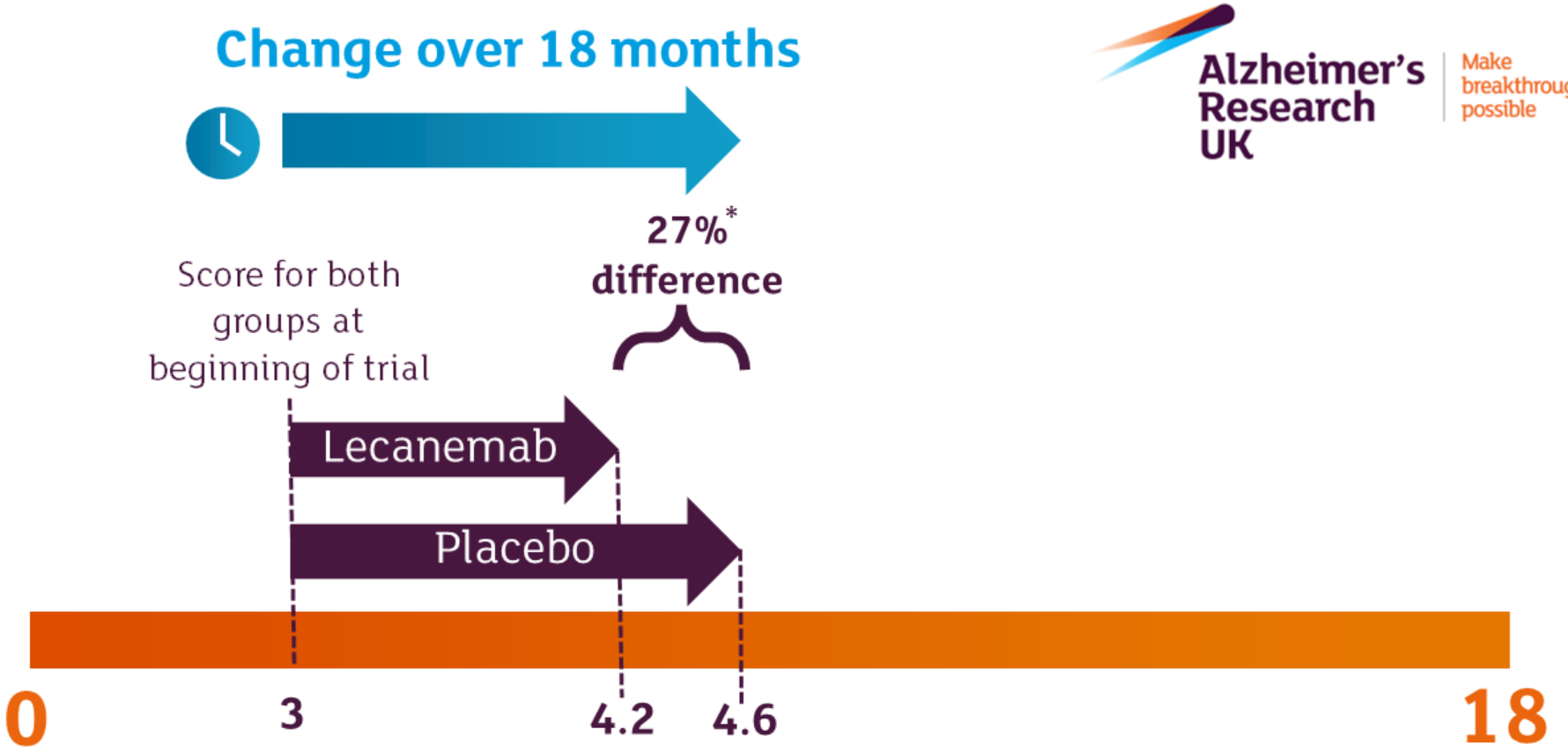
July 14, 2020 - Other press release

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

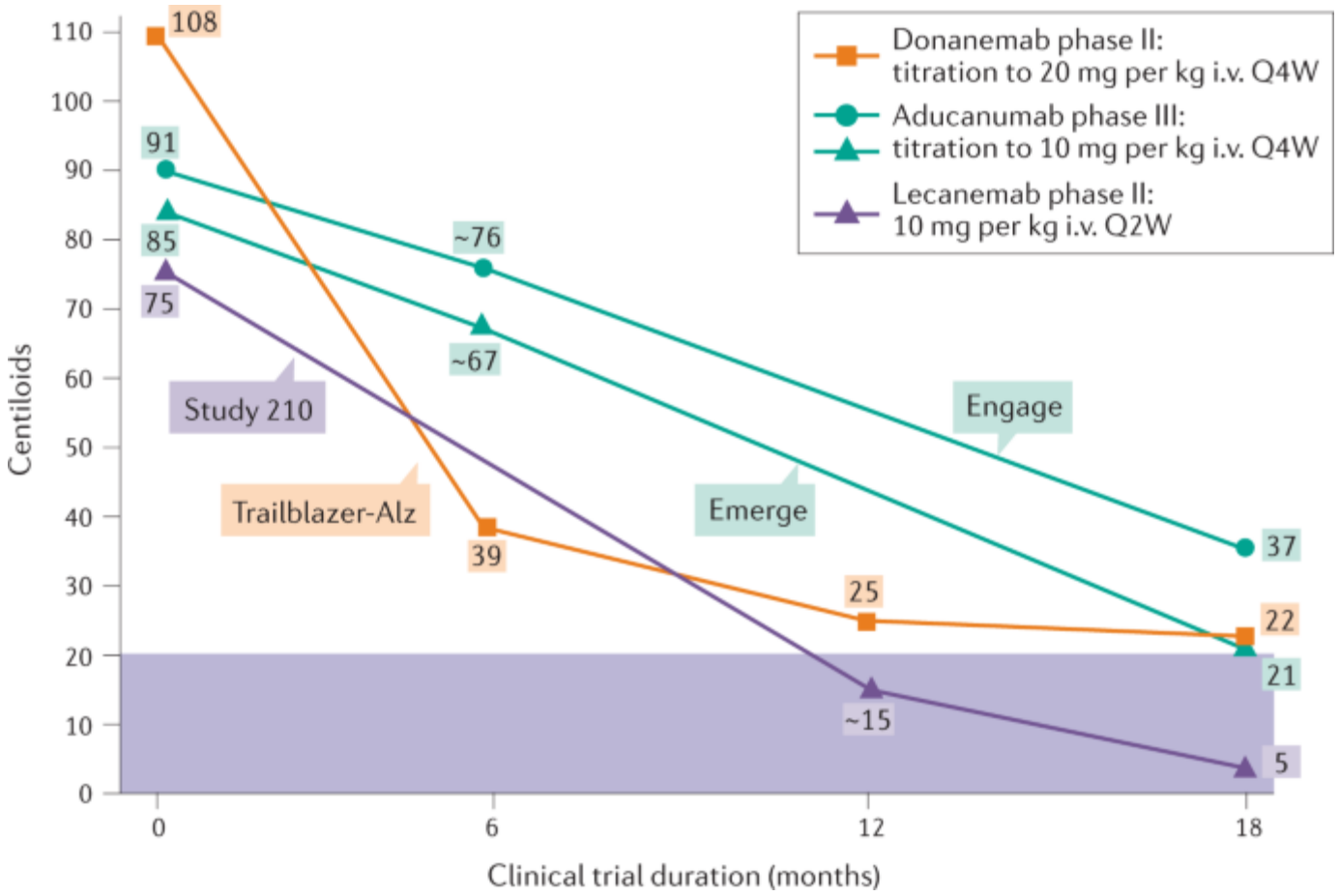
FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval

Action Follows Confirmatory Trial to Verify Clinical Benefit

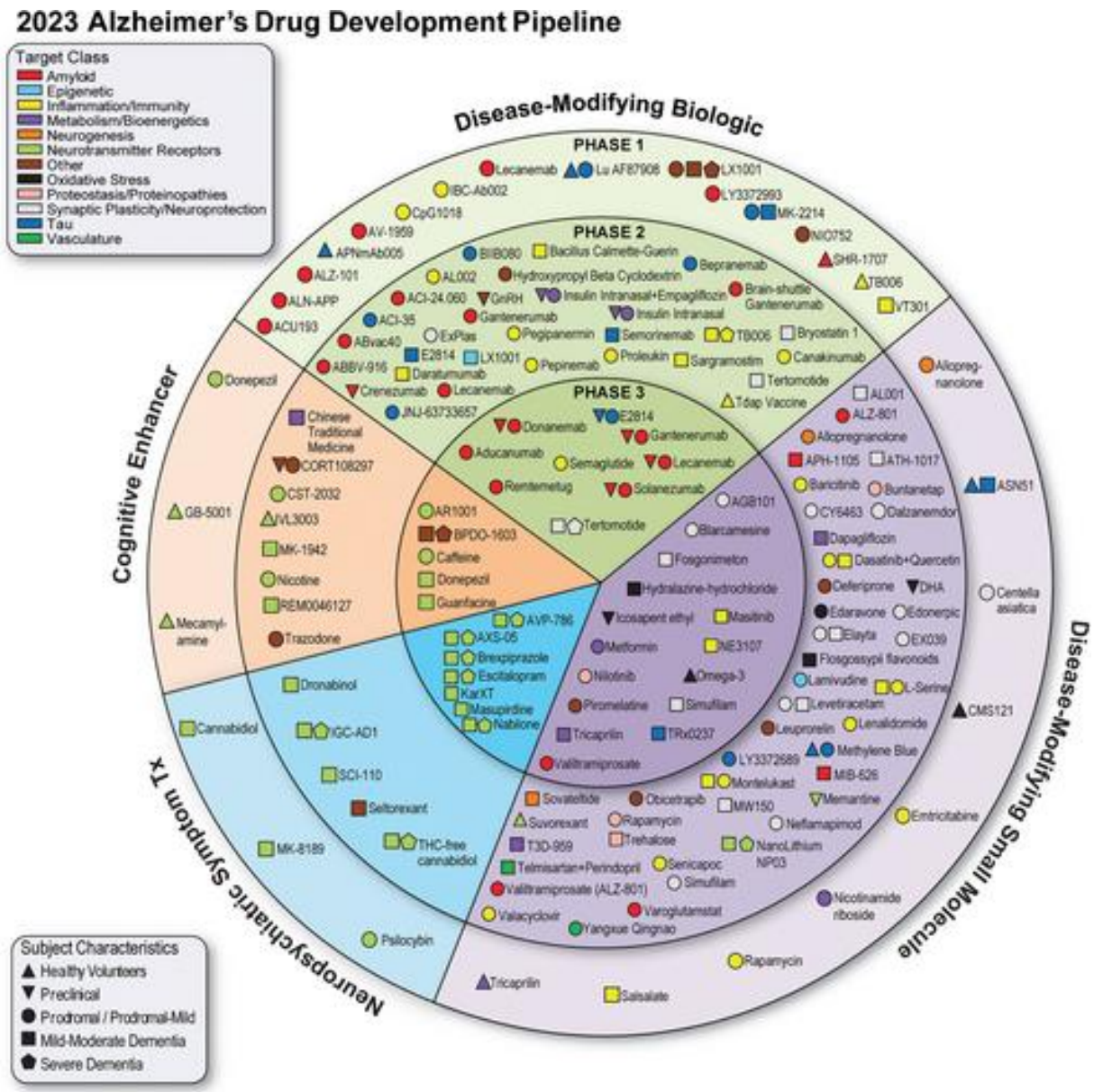
For Immediate Release:

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:

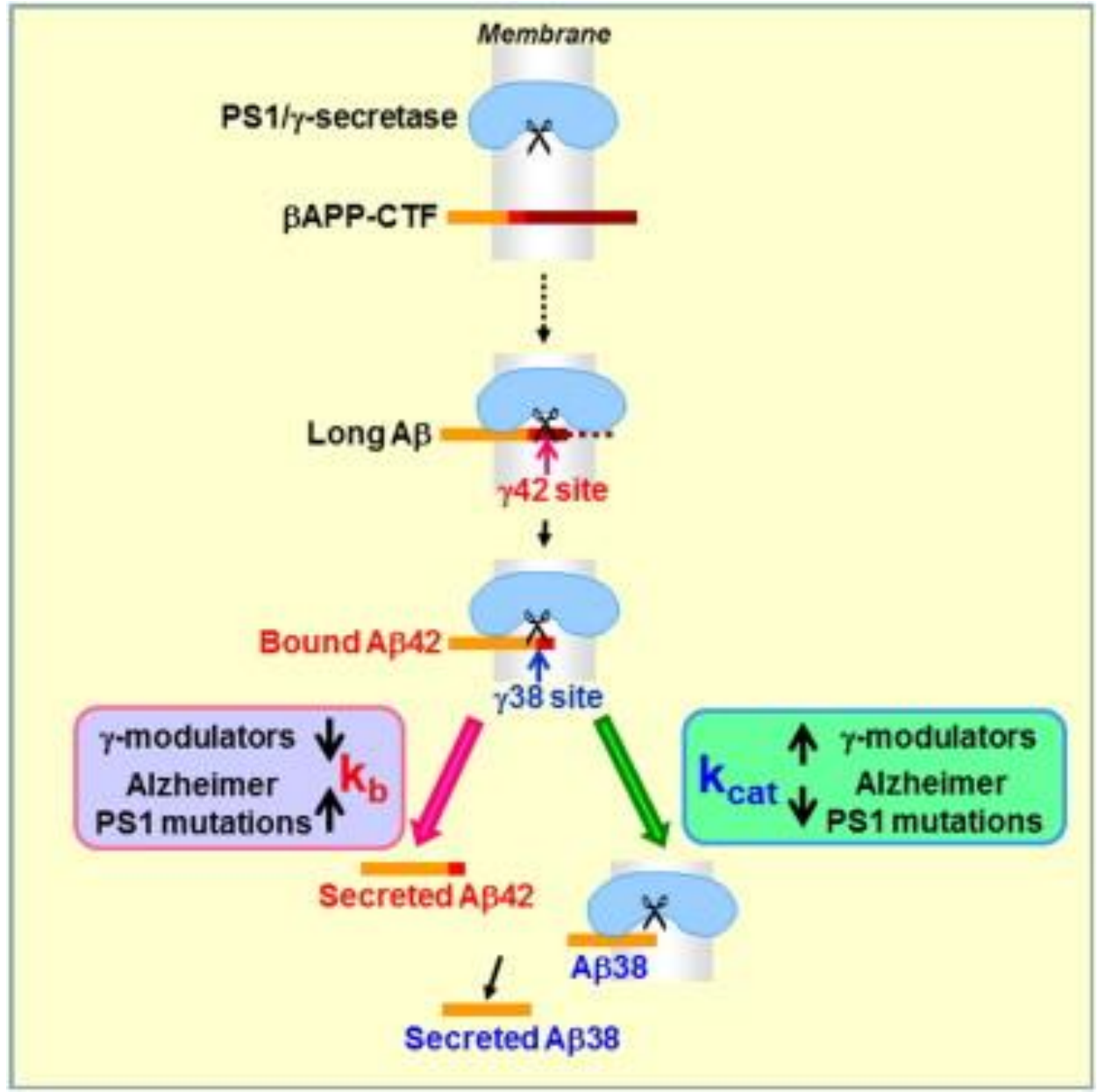
Amyloid-related imaging abnormalities

Expensive

Neuronal network damage may have already occurred

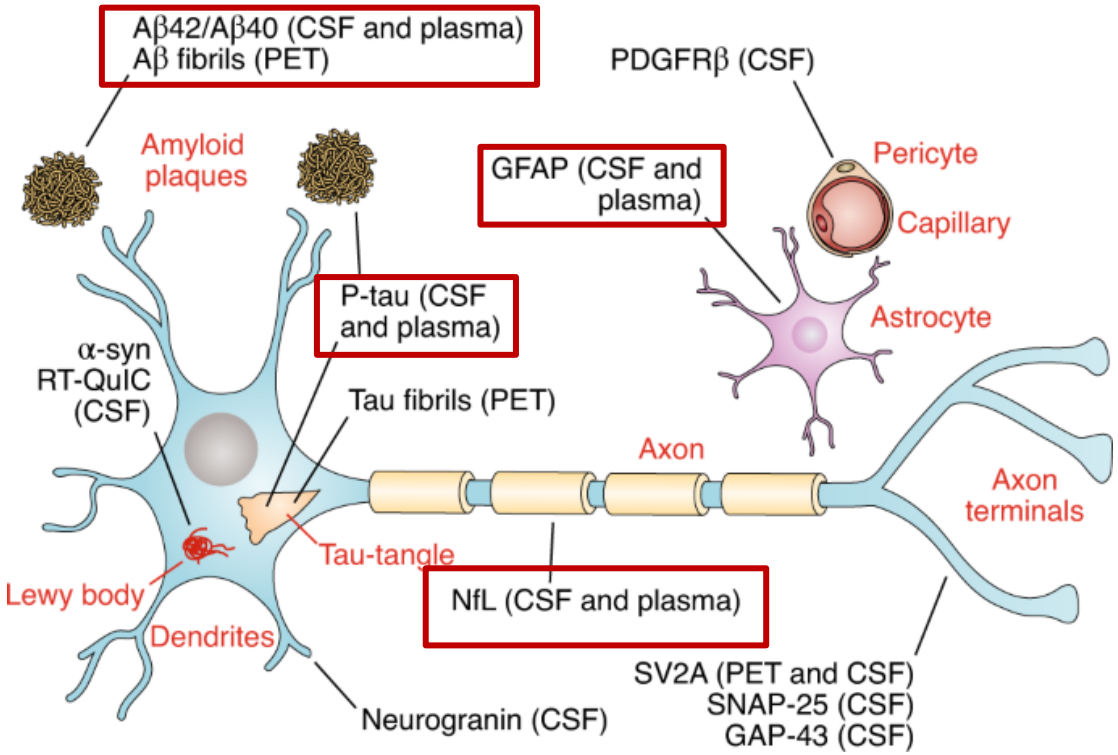
Tau pathology may have taken off

The case for gamma-secretase modulation



Okochi *et al*., 2013

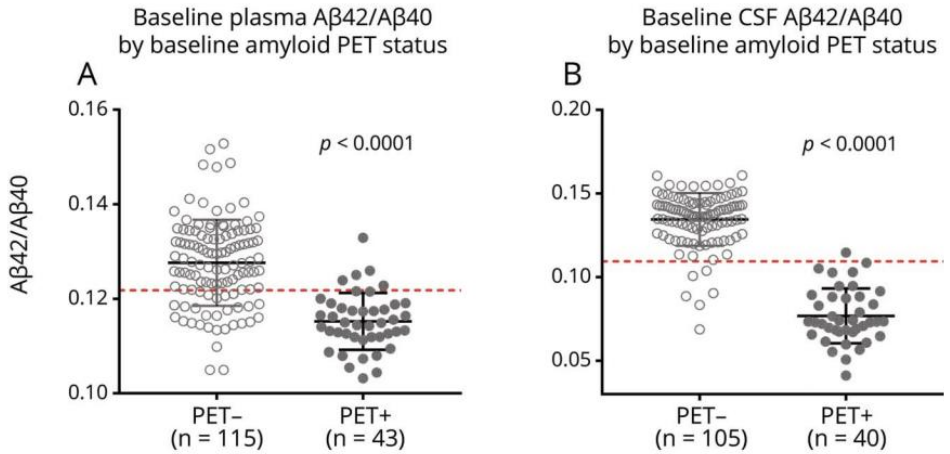
Available targeted protein biomarkers for dementias



Hansson 2022 Nature Medicine (PMID: 34083813)

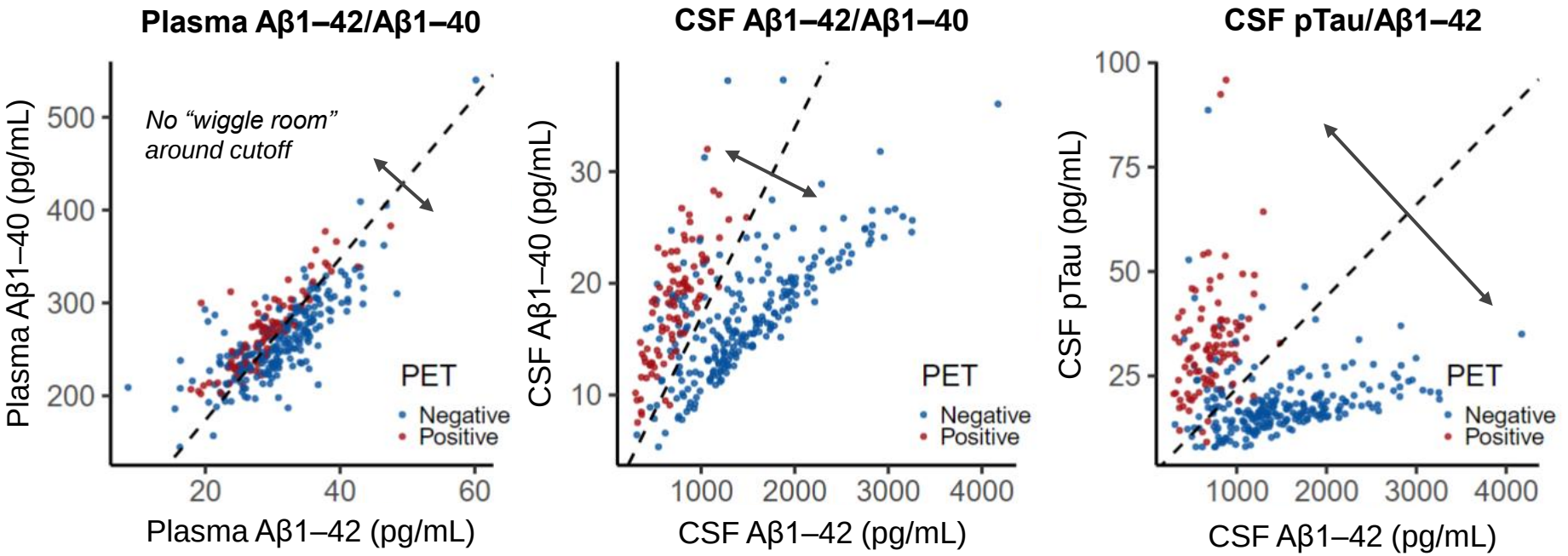
Plasma amyloid β

- 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

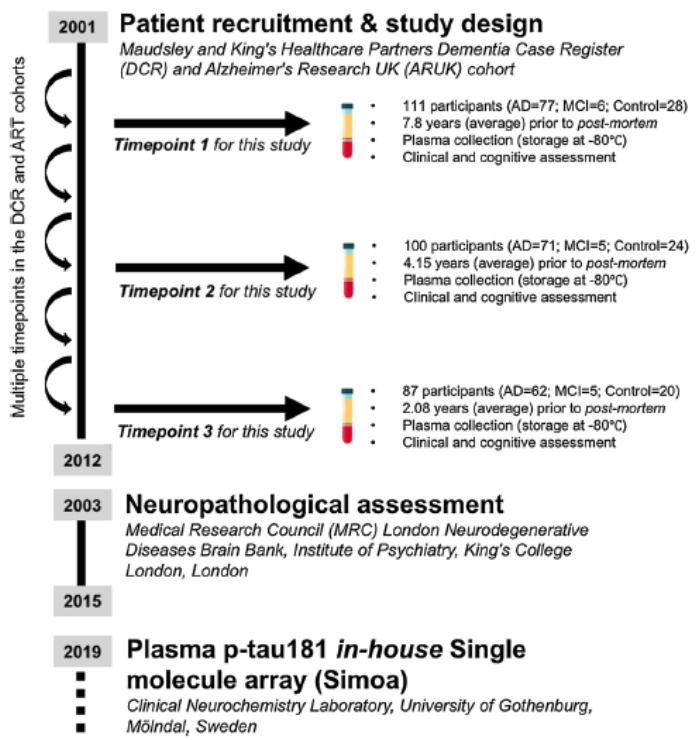


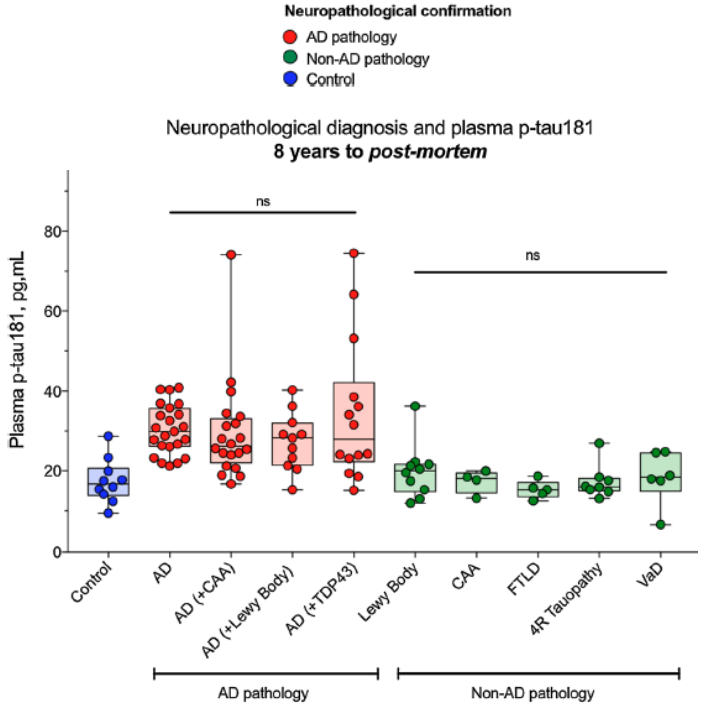
Rabe C *et al*., 2022

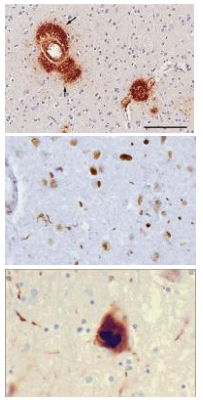
Plasma p-tau indicates AD pathology (including amyloid)

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

Plasma p-tau indicates AD pathology (including amyloid)





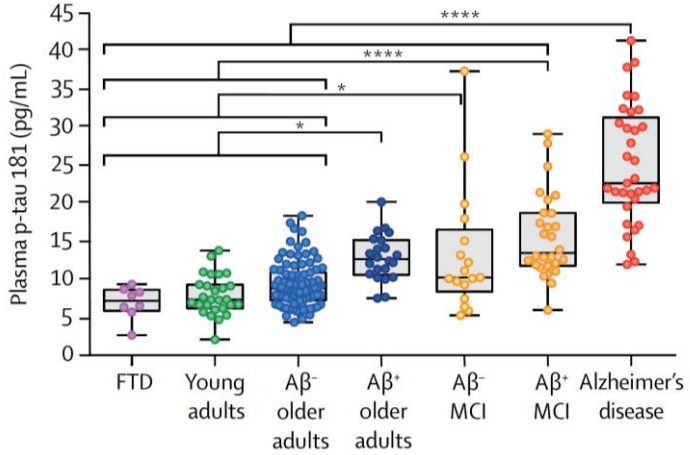


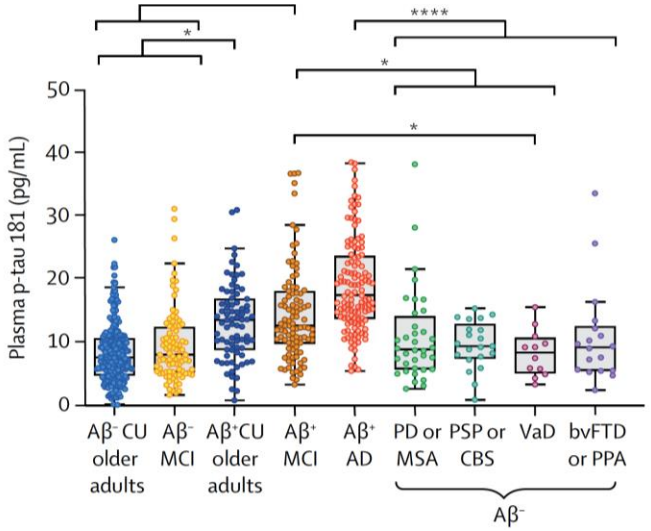
Lantero-Rodriguez et al., 2020 Acta Neuropathologica (PMID: 32720099)

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†





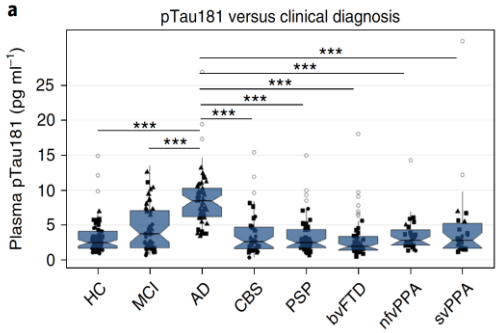
Karikari, Pascoal et al., 2020 Lancet Neurology (PMID: 32333900)

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

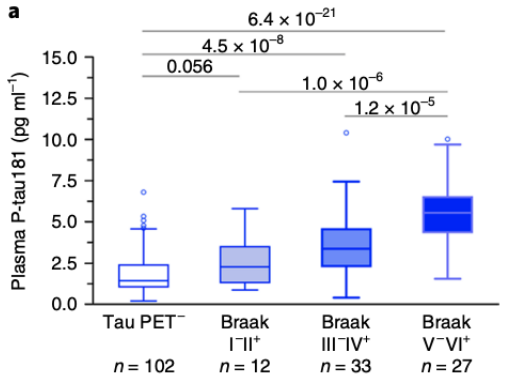
Elisabeth H. Thijssen[1,2], Renaud La Joie[1], Amy Wolf[1], Amelia Strom[1], Ping Wang[1], Leonardo Iaccarino[1], Viktoriya Bourakova[1], Yann Cobigo[1], Hilary Heuer[1], Salvatore Spina[1], Lawren VandeVrede[1], Xiyun Chai[3], Nicholas K. Proctor[3], David C. Airey[3], Sergey Shcherbinin[3], Cynthia 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

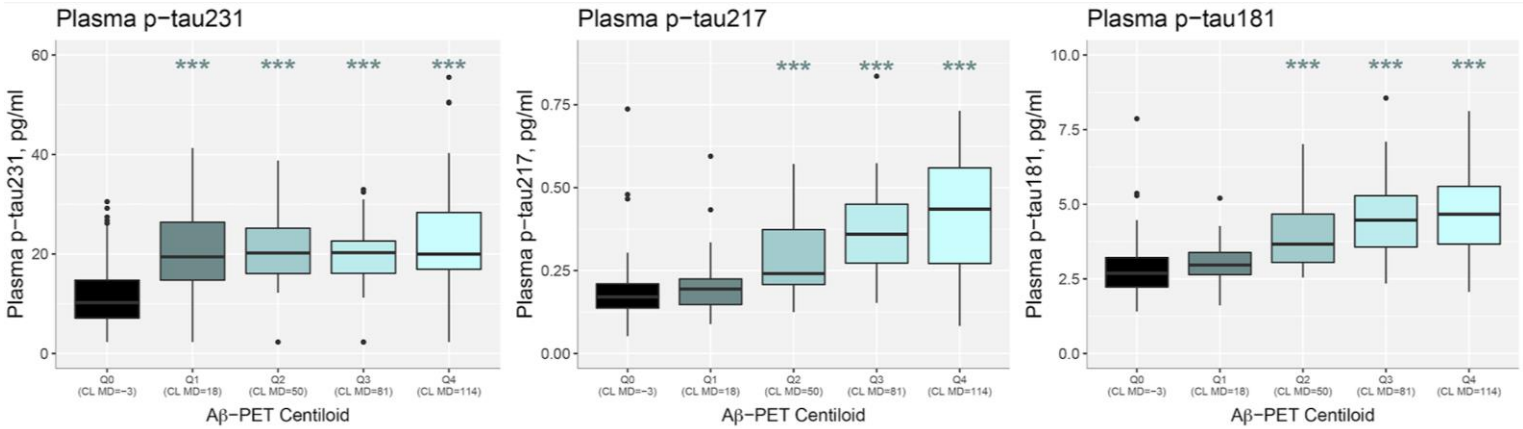
Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia

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]*



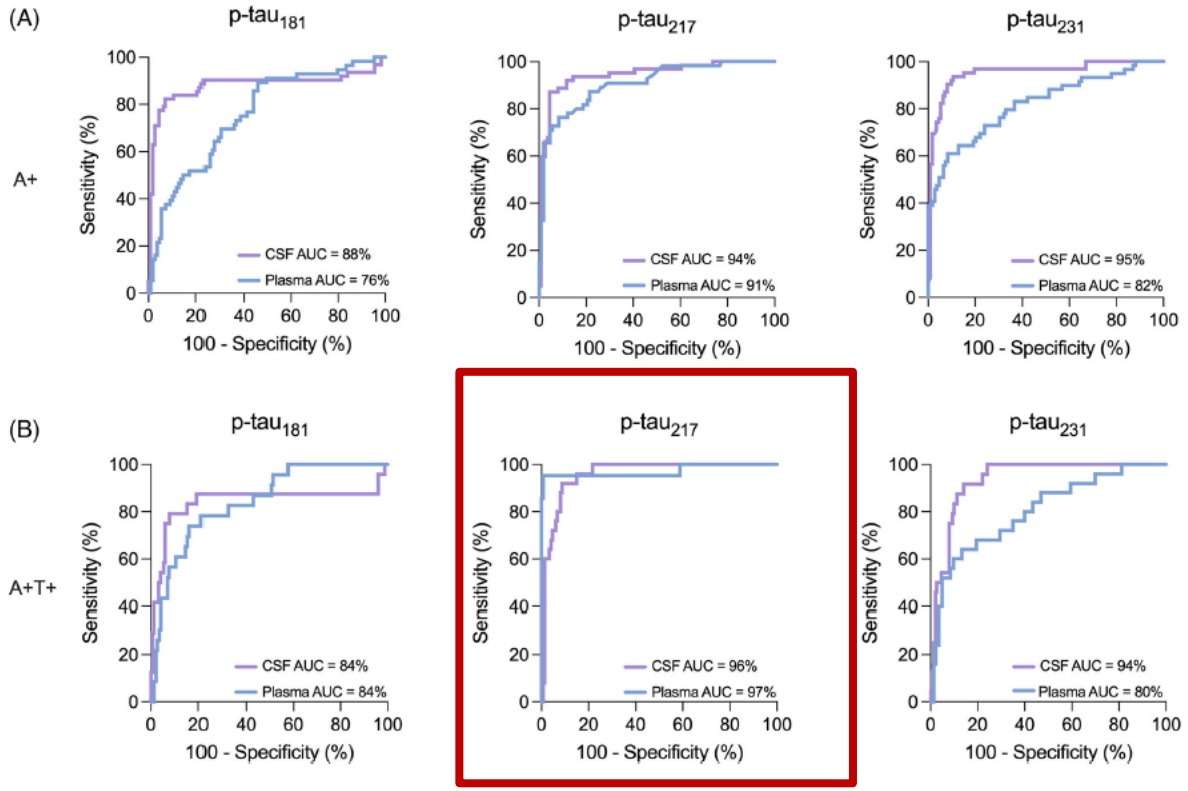
Thijssen et al., 2020 Nature Medicine (PMID: 32123386) / Janelidze et al., 2020 Nature Medicine (PMID: 32123385) / Mielke et al., 2018 Alzheimer's & Dementia (PMID: 29626426)

Different phospho-forms of tau can be measured in plasma



Ashton *et al*., Nature Med. 2022

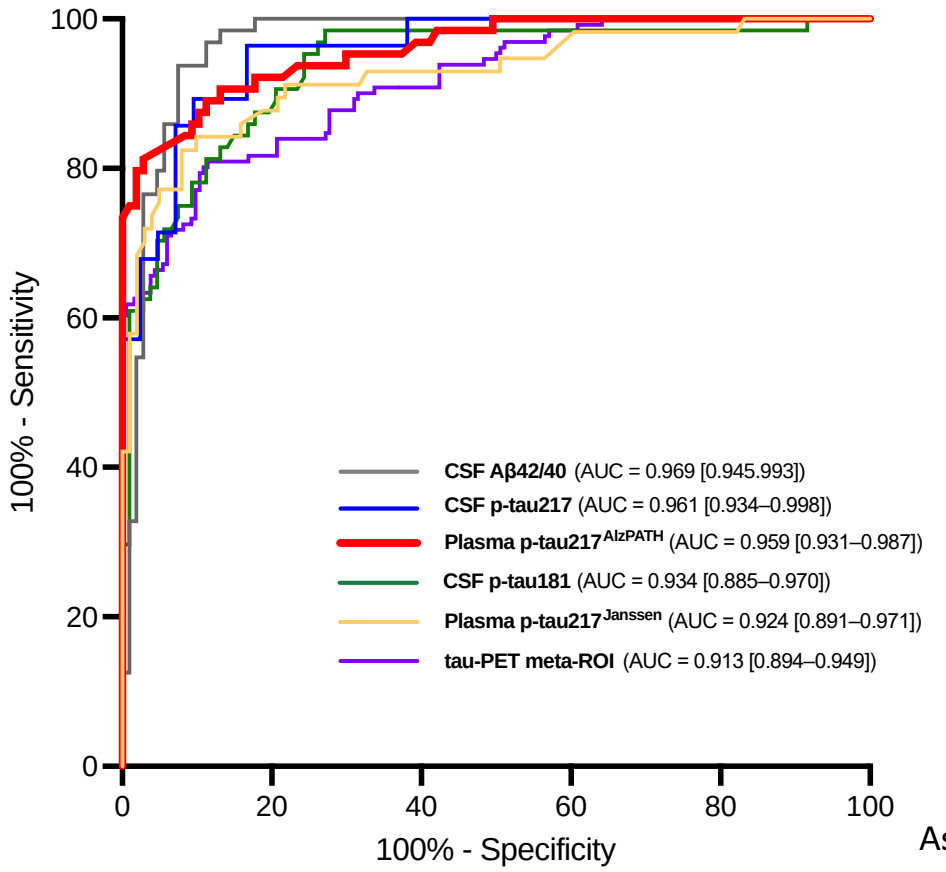
Equivalence of plasma p-tau217 with cerebrospinal fluid in the diagnosis of Alzheimer's disease



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

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

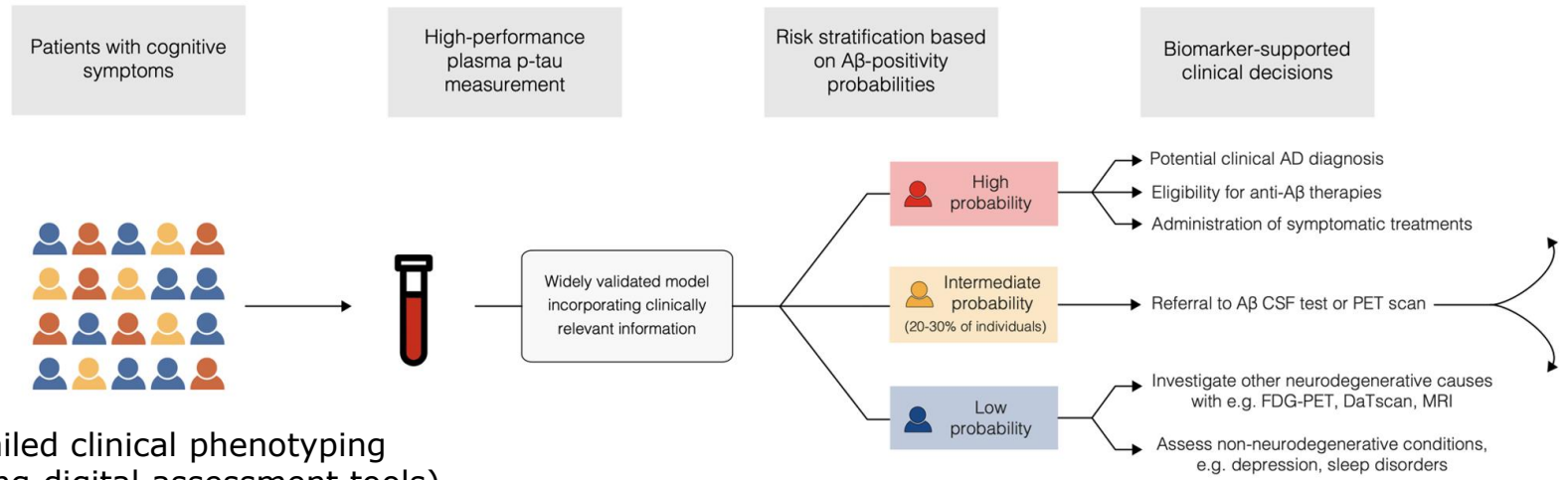
Figure 1A – predicting amyloid PET positivity



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)

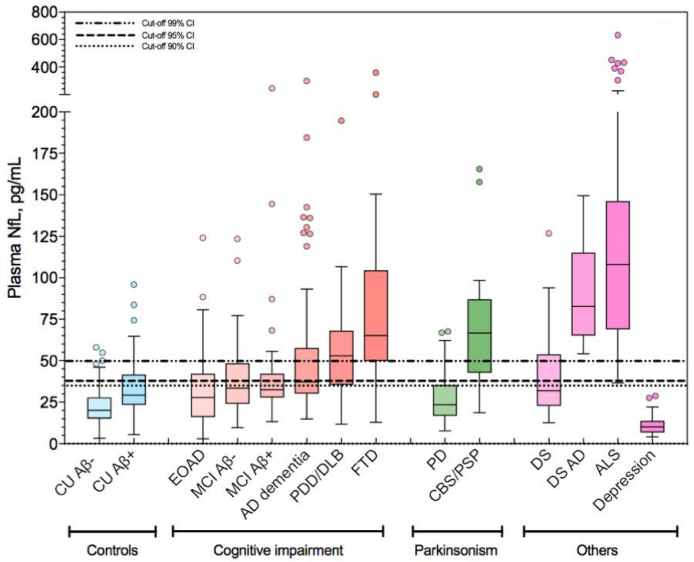


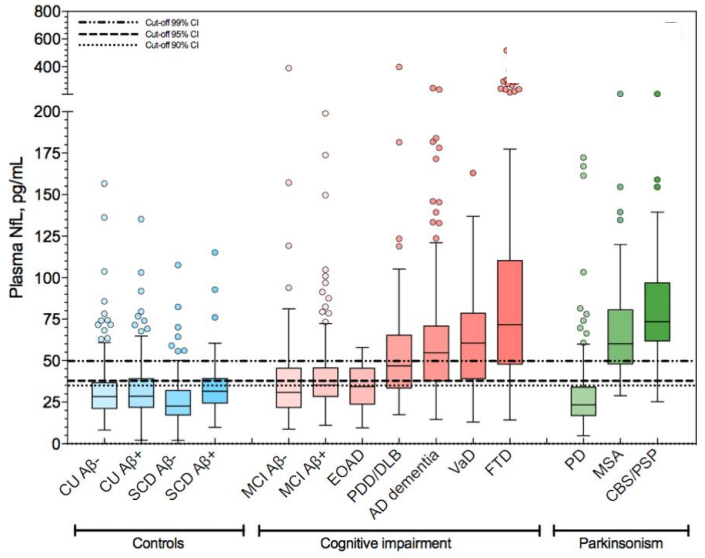
Detailed clinical phenotyping
(including digital assessment tools)

Brum, Cullen et al., *2023*

Plasma neurofilament light

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

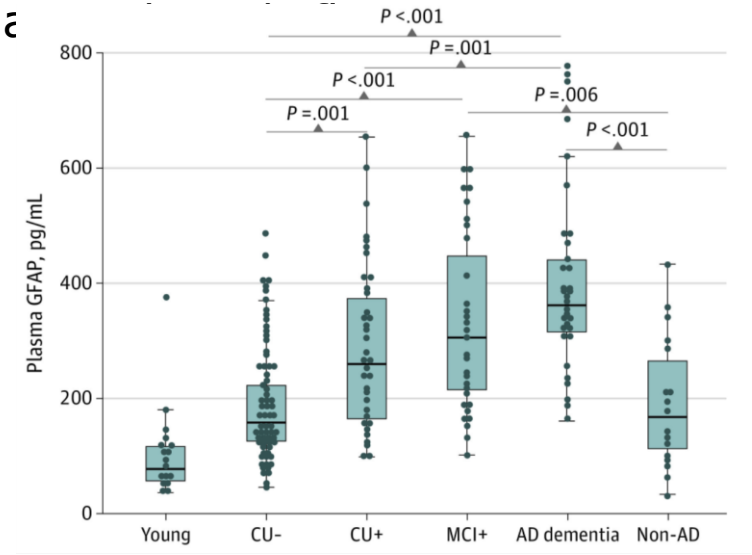


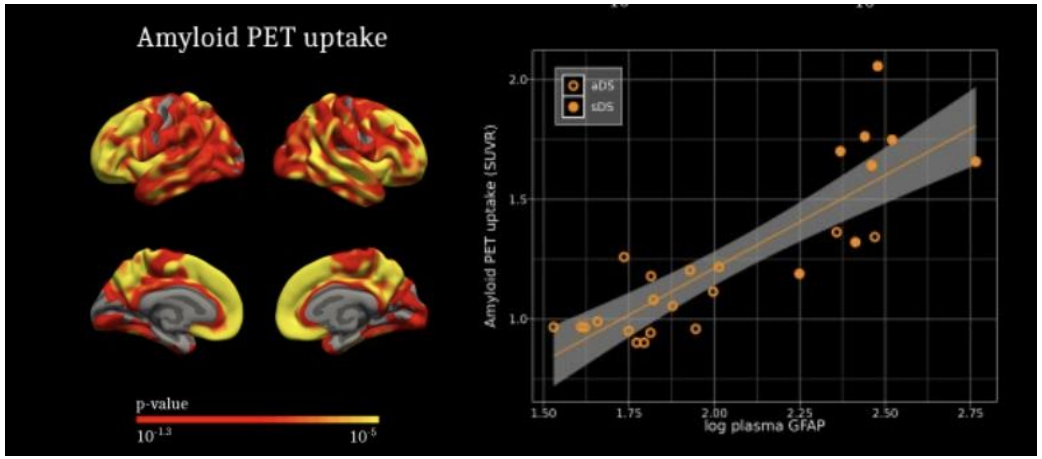


Ashton et al., 2020 Nature Communications (PMID: 34099648)

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

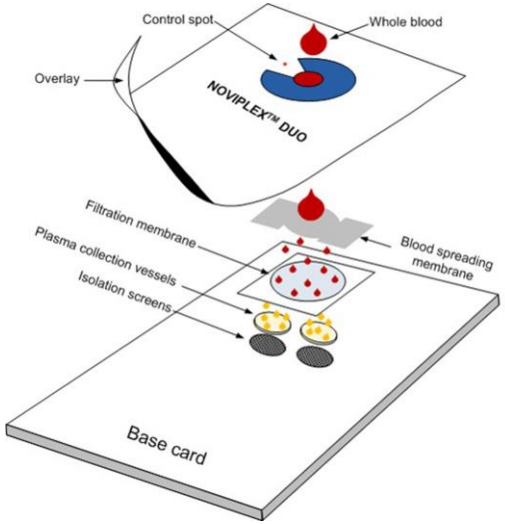
Advantages

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

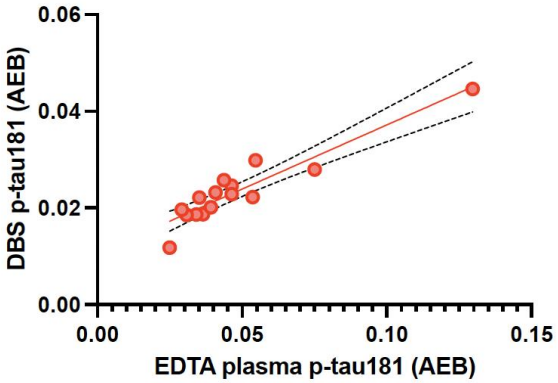
- Stable at room temperature >1-month
(Transferrable by normal post or stored without cooling/freezing)

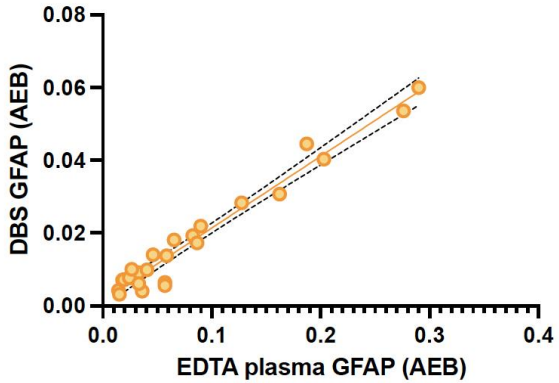
- Capillary blood is possible
(Remote self-collection, paediatric neurology, onset sports injuries, field clinicis)

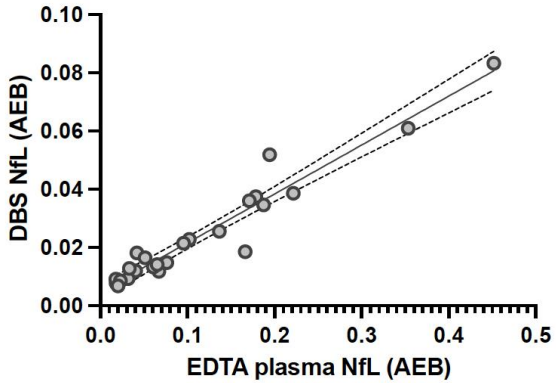
- Dementia biomarkers are measurable by Simoa with a modified extraction protocol



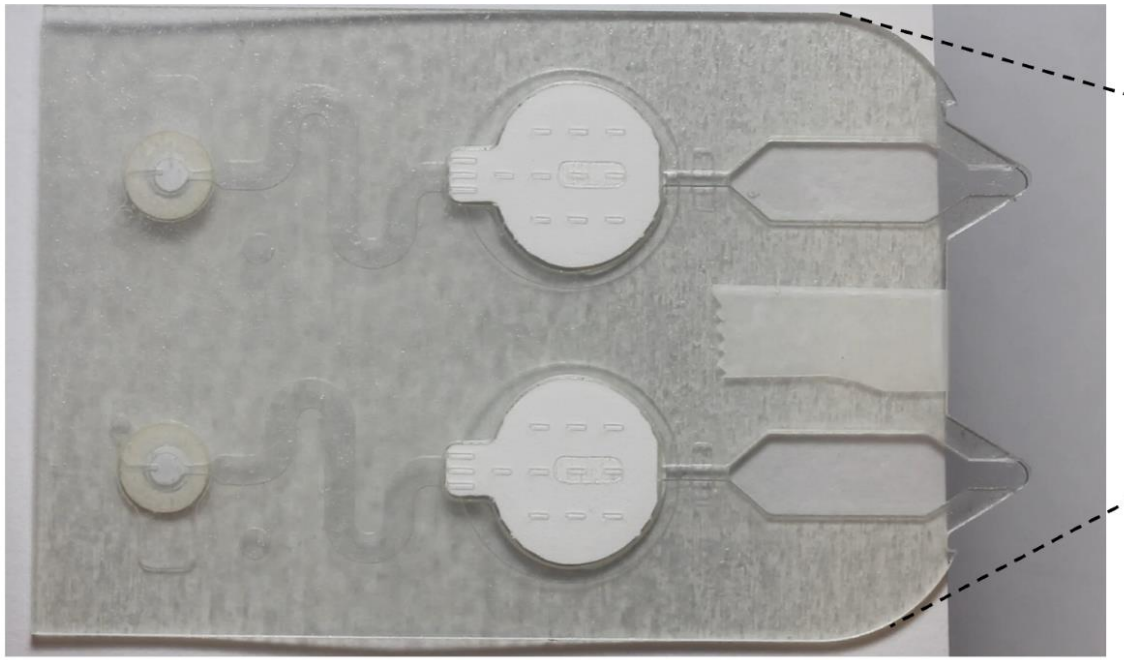
Blood spot collection – venous blood







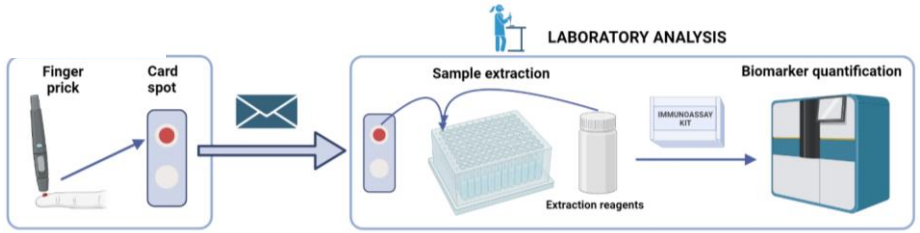
Capitainer®CF

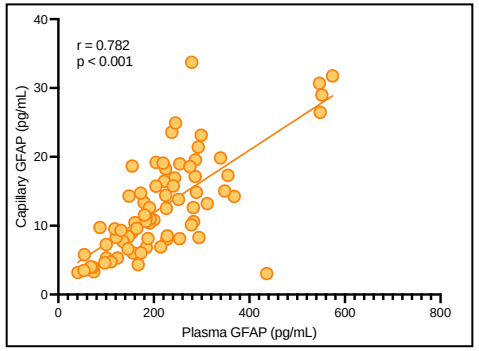


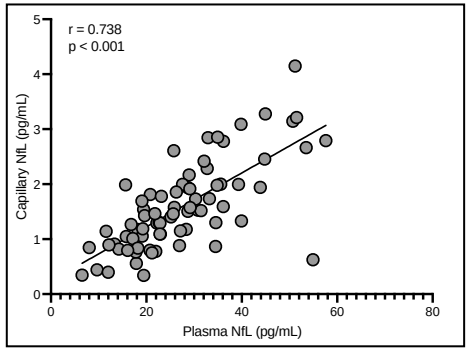
Storage | Metering | Filtration | Pre metering 70 µl

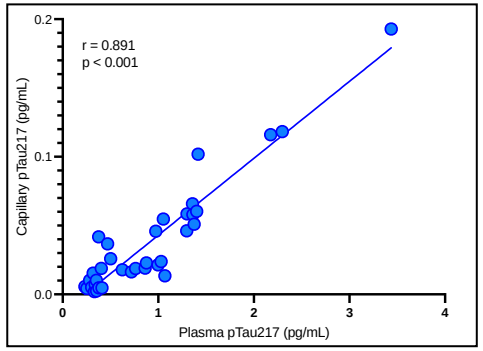
DROP-AD: detecting AD blood biomarkers using a finger-prick

- 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!!

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h.zetterberg@ucl.ac.uk

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

February 19, 2024

Alzstatin

- a small molecule disease modifying therapy against Alzheimer's disease

Johan Sandin, CSO

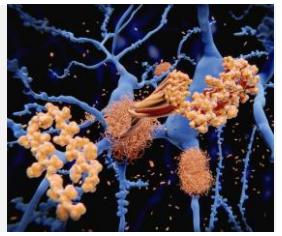
AlzeCure

Alzstatin® - Gamma-Secretase Modulator for Preventive Treatment of Alzheimer's

PROJECT OVERVIEW

Emanates from Big Pharma

- AlzeCure staff was **part of the conception** of the project at AstraZeneca
- Approximately **SEK 150m** already **invested** on project development
- Only Biotech with a gamma-secretase modulator (GSM)



Strong linkage to disease

- Gamma-secretase is a **key enzyme** producing **toxic Aβ42**
- **Genetic linkage to disease** - majority of all familiar mutations are linked to the gamma-secretase complex causing early onset of disease
- Alzstatin compounds **reduce** production of **Aβ42**

Positive preclinical data

- Two drug candidates, ACD679 and ACD680, in pre-clinical development phase
- Compounds **potently reduce Aβ42 production** - up to 60% in vivo
- GSM's also **produce shorter peptides** with suggested added beneficial effects

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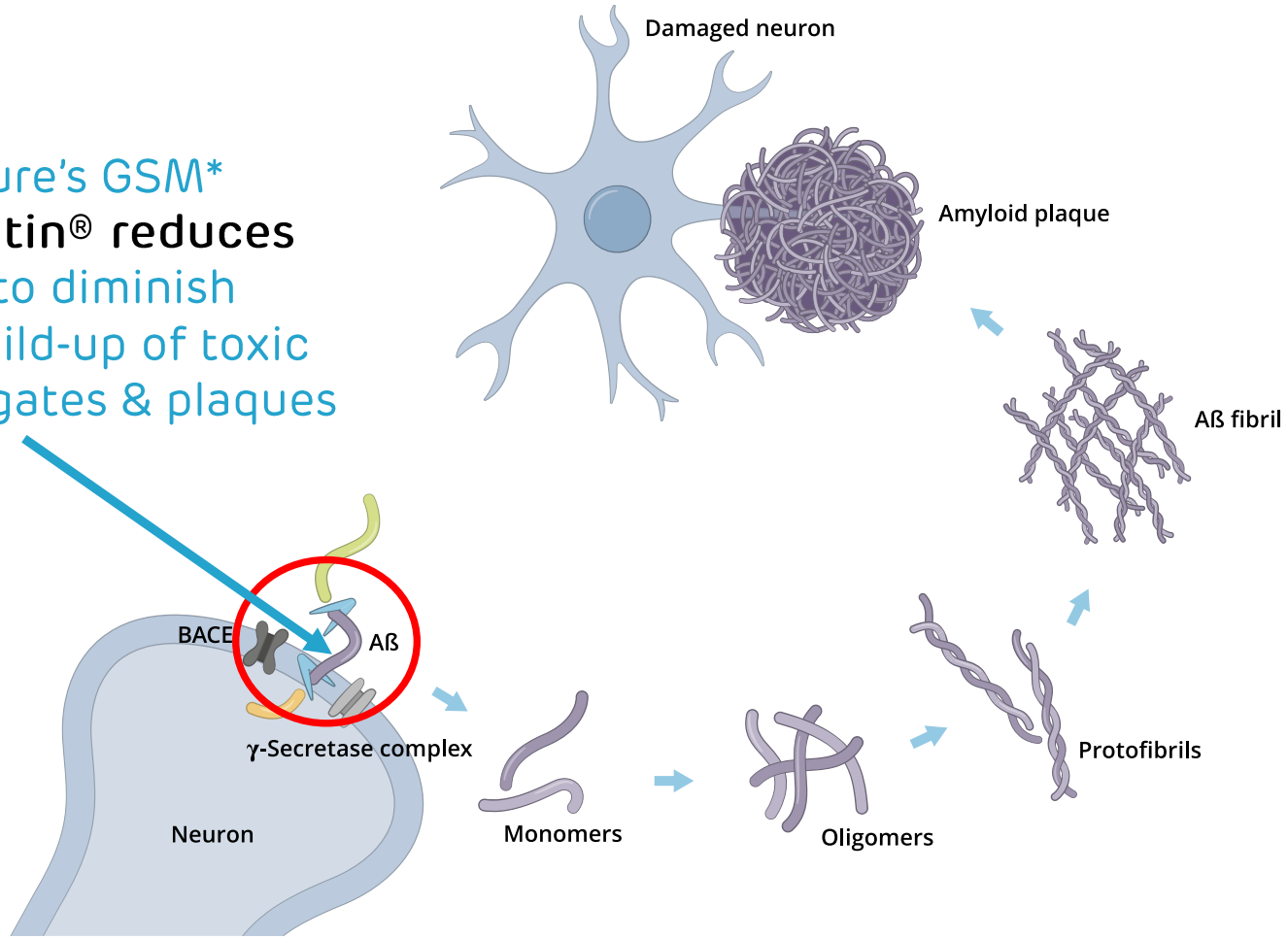
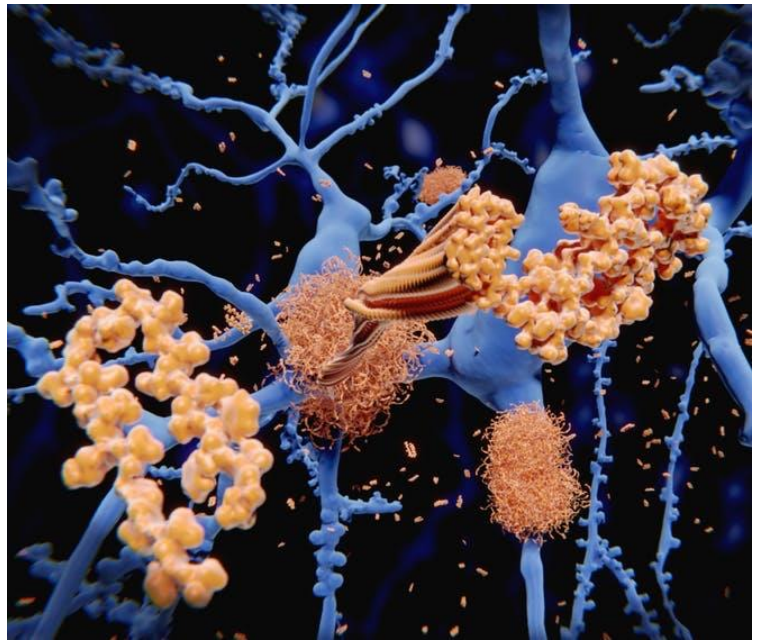
The Amyloid Cascade - Validated pathway that generates toxic Aβ fragments, resulting in damage to neurons and brain structures

AlzeCure's GSM*
Alzstatin® reduces
Aβ42 to diminish
the build-up of toxic
aggregates & plaques





*) GSM = Gamma Secretase Modulator

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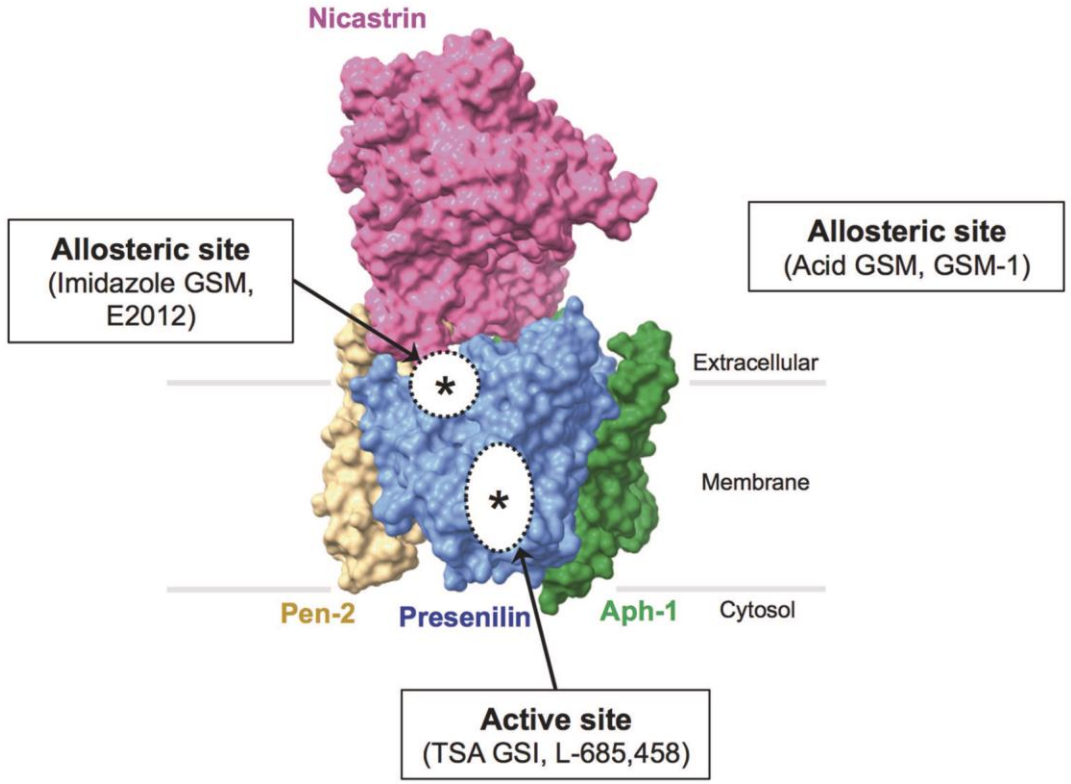
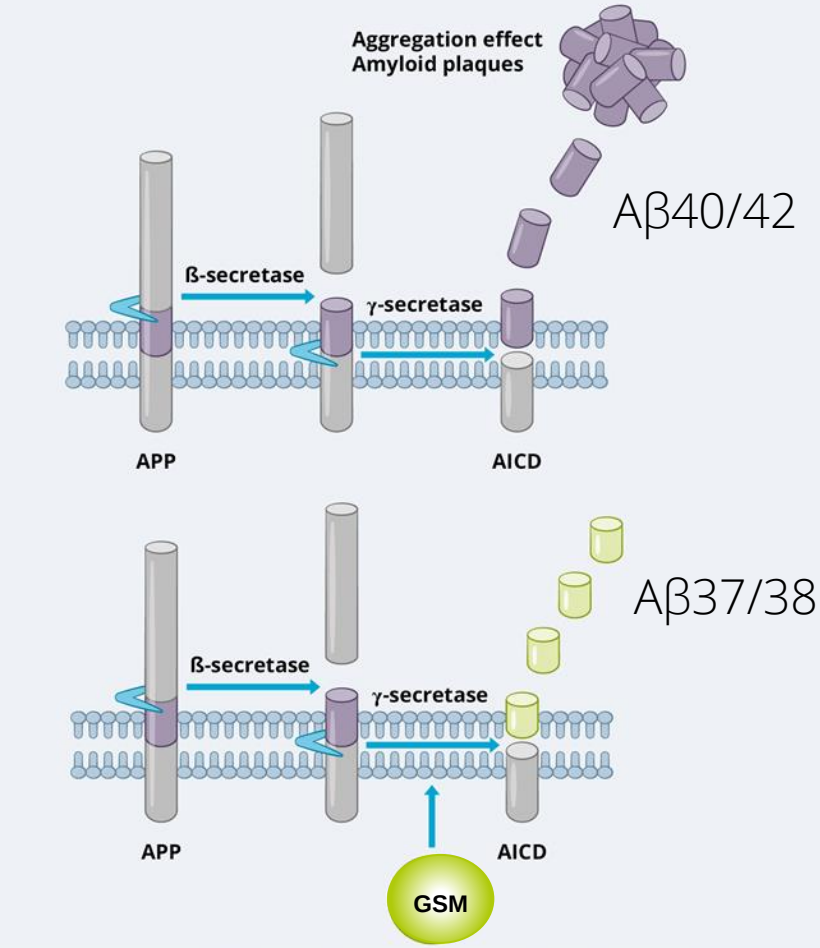
Mechanism of gamma-secretase modulators

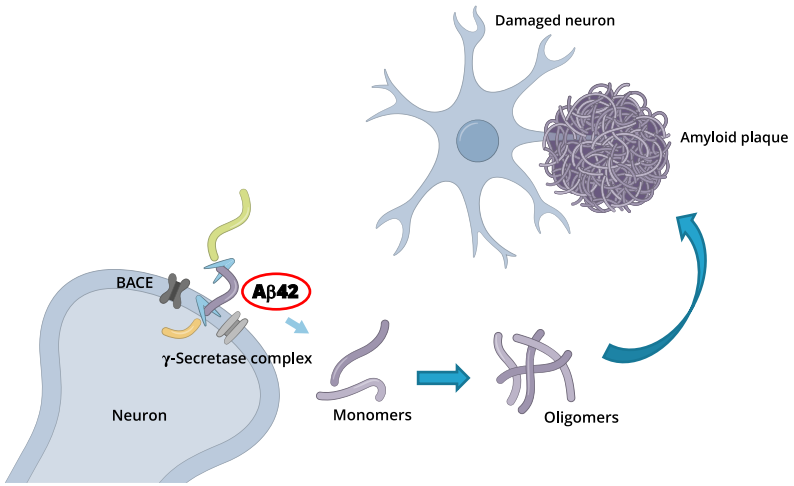




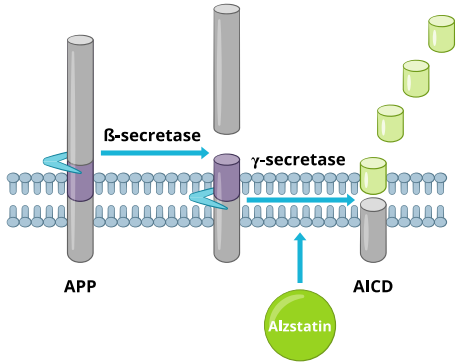
Alzstatin modulates the gamma secretase enzyme which results in the formation of shorter fragments that prevents the aggregation effect

Alzstatin, an Alzheimer's Disease Modifier – Preventing or Delaying Disease Progression

Aβ42 peptide is the main **culprit in AD progression**



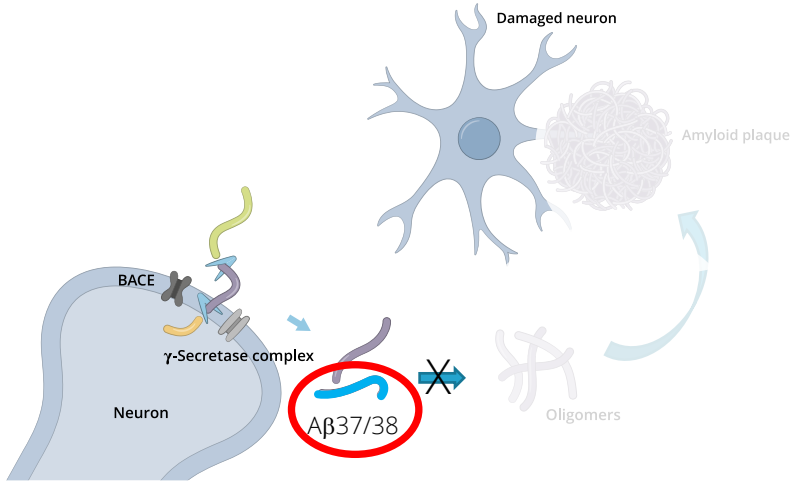
GSMs modulate the enzyme**, reducing Aβ42 & Aβ40** and shifting its cleaving pattern towards shorter forms and thereby **limits toxic oligomerization**



*Alzstatin **targets the gamma-secretase***

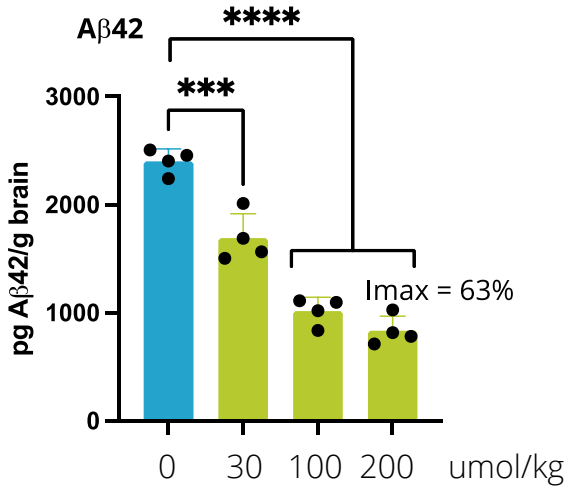
	Prone to self-aggregate	Inhibits formation of amyloid plaques	Toxic to cells
Aβ42	✓ ✓		✓ ✓
Aβ40	✓		✓
Aβ38		✓	
Aβ37		✓	

Alzstatin **produces more** non-toxic **Aβ37/38** which do not form amyloid aggregates, including oligomers

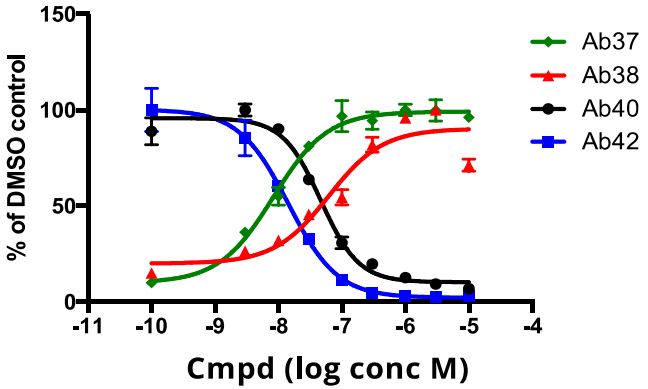


Aβ42 peptide is aggregation prone and toxic, while the **shorter forms Aβ37/38 exhibit protective properties**

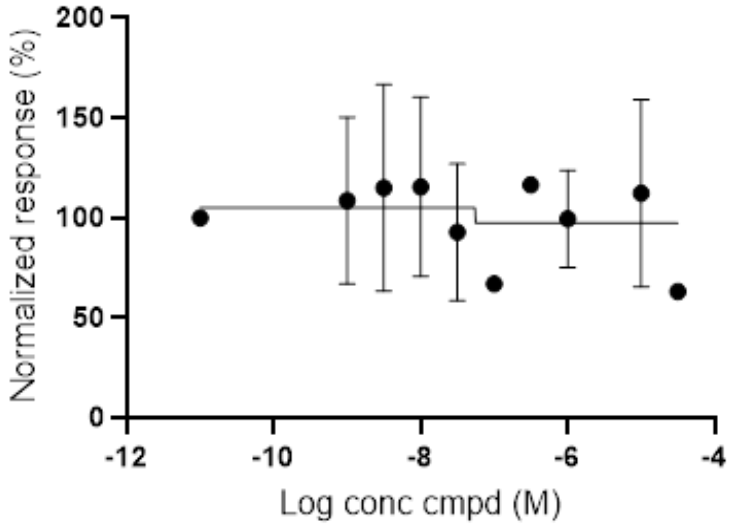
Alzstatin – Potent & Selective Reduction of Aβ42



Alzstatin compounds potently and dose-dependently **reduces the amount of toxic brain Aβ42** in mice after a single dose



GSMs reduce the amount of toxic Aβ42 & Aβ40, while **increasing the amount of the protective Aβ37 & Aβ38** species



Alzstatin compounds do not have any effect on total Aβ levels

➢ **GSMs - Potent Effect on toxic Aβ42 Production without affecting total enzyme activity**

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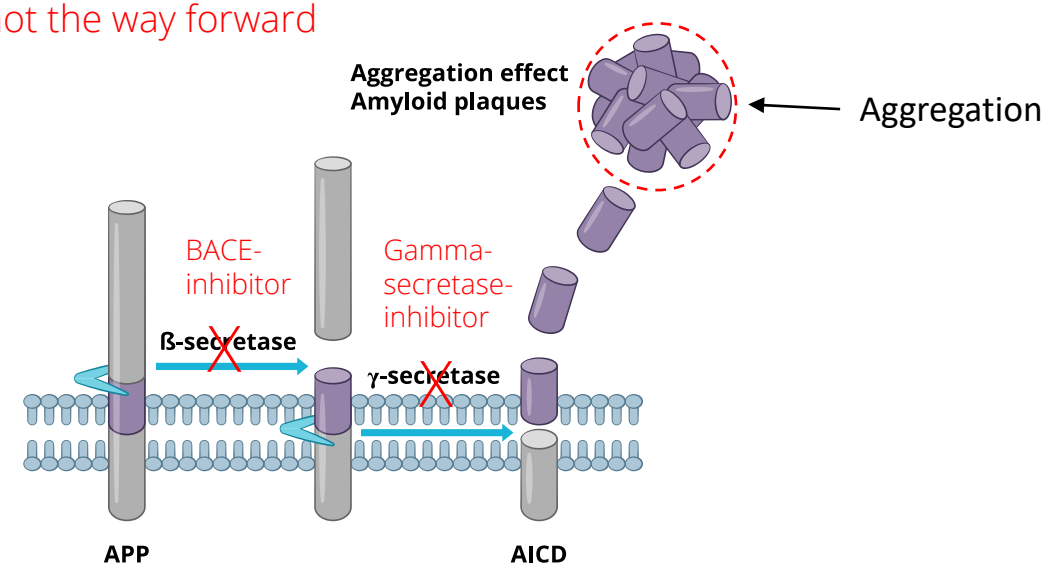
Differentiation from BACE* and Gamma secretase inhibitors

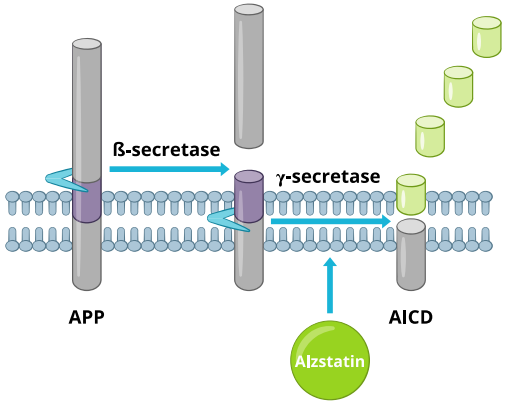
Both BACE- and gamma-secretase inhibitors caused significant side-effects due to inhibition of other key substrates of the enzyme → **inhibition** not the way forward

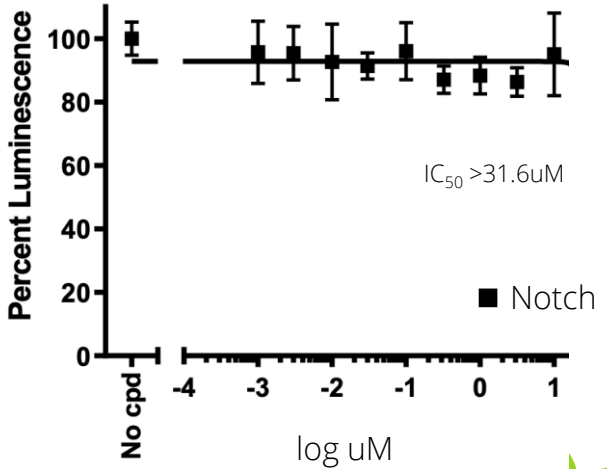


Aβ42 - main culprit in Alzheimer progression

GSM is a safer MoA than an inhibitor, e.g. BACE- or gamma-secretase inhibitor

Alzstatin **targets gamma secretase** as a **modulator** – does ***not*** block enzyme activity

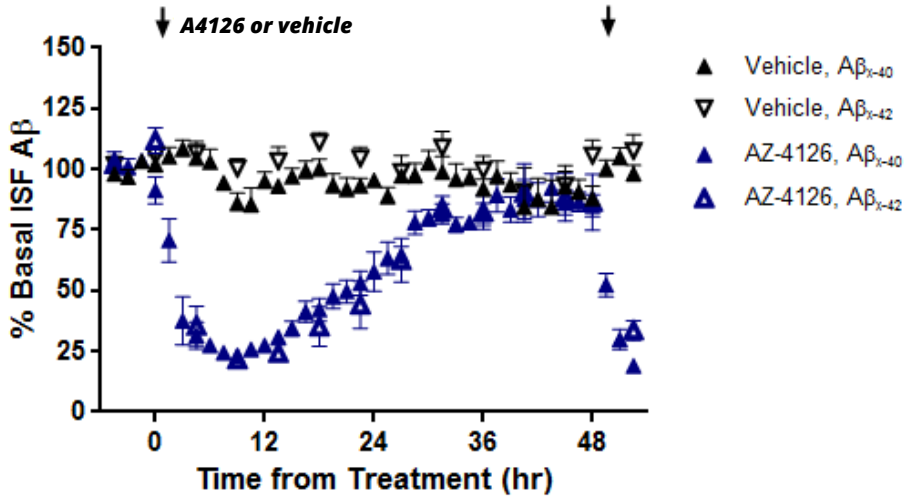




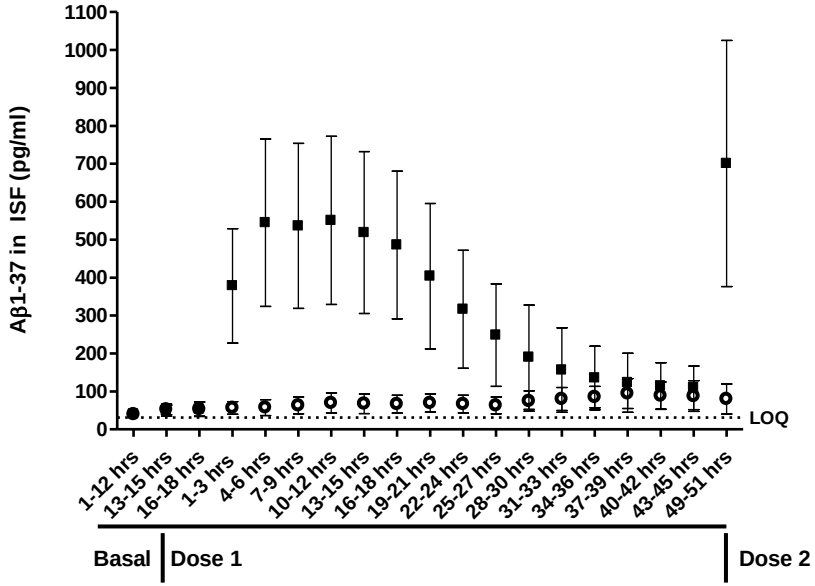
Alzstatin compounds **does not block the cleavage of other gamma-secretase substrates**, such as Notch

***BACE = beta-secretase**

Alzstatin compounds effectively modulate Aβ production in the brain in vivo



Tg2576 mice (6 months) treated with 100 μmol/kg A4126 (p.o.) show significant lowering of Aβ42 and Aβ40 in interstitial fluid



100 μmol/kg A4126 show significant increase in Aβ37 in interstitial fluid

Systemic administration of a GSM results in a large decrease in Aβ42/40 and an increase in Aβ37 in the interstitial fluid in an established mouse AD model

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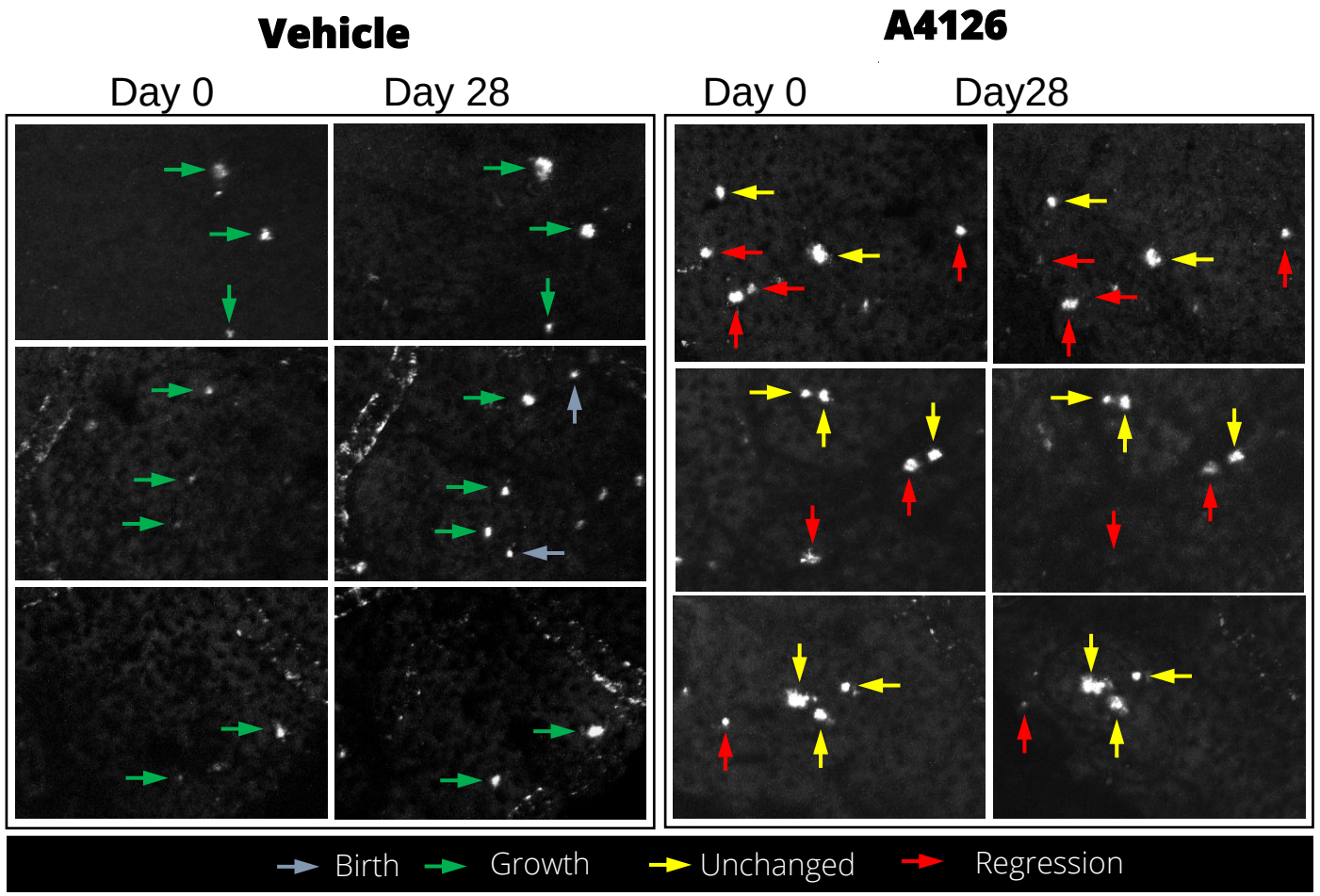
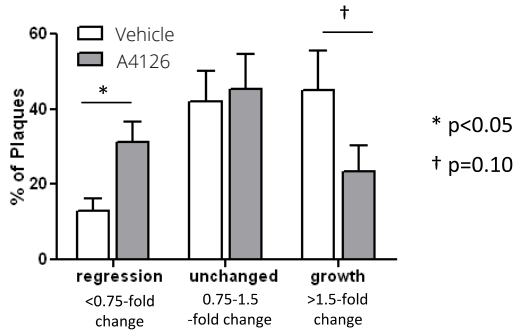
AlzeCure's GSM affects amyloid aggregation in APP/PS1 mice



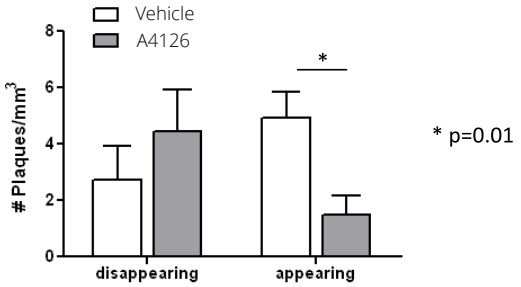
Distribution of Plaque Growth and Regression



* p<0.05

† p=0.10

Plaque appearance or disappearance



* p=0.01

28-day GSM treatment:

- **Attenuates amyloid plaque growth**
- **Decreases new plaque appearance**
- **Induces modest plaque regression**

Beneficial effect of shorter Aβ peptides

RESEARCH ARTICLE OPEN ACCESS

Association of CSF $A\beta_{38}$ Levels With Risk of Alzheimer Disease–Related Decline

Nicholas Cullen, BS, Shorena Janelidze, PhD, Sebastian Palmqvist, MD, PhD, Erik Stomrud, MD, PhD, Niklas Mattsson-Carlgren, MD, PhD, and Oskar Hansson, MD, PhD, for the Alzheimer's Disease Neuroimaging Initiative

Correspondence
Mr. Cullen
nicholas.cullen@med.lu.se

Neurology® 2022;98:e958-e967. doi:10.1212/WNL.0000000000013228

Patients/populations that have:

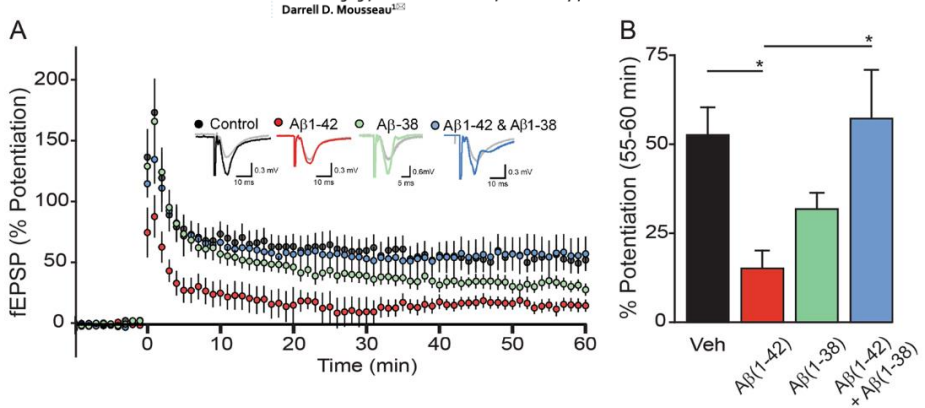
- Higher Aβ38 has a slower decline in MMSE
- High Aβ38 has a slower conversion in to AD

scientific reports

OPEN

The Aβ(1–38) peptide is a negative regulator of the Aβ(1–42) peptide implicated in Alzheimer disease progression

Maa O. Quartey[1], Jennifer N. K. Nyarko[1], Jason M. Maley[2], Jocelyn R. Barnes[3], Maria A. C. Bolanos[4], Ryan M. Heistad[1], Kaeli J. Knudsen[1], Paul R. Pennington[1], Josef Buttigieg[4], Carlos E. De Carvalho[5], Scot C. Leary[6], Matthew P. Parsons[3] & Darrell D. Mousseau[1,2]



Aβ38 reverses the negative impact of Aβ42 on long-term potentiation in acute hippocampal slices and on membrane conductance in primary neurons

Shorter peptides attenuates Aβ42 toxicity in C. elegans and Drosophila

Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

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Cite this: *Chem. Sci.*, 2022, **13**, 2423

All publication charges for this article have been paid for by the Royal Society of Chemistry

Amyloid-β peptide 37, 38 and 40 individually and cooperatively inhibit amyloid-β 42 aggregation†

Gabriel A. Braun, ‡[a] Alexander J. Dear, [abcd] Kalyani Sanagavarapu,§[a] Henrik Zetterberg[efgh] and Sara Linse *[a]

Higher levels of Aβ37/38 appear beneficial

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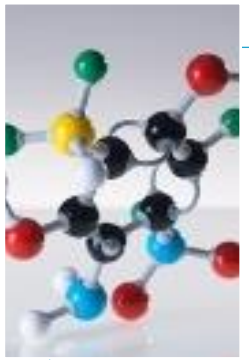
How Alzstatin is expected to differ from the Antibodies*
- Key advantages

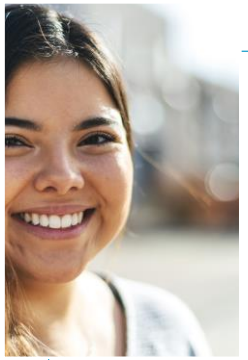


Small molecule therapy

- Small molecules generally pass much more readily across the BBB to its target site - the brain
- Provides a more cost-effective treatment for chronic use than biologics

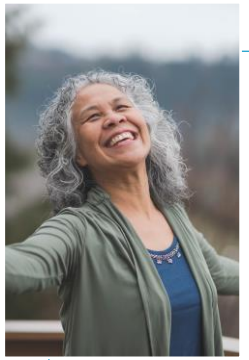
Oral formulation => Home treatment

- Don't need to go to the hospital once or twice a month for an infusion of the drug



Stand-alone or combination therapy

- Suitable both as stand-alone therapy as well as combination therapy together with anti-amyloid antibodies



Fewer side effects

- Not expected to have the side effects of brain oedema and brain microbleedings (ARIA)
  - => Is not expected to demand regular brain scans, => minimizing hospital visits and costs

*) E.g. Leqembi (lecanumab), Aduhelm (aducanumab), Donanemab

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Early Value Driving Proof-of-Mechanism in Phase I

- **Proof of Mechanism & Central Target Engagement**
  - Phase I - SAD/MAD studies to be performed
    - Evaluation of safety and tolerability after single and repeated administration
  - Possible to explore biomarker effects **showing central target engagement**
    - Aβ42/40 – show **reduction of toxic Aβ-species**
    - Aβ37/38 – show **increase of shorter protective Aβ-species**, establishing gamma-secretase involvement and MoA
    - Biomarker strategy employed previously by Pfizer (PMID: 31314925)
    - Measurements done both in CSF & plasma utilizing readily **available kits**

- **BBB-penetrant Small Molecule for Oral Use**
  - **Not expected to cause brain oedema** (ARIA-E) and brain microbleeds (ARIA-H) associated with mAb therapies*

* E.g., antibodies (mAb) like Leqembi ™ (lecanumab) & donanemab

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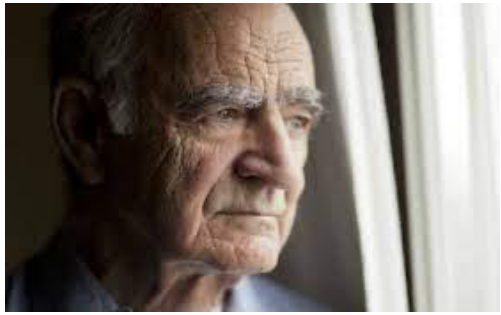
Multiple target populations - maintenance and preventive therapy

Maintenance therapy in patients with established Alzheimer's

- Treatment after initial plaque clearance by monoclonal antibody treatment (as initially proposed by Lilly) e.g., with: Lecanemab (Eisai/Biogen/Bioarctic), Donanemab (Lilly), Remternetug (Lilly)

Combination therapy together with monoclonal antibody treatment - early AD

- Combine plaque clearance by monoclonal antibody treatment and reduction of Aβ42 production by GSM



Preventive therapy based on genetic risk factors* & biomarkers (long-term possibility)

- Early stand-alone treatment before onset of symptoms and any major neurodegeneration occurs (prior to rapid increase in Tau pathology)
- Prevents build-up of amyloid – an early pathological feature of AD
- Familiar forms of the disease (incl. Downs syndrome) suitable for initial proof of concept clinical studies

*) E.g. ApoE4

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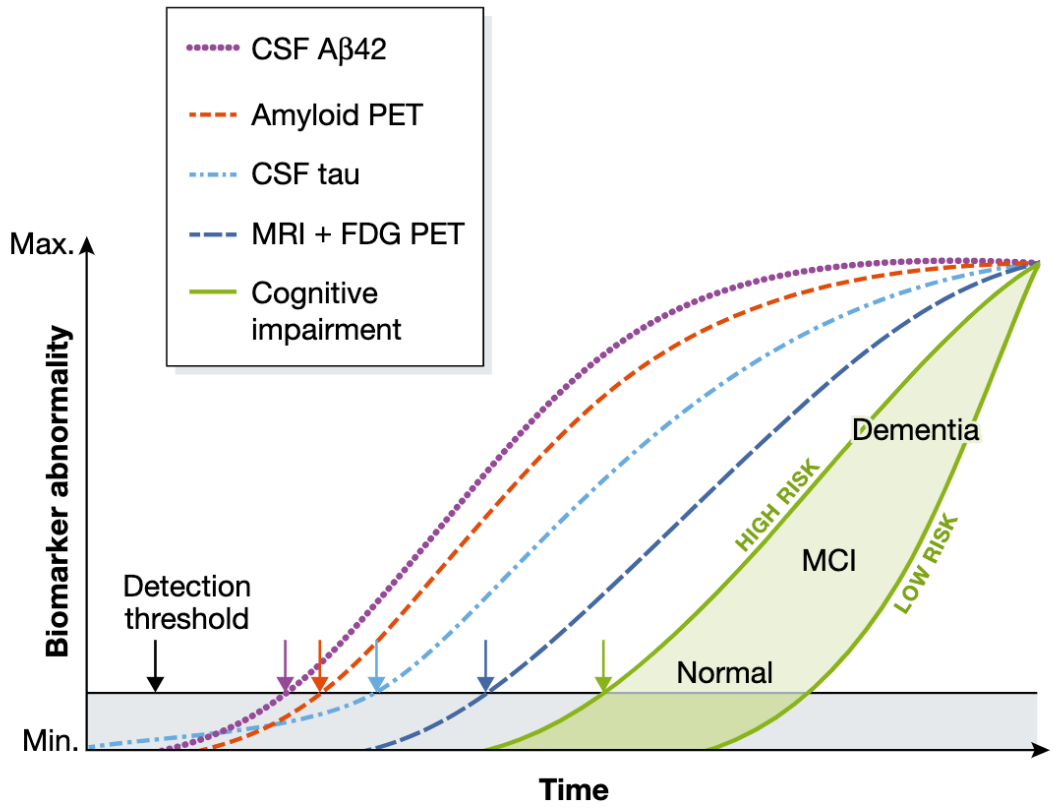
Well established biomarkers in the field



Possible blood/CSF biomarkers
Aβ42/40/38/37 and different ratios thereof
Tau: T-tau, pTau181, pTau217, and pTau231

NFL - neurodegeneration
GFAP - neuroinflammation

Collaboration with Prof. Zetterberg will enable us to select best biomarkers

Blood biomarker development will allow for early patient selection & detection, but at present confirmation by PET/CSF biomarkers is needed

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Summary

Advantages with Alzstatin

- ✓ Decreases Aβ42 production – reduces all forms of amyloid aggregates (oligomers, fibrils etc.)
- ✓ Increases the shorter peptides Aβ37 and Aβ38 - suggested to have protective properties
- ✓ Do not block enzyme activity and spares important physiological signaling – key for safety
- ✓ Genetically supported mechanism - mode of action is the reverse of most familiar Alzheimer mutations
- ✓ Small molecule compound – allows for cost-effective oral administration & good CNS exposure
- ✓ PoM data achievable already in phase 1 clinical trials
- ✓ Could also be used together with other disease-modifier therapies, e.g. antibodies
- ✓ Potential to prevent or slow disease progression

Bart De Strooper on Alzforum regarding Lecanemab Phase 3 results:

"These results strongly suggest that we revisit previous drug targets such as y-secretase and BACE, as small compounds modulating these activities might be, in the long run, the only cheap and feasible prevention for AD."

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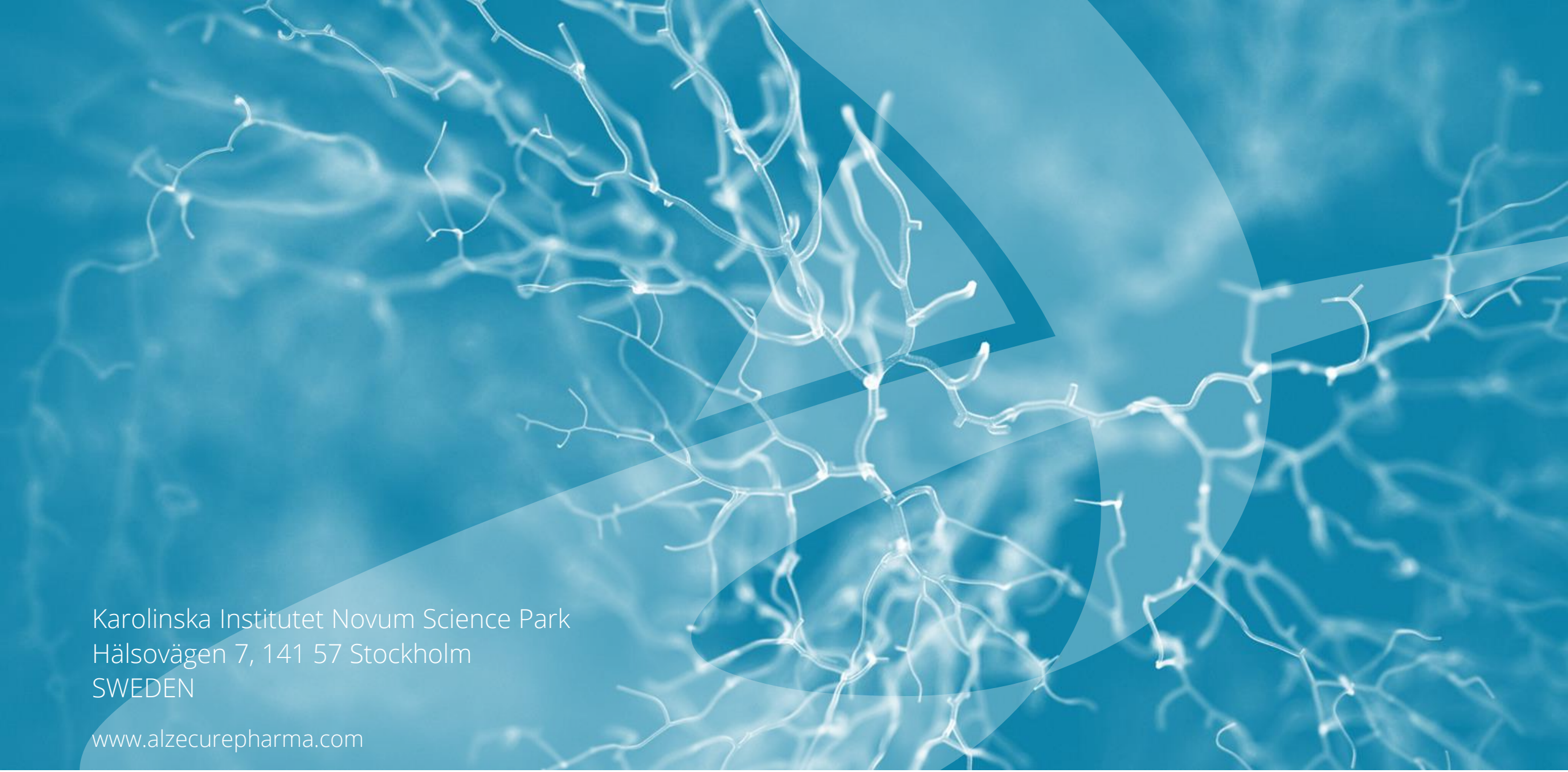

Karolinska Institutet Novum Science Park
Hälsovägen 7, 141 57 Stockholm
SWEDEN

www.alzecurepharma.com

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Expert Event

Advances in the treatment of Alzheimer's disease

– Small molecule **Gamma-Secretase Modulators** (GSMs) as promising disease-modifying treatments

Q&A session

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Closing remarks & Take Home Messages

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Take Home Messages

On the Alzheimer's market & unmet medical needs

- **Early detection** of the risk to develop Alzheimer's, **up to 15 years before clinical symptoms**, opens up the **need for new treatments** aiming to minimize toxic amyloid load
- There is a **huge unmet medical need** in the Alzheimer's therapy market, **even if antibodies are available** (- only 5-8% of Alzheimer's pts are eligible)
- There are still **no curative or preventive Alzheimer's treatments approved**
- **Gamma-secretase modulators** is a new and **promising class of Alzheimer's therapies**, with **several different target patient populations**

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Take Home Messages

On AlzeCure Pharma

- AlzeCure is a clinical stage Alzheimer's and CNS company with **several novel first-in-class and/or best- in-class assets**
- AlzeCure's ambition is to develop Alzheimer's **therapies that both stop disease progression and improve cognition**
- **NeuroRestore ACD856**, currently in **preparation for clinical phase 2 studies**, is being developed as a cognitive enhancer with potential neuroprotective and neurodegenerative properties
- **Alzstatin,** AlzeCure's **gamma-secretase modulator** program, is currently in preclinical phase and is **planned to initiate clinical phase 1 studies in 2025**
- **Efficacy data & Proof of Mechanism** could be **established already in phase 1** for our gamma-secretase modulator, which is expected to be a strong value driver

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Download the presentation

- The recorded presentation and slide sets will be made available on AlzeCure's web page
  - www.alzecurepharma.com

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