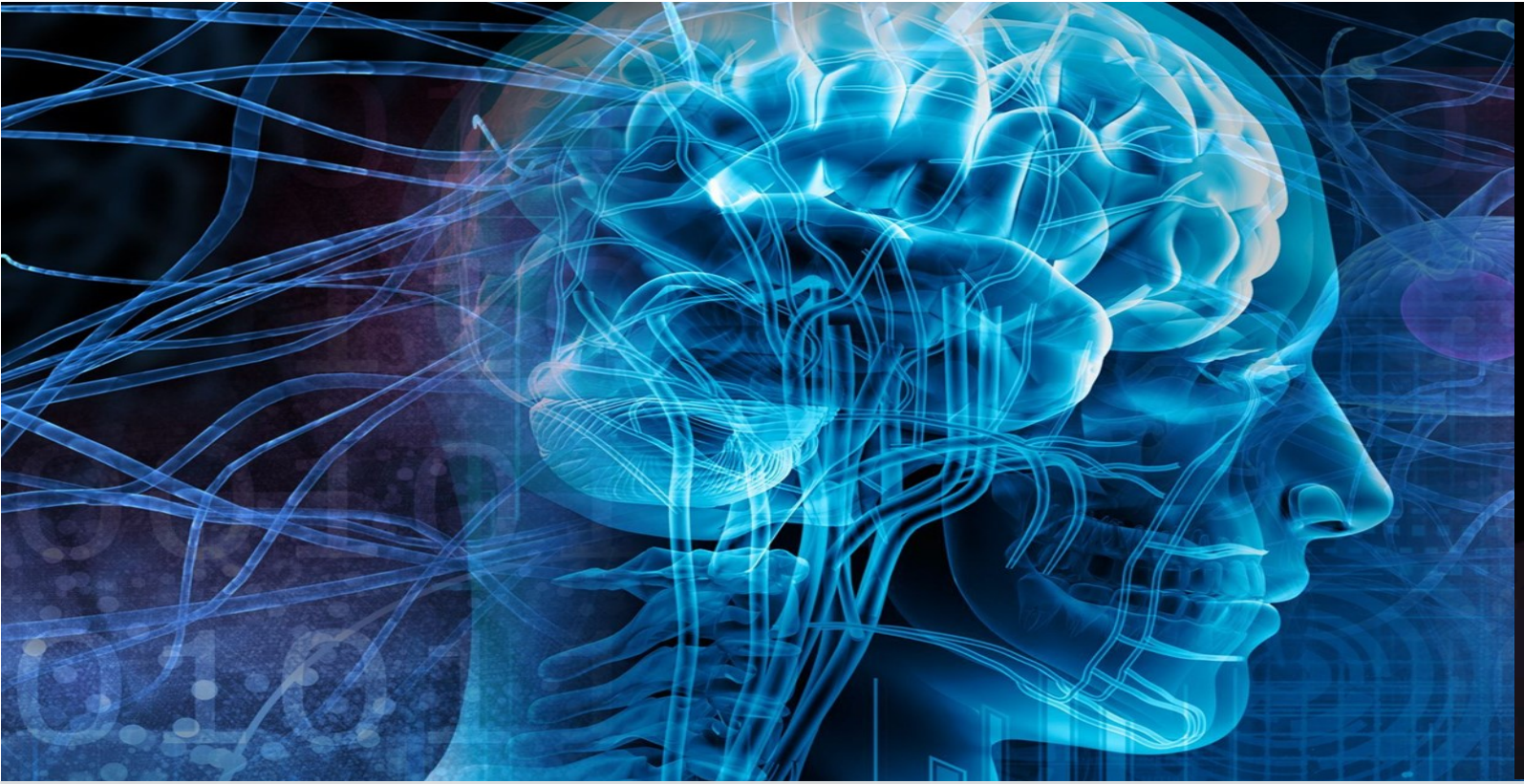


# Keynote 2: Integration of Biomarkers and Quantitative Modeling – Cerebrospinal Fluid

October 27, 2020

**Kaj Blennow, Professor**
**University of Gothenburg**



CRITICAL PATH INSTITUTE 15 YEARS

CPAD
CRITICAL PATH FOR ALZHEIMER'S DISEASE
CRITICAL PATH INSTITUTE

# Integration of Biomarkers and Quantitative Modeling – Cerebrospinal Fluid

**Kaj Blennow, Professor**

**Academic Chair in Neurochemistry, University of Gothenburg**

# Use of CSF biomarkers for Alzheimer's disease

J Neuropathol Exp Neurol
Vol. 71, No. 4
April 2012
pp. 266–273


ORIGINAL ARTICLE

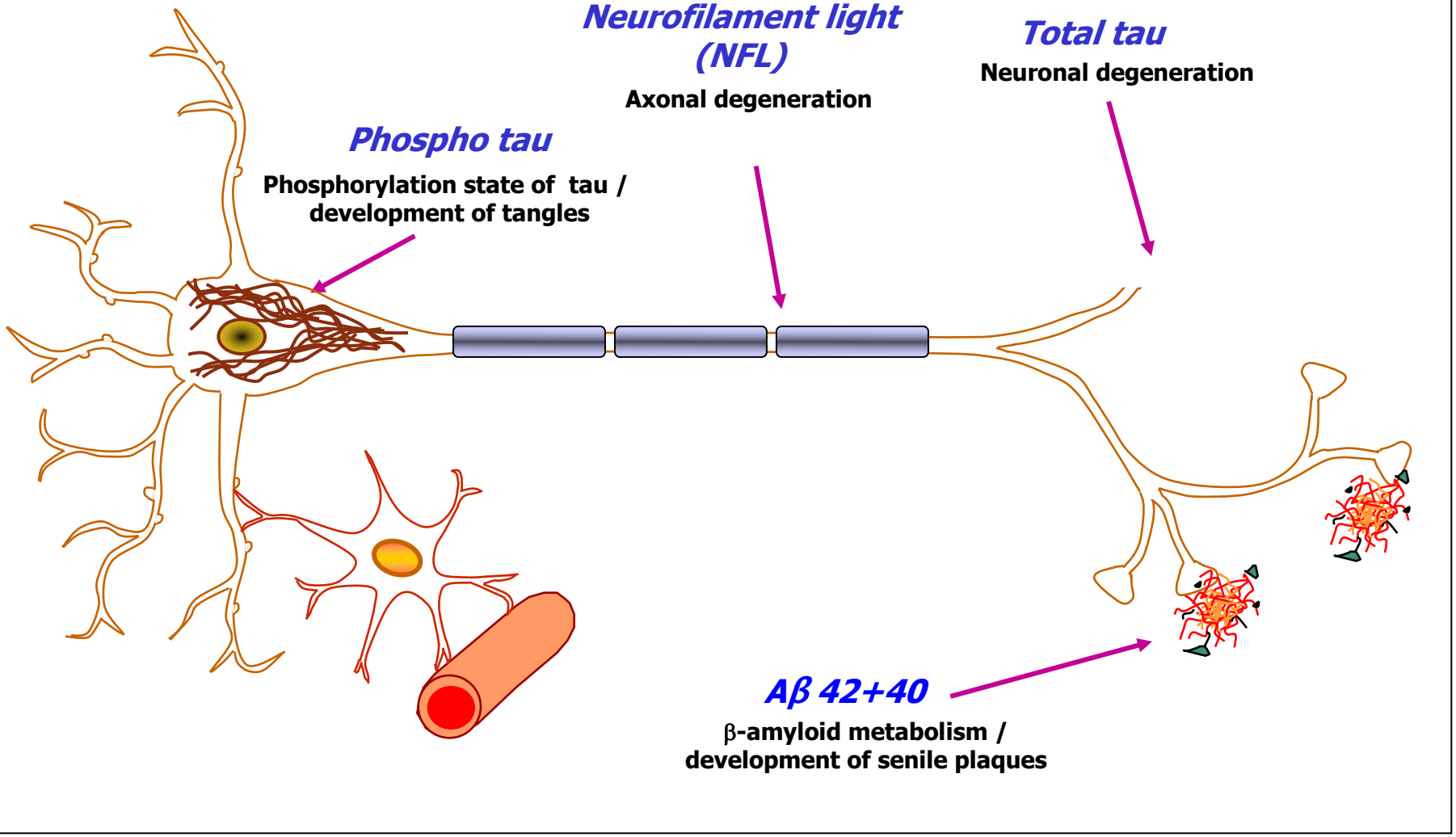
## Accuracy of the Clinical Diagnosis of Alzheimer Disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010

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% | |

- **Diagnostics**
  - Select true AD cases for inclusion in clinical trials
  - Make a correct diagnosis for initiation of treatment, especially DMTs in the future
- **Theragnostics**
  - Identify target engagement of a drug candidate
  - Identify downstream effects of drug candidates on AD pathophysiology (e.g. on synaptic and neuronal degeneration)
- **Research: clinical and epidemiology**
  - Study AD pathophysiology directly in patients and elderly
  - Identify genetic and environmental / life-style risk factors for specific AD pathophysiology (amyloid, tau, neurodegeneration)

# The core fluid biomarkers for Alzheimer's disease



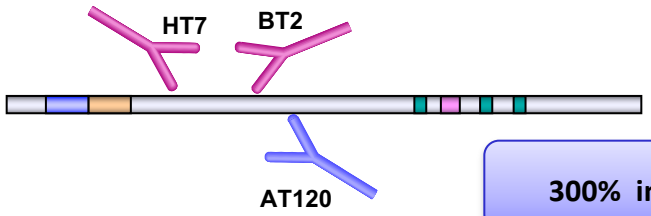
# The three Innotest ELISA methods for AD CSF biomarkers

## tau Protein in Cerebrospinal Fluid

### A Biochemical Marker for Axonal Degeneration in Alzheimer Disease?

K. BLENNOW,*,[1] A. WALLIN,[2] H. ÅGREN,[2]
C. SPENGER,[3] J. SIEGFRIED,[4] AND E. VANMECHELEN[5]

*Mol Chem Neuropathol 1995*




300% increase in AD

➔ Intensity of neurodegeneration

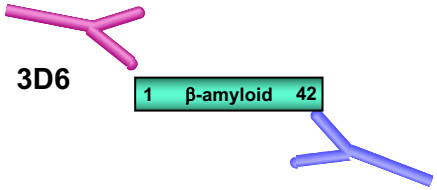
ORIGINAL CONTRIBUTION

## Cerebrospinal Fluid β-Amyloid(1-42) in Alzheimer Disease

*Differences Between Early- and Late-Onset Alzheimer Disease and Stability During the Course of Disease*

Niels Andreasen, MD; Camilla Hesse; Pia Davidsson, PhD; Lennart Minthon, MD, PhD; Anders Wallin, MD, PhD; Bengt Winblad, MD, PhD; Hugo Vanderstichele, PhD; Eugeen Vanmechelen, PhD; Kaj Blennow, MD, PhD

*Arch Neurol 1999*



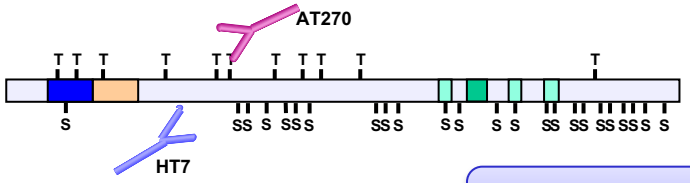

50% decrease in AD

➔ β-amyloid aggregation / deposition

ELSEVIER
Neuroscience Letters 285 (2000) 49–52
Neuroscience Letters
www.elsevier.com/locate/neulet

## Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization

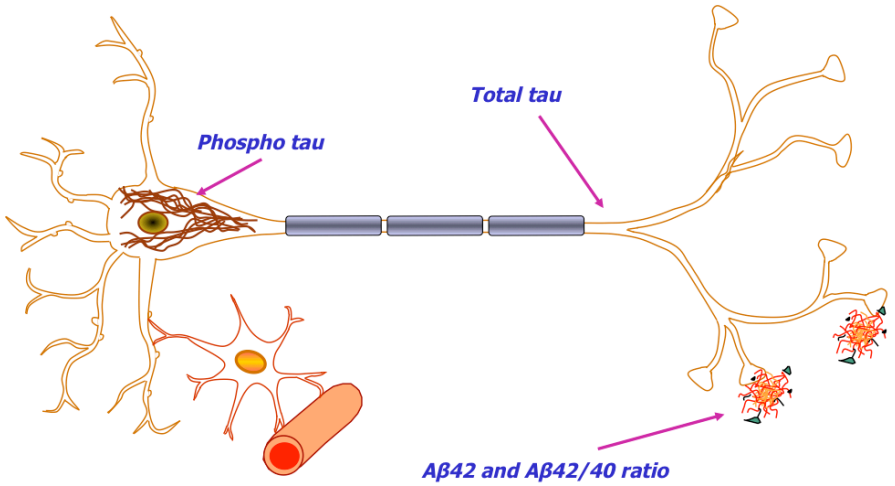
E. Vanmechelen[a,*], H. Vanderstichele[a], P. Davidsson[b], E. Van Kerschaver[a], B. Van Der Perre[a], M. Sjögren[c], N. Andreasen[d], K. Blennow[b,e]




200% increase in AD

➔ tau phosphorylation / pathology ?

# The AD core CSF biomarkers reflect key pathogenic events and are highly clinically validated




Articles

CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis

Bob Olsson, Ronald Lautner, Ulf Andreasson, Annika Öhrfelt, Erik Portelius, Maria Bjerke, Mikko Hölttä, Christoffer Rosén, Caroline Olsson, Gabrielle Strobel, Elizabeth Wu, Kelly Dakin, Max Petzold, Kaj Blennow, Henrik Zetterberg

**CSF T-tau**

➔Intensity of neurodegeneration

- 250% increase in AD

**CSF Aβ42**

➔ Brain amyloid deposition

- Reduction to 50% in AD

**CSF P-tau**

➔ Phosphorylation state of tau and tau pathology?

- 200% increase in AD

- 188 studies
- 20.600 AD patients and controls

- 168 studies
- 19.600 AD patients and controls

- 116 studies
- 14.300 AD patients and controls

# The core AD CSF biomarkers – performance to identify prodromal AD

Lancet Neurol 2006; 5: 228–34

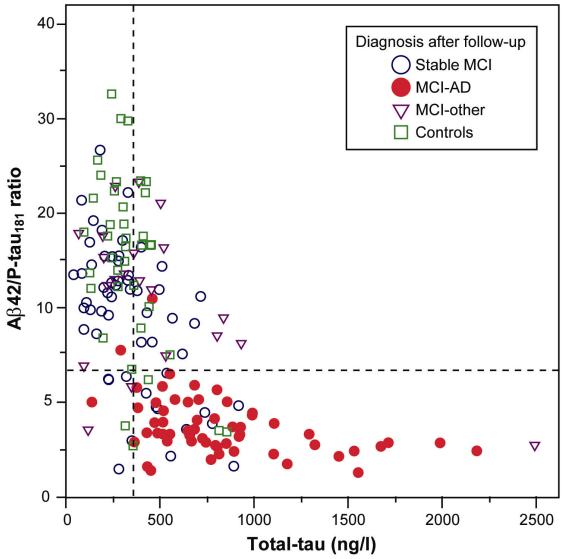
Articles

Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study

Oskar Hansson, Henrik Zetterberg, Peder Buchhave, Elisabet Londos, Kaj Blennow, Lennart Minthon

Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective, cohort study

Pieter Jelle Visser, Frans Verhey, Dirk L Knol, Philip Scheltens, Lars-Olof Wahlund, Yvonne Freund-Levi, Magda Tsolaki, Lennart Minthon, Åsa K Wallin, Harald Hampel, Katharina Bürger, Tuula Pirttila, Hilkka Soininen, Marcel Olde Rikkert, Marcel M Verbeek, Luiza Spiru, Kaj Blennow




Cerebrospinal Fluid Biomarker Signature in Alzheimer's Disease Neuroimaging Initiative Subjects

Leslie M. Shaw, PhD,[1] Hugo Vanderstichele, PhD,[2] Malgorzata Knapik-Czajka, PhD,[1] Christopher M. Clark, MD,[3] Paul S. Aisen, MD,[4] Ronald C. Petersen, MD,[5] Kaj Blennow, MD, PhD,[6] Holly Soares, PhD,[7] Adam Simon, PhD,[8] Piotr Lewczuk, MD, PhD,[9] Robert Dean, MD,[10] Eric Siemers, MD,[10] William Potter, MD,[8] Virginia M.-Y. Lee, PhD,[1] John Q. Trojanowski, MD, PhD,[1] and the Alzheimer's Disease Neuroimaging Initiative

ORIGINAL CONTRIBUTION

JAMA, July 22/29, 2009—Vol 302, No. 4

CSF Biomarkers and Incipient Alzheimer Disease in Patients With Mild Cognitive Impairment

**Sensitivity for MCI-AD 95%**
**Specificity for stable MCI and MCI-other 87 %**

**Large multi-center studies confirm high predicitve value of the AD core biomarker profile for prodromal AD**

➔ **The core AD CSF biomarkers show high diagnostic performance also in the MCI stage, when disease-modifying compounds have a chance to be effective**

Brain Advance Access published March 2, 2016
doi:10.1093/brain/aww015 BRAIN 2016: Page 1 of 11 | 1
BRAIN
A JOURNAL OF NEUROLOGY

# Cerebrospinal fluid analysis detects cerebral amyloid-β accumulation earlier than positron emission tomography

Sebastian Palmqvist[1,2] Niklas Mattsson[1,3] and Oskar Hansson[1,3] for the Alzheimer's Disease Neuroimaging Initiative*

- 437 non-demented subjects from ADNI
- Baseline CSF Aβ42 and amyloid PET
- Follow-up amyloid PET after 2 years

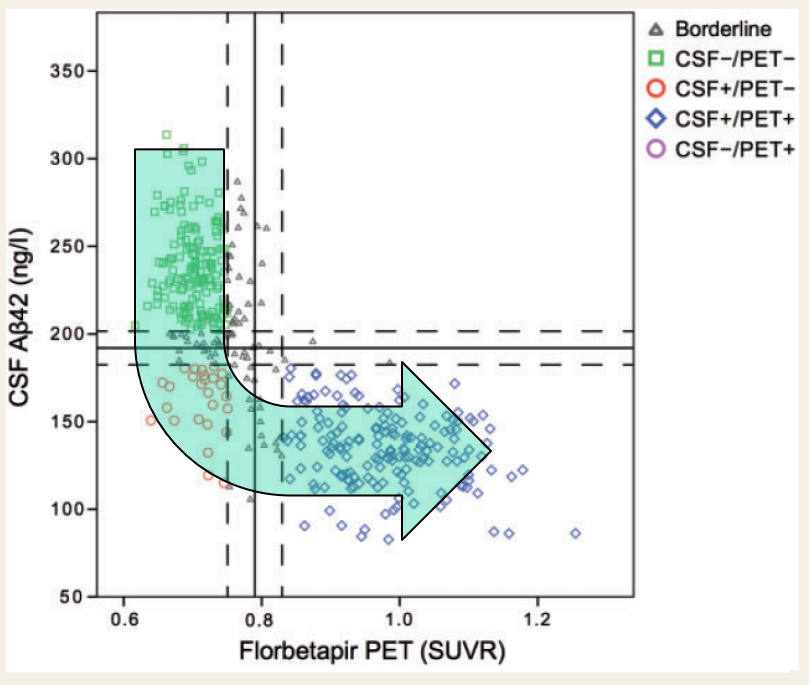



Table 2 Longitudinal comparisons of amyloid-β accumulation

| | A CSF−/PET− | B CSF+/PET− | C CSF+/PET+ | *P*-value |
|---|---|---|---|---|
| *n* | 160 | 26 | 167 | |
| Global amyloid-β PET (% SUVR change/year) | 0.35% (0.14–0.56) | 1.2% (0.49–1.8) | 1.2% (0.90–1.4) | **A-B = 0.018** B-C = 0.86 |

➔ CSF +/ PET - subjects show future amyloid accumulation (similar to CSF and PET + ) but not yet evidence of neurodegeneration

➔ CSF Aβ42 is an earlier biomarker than amyloid PET

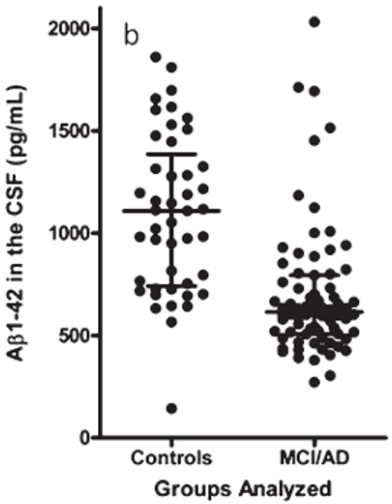
# The CSF Aβ 42/40 ratio

Journal of Alzheimer's Disease 43 (2015) 183–191
DOI 10.3233/JAD-140771
IOS Press

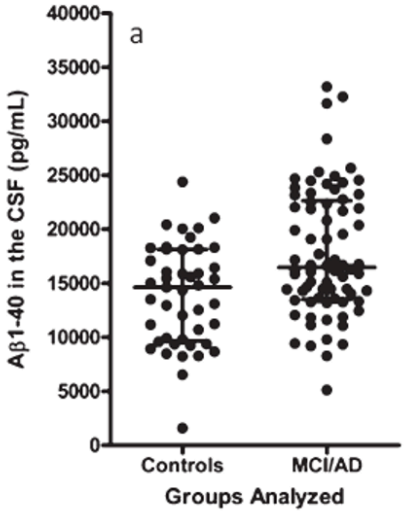


Amyloid-β 42/40 Cerebrospinal Fluid Concentration Ratio in the Diagnostics of Alzheimer's Disease: Validation of Two Novel Assays

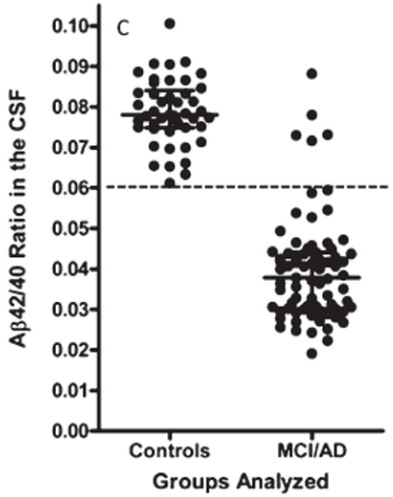
Piotr Lewczuk*, Natalia Lelental, Philipp Spitzer, Juan Manuel Maler and Johannes Kornhuber
*Department of Psychiatry and Psychotherapy, Universitätsklinikum Erlangen, and Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany*




Clear reduction in CSF Aβ42 but with overlap




No change in CSF Aβ40




Marked reduction in CSF Aβ42/40 ratio with minor overlap

➔ CSF Aβ 42/40 ratio compensates for
- low/high "total" Aβ production ?
- biomarker dependence on CSF dynamics ?
- pre-analytical loss of Aβ42 (and Aβ40) ?

# What is needed to get the core AD CSF biomarkers into the clinic ?

**Reference Measurement Procedure (RMP)**

Clinical Chemistry 60:7
987–994 (2014)

Proteomics and Protein Markers

Mass Spectrometry–Based Candidate Reference Measurement Procedure for Quantification of Amyloid-β in Cerebrospinal Fluid

Andreas Leinenbach,[1†] Josef Pannee,[2†] Thomas Dülffer,[1] Andreas Huber,[1] Tobias Bittner,[1] Ulf Andreasson,[2] Johan Gobom,[2] Henrik Zetterberg,[2,3] Uwe Kobold,[1] Erik Portelius,[2] and Kaj Blennow[2*] on behalf of the IFCC Scientific Division Working Group on CSF proteins

Mass spectrometry
gold standard method

✔ SRM mass spec method for CSF Aβ42 published (2014)
and approved by JCTLM - RMP # C11RMP9 (2015)

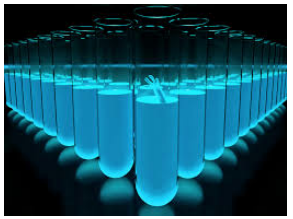
**Certified Reference Material (CRM)**

CERTIFICATION REPORT

**The certification of Amyloid $\beta_{1-42}$ in CSF in ERM®-DA480/IFCC, ERM®-DA481/IFCC and ERM®-DA482/IFCC**

Julia Kuhlmann[1], Sébastien Boulo[1], Ulf Andreasson[2], Maria Bjerke[2], Josef Pannee[2], Jean Charoud-Got[1], Guy Auclair[1], Stéphane Mazoua[1], Stefanie Trapmann[1], Heinz Schimmel[1], Hendrik Emons[1], Doris Florian[1], Milena Quaglia[3], Erik Portelius[2], Magdalena Korecka[4], Leslie M. Shaw[4], Mary Lame[5], Erin Chambers[6], Hugo Vanderstichele[6], Erik Stoops[6], Andreas Leinenbach[7], Tobias Bittner[7], Rand G. Jenkins[8], Vesna Kostanjavecki[9], Piotr Lewczuk[10], Henrik Zetterberg[2], Ingrid Zegers[1], Kaj Blennow[2]

Gold standard CSF pool
with exact levels



✔ Certified Aβ42 CRMs available
✔ Re-calibration of assays successful

**Fully automated instruments**

High precision methods
without manual steps

Roche – Cobas Elecsys
Fujirebio – Lumipulse
Euroimmune – RA Analyzer

# The core AD CSF biomarkers – performance compared with amyloid PET

ELSEVIER

Alzheimer's & Dementia

Alzheimer's & Dementia ■ (2018) 1-12

Featured Article

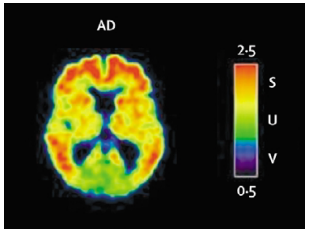
CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts

Oskar Hansson[a,b,*,1], John Seibyl[c], Erik Stomrud[a,b], Henrik Zetterberg[d,e,f,g], John Q. Trojanowski[h], Tobias Bittner[i,2], Valeria Lifke[i], Veronika Corradini[k], Udo Eichenlaub[j], Richard Batrla[k], Katharina Buck[j], Katharina Zink[j], Christina Rabe[i,2], Kaj Blennow[d,e,**,1], Leslie M. Shaw[l,***,1], for the Swedish BioFINDER study group[3], the Alzheimer's Disease Neuroimaging Initiative[4]

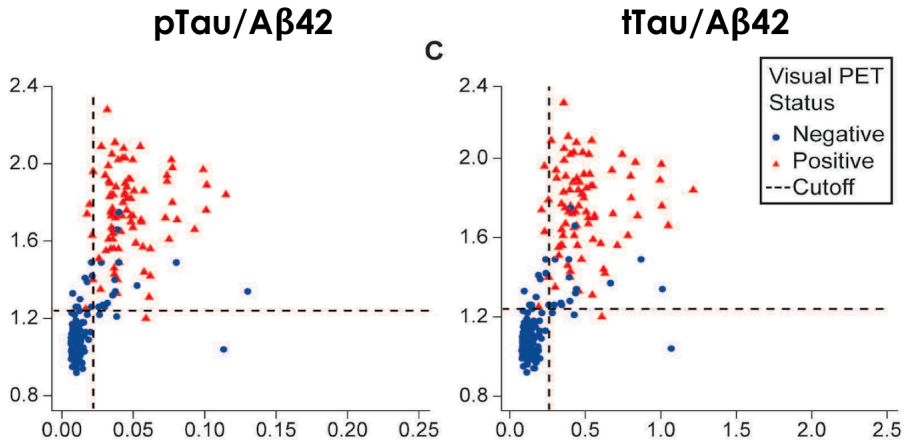
**Study cohorts:**

**BioFINDER (n= 277)**
**ADNI (n= 646)**

**Cobas Elecsys assays:**
**Aβ1-42, tTau and Ptau**




**Amyloid PET:**
**Visual read (3 raters)**




**Concordance vs. visual amyloid PET:**

| | |
|---|---|
| CSF pTau/Aβ42 | OPA = 89.9 - 90.3 % |
| CSF tTau/Aβ42 | OPA = 89.2 – 89.9 % |
| Inter-rater PET agreement | OPA = 90% |

➔ **CSF biomarkers and amyloid PET can be used interchangeably**

# Tau protein is cleaved to fragments before being secreted to the CSF (and blood?)

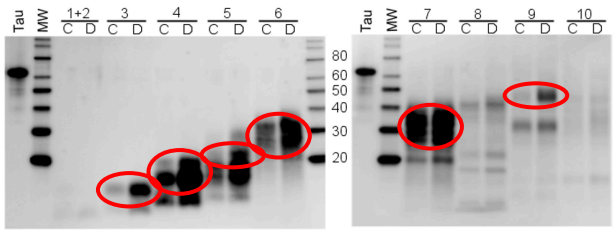
October 2013 | Volume 8 | Issue 10 | e76523
OPEN ACCESS Freely available online
PLOS ONE

## Characterization of Novel CSF Tau and ptau Biomarkers for Alzheimer's Disease

Jere E. Meredith Jr.[1*], Sethu Sankaranarayanan[1], Valerie Guss[1], Anthony J. Lanzetti[1], Flora Berisha[2], Robert J. Neely[2], J. Randall Slemmon[1], Erik Portelius[3], Henrik Zetterberg[4], Kaj Blennow[3], Holly Soares[1], Michael Ahlijanian[1], Charles F. Albright[1]

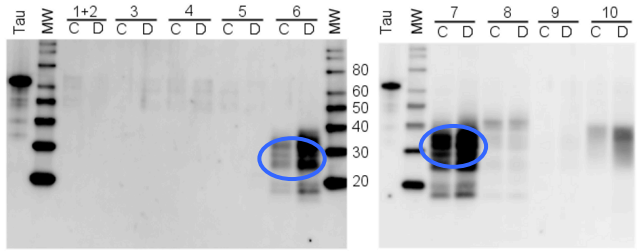
**RP-HPLC separation of CSF proteins ➔ SDS-PAGE + Western**

A HT7 (aa 159-163)

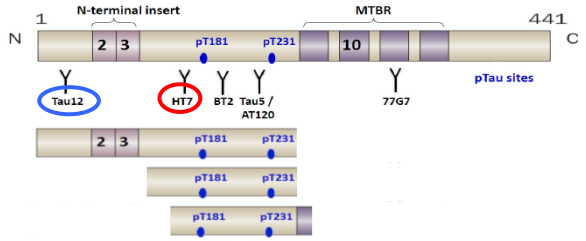



- No full length tau
- Several shorter tau fragments with different MW

B Tau12 (aa 9-18)



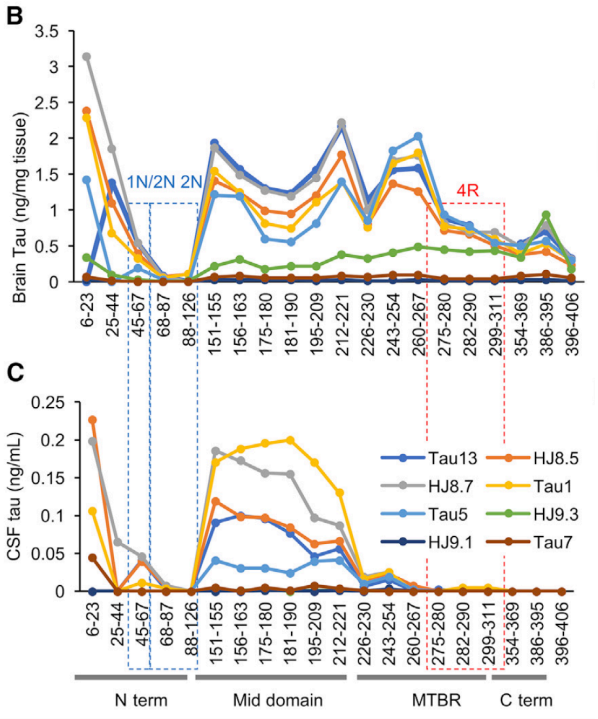

- Two identical tau fragments as with HT7
- Other HT7 tau fragments missing
- Weak Tau12 unique tau fragment




Neuron 97, 1284–1298, March 21, 2018

## Tau Kinetics in Neurons and the Human Central Nervous System

Chihiro Sato,[1,8,*] Nicolas R. Barthélemy,[1,8] Kwasi G. Mawuenyega,[1] Bruce W. Patterson,[2] Brian A. Gordon,[3] Jennifer Jockel-Balsarotti,[1] Melissa Sullivan,[1] Matthew J. Crisp,[1] Tom Kasten,[1] Kristopher M. Kirmess,[2] Nicholas M. Kanaan,[4] Kevin E. Yarasheski,[2] Alaina Baker-Nigh,[2] Tammie L.S. Benzinger,[3] Timothy M. Miller,[1,5] Celeste M. Karch,[5,6,*] and Randall J. Bateman[1,5,7,9,*]




**Brain**

**CSF**

➔ CSF tau is truncated at the end of the mid-domain

# Asparigine endopeptidase (AEP) cleaved Tau368 may be a biomarker for tau pathology

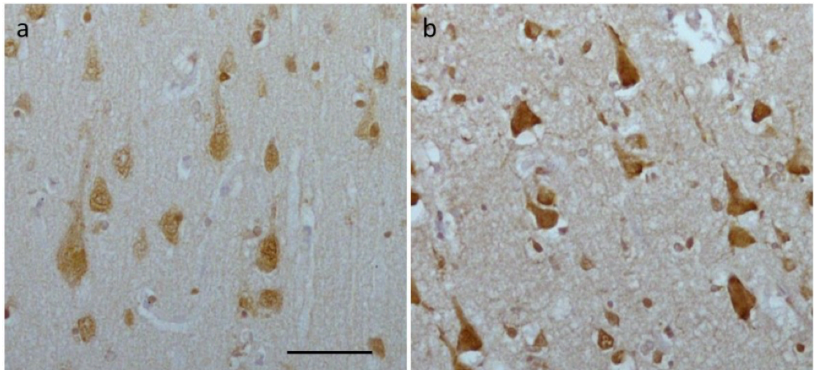
nature medicine 2014;20:1254-1262

## Cleavage of tau by asparagine endopeptidase mediates the neurofibrillary pathology in Alzheimer's disease

Zhentao Zhang[1,2], Mingke Song[3], Xia Liu[1], Seong Su Kang[1], Il-Sun Kwon[1], Duc M Duong[4,5], Nicholas T Seyfried[4,5], William T Hu[6], Zhixue Liu[7], Jian-Zhi Wang[8], Liming Cheng[9], Yi E Sun[9], Shan Ping Yu[3], Allan I Levey[5,6] & Keqiang Ye[1]

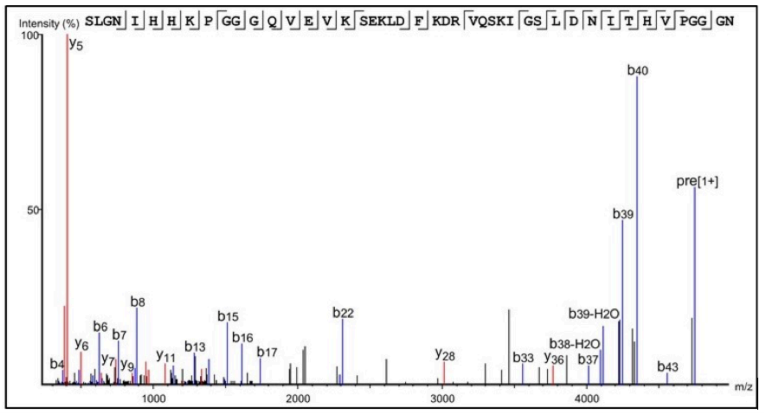
- Asparagine endopeptidase (AEP) cleaves tau at position 368
- AEP cleavage impairs microtubule assembly function
- AEP cleavage induces tau aggregation, with truncated tau in NFTs

**Immunohistochemistry (tau368 antibody)**




Control AD

**IP of CSF (ab KJ9A) followed by MS/MS**



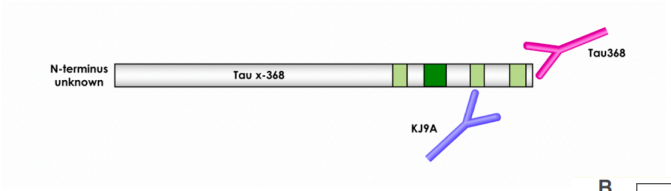

SLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN

324 368

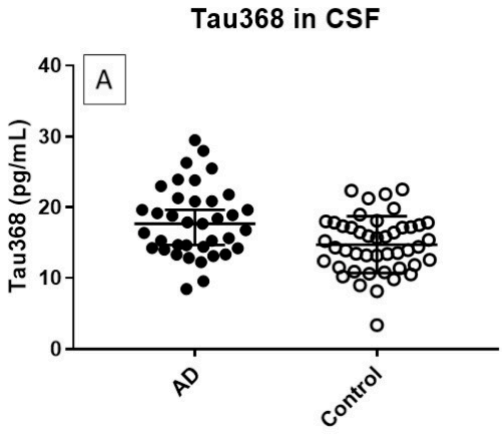
➔ CSF contains semi-tryptic AEP-cleaved tau (ending at tau368)

# CSF Tau368 is a novel candidate biomarker for tau pathology

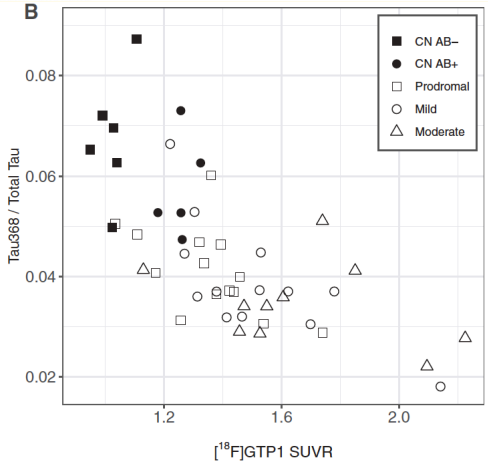
- **Clinical cohort:**
  **37 IWG-2 pos AD; 45 controls**



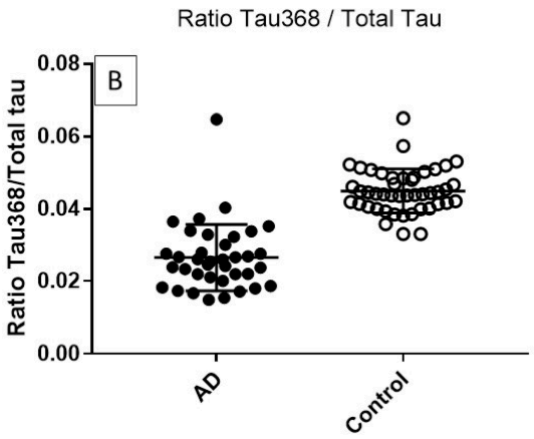

- **Simoa method for tau 368 KJ9A and tau368 Abs**

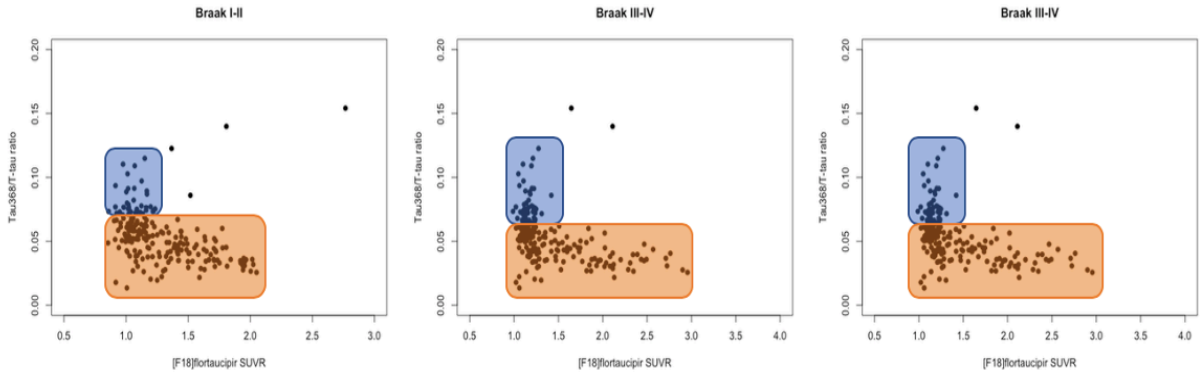



**GTP1 tau PET cohort, n= 49**
**Classification by amyloid PET**




**Large clinical cohort with tauPET**
**N>300 (control, MCI, AD)**

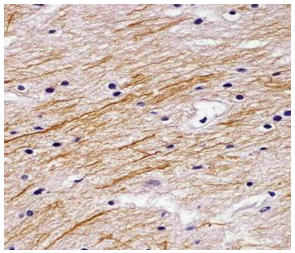


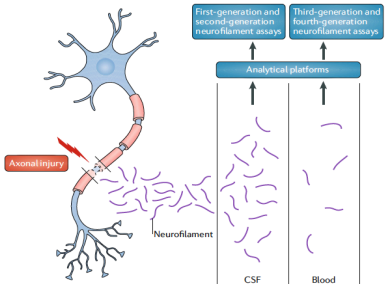




➔ CSF tau368/T-tau ratio may compensate for basic tau secretion to CSF – in analogy with the Aβ 42/40 ratio

➔ C-terminal tau fragments are retained in tau aggregates, while N-mid domain fragments are secreted ?

# Neurofilament light (NFL) protein in different neurodegenerative disorders



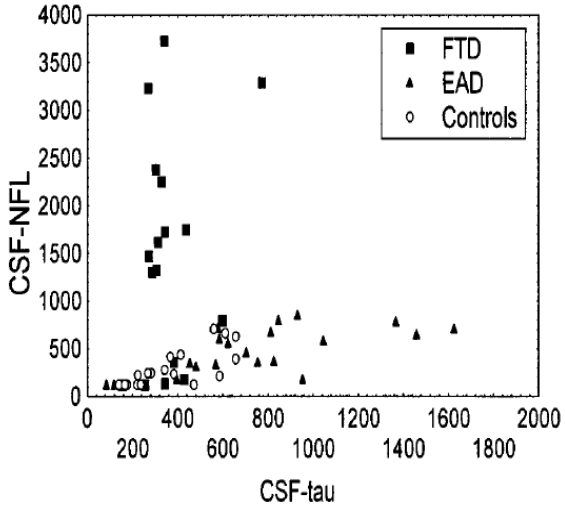



## Cytoskeleton proteins in CSF distinguish frontotemporal dementia from AD

M. Sjögren, MD, PhD; L. Rosengren, MD, PhD; L. Minthon, MD, PhD; P. Davidsson, PhD; K. Blennow, MD, PhD; and A. Wallin, MD, PhD

NEUROLOGY 2000;54:1960–1964

| Diagnosis | NFL (pg/mL)* | Tau (pg/mL)* |
|---|---|---|
| FTD | 1442 ± 1183† | 354 ± 140 |
| EAD | 498 ± 236 | 751 ± 394‡ |
| LAD | 1006 ± 727§ | 699 ± 319‡ |
| Controls | 241 ± 166 | 375 ± 176 |



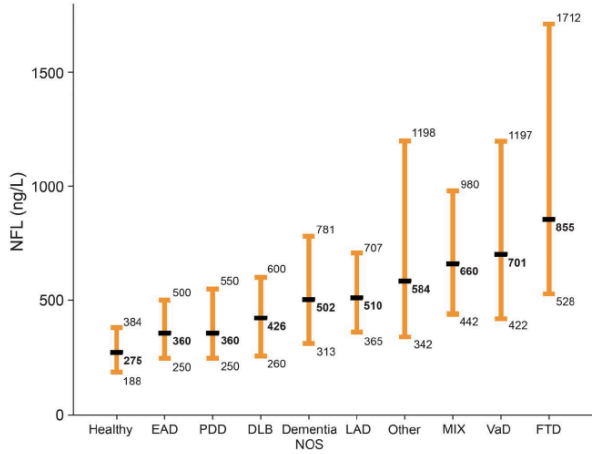

## CSF neurofilament light differs in neurodegenerative diseases and predicts severity and survival

*Neurology*® 2014;83:1945-1953

Tobias Skillbäck, MD ABSTRACT

- **Patients with dementia (n= 3.356)**

**Figure 1** NFL levels across diagnosis groups and biomarker patterns



# CSF NFL in the ADNI study

Research

*JAMA Neurol*. 2016;73(1):60-67.

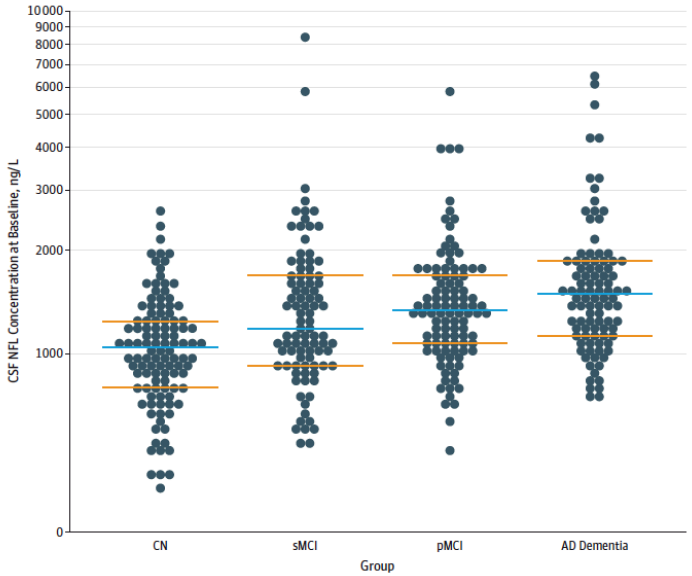
Original Investigation

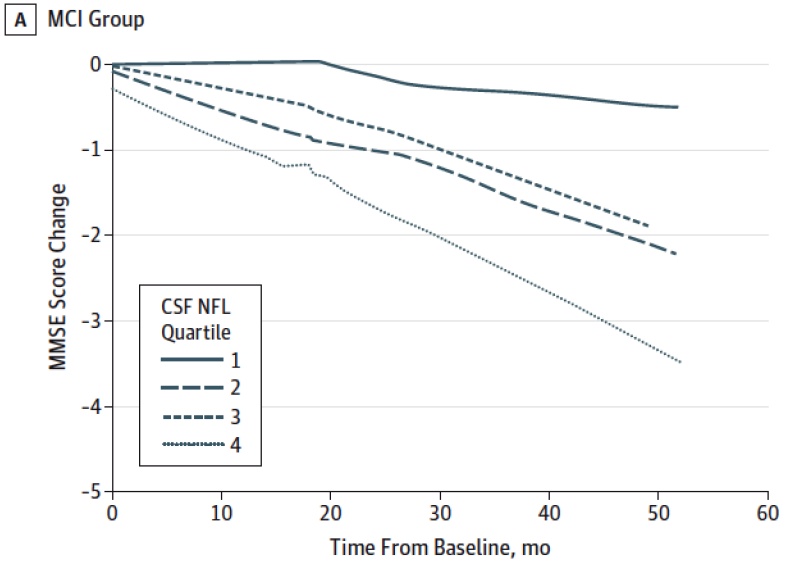
## Association of Cerebrospinal Fluid Neurofilament Light Concentration With Alzheimer Disease Progression

Henrik Zetterberg, MD, PhD; Tobias Skillbäck, MD; Niklas Mattsson, MD, PhD; John Q. Trojanowski, MD, PhD; Erik Portelius, PhD; Leslie M. Shaw, PhD; Michael W. Weiner, MD, PhD; Kaj Blennow, MD, PhD; for the Alzheimer's Disease Neuroimaging Initiative

**ADNI cohort: 110 Controls**
**91 stable MCI**
**101 progressive MCI**
**95 AD dementia**

Figure 1. Cerebrospinal Fluid Neurofilament Light (CSF NFL) Concentration in the Diagnostic Groups



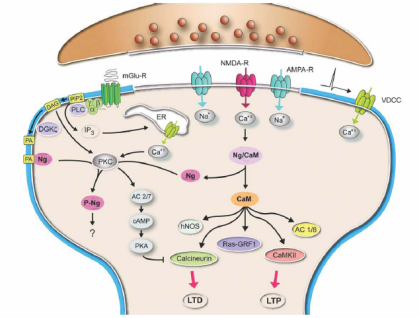

**Higher CSF NFL in AD dementia and progressive MCI**
**Intermediate levels in stable MCI**

**Within the MCI group –**
**higher CSF NFL predicts faster rate of cognitive decline**

# Biomarkers for synaptic dysfunction and degeneration

**The synaptic protein neurogranin:**

- **Abundant in cortex, hippocampus, amygdala**
- **Concentrated in dendritic spines**
- **Important for memory consolidation and LTP induction**




ELSEVIER

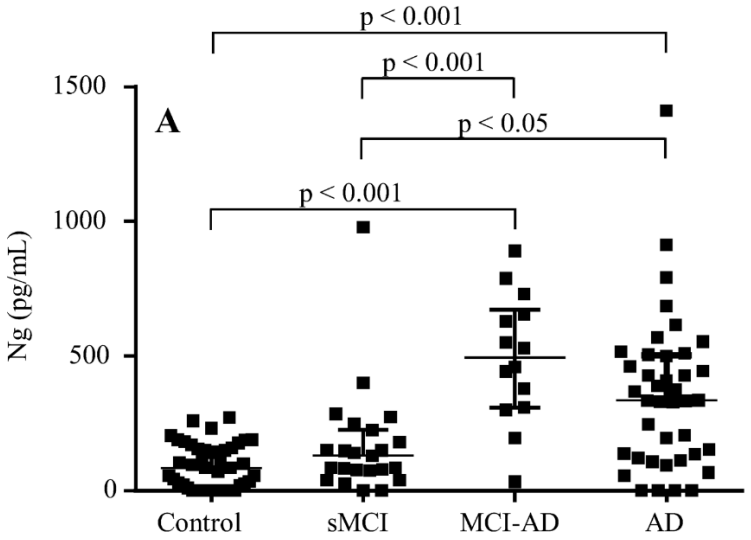
Alzheimer's & Dementia ■ (2014) 1-11

Alzheimer's & Dementia

Research Article

Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's disease

Hlin Kvartsberg[a,1], Flora H. Duits[b,1], Martin Ingelsson[c], Niels Andreasen[d], Annika Öhrfelt[a], Kerstin Andersson[a], Gunnar Brinkmalm[a], Lars Lannfelt[c], Lennart Minthon[c], Oskar Hansson[c], Ulf Andreasson[a], Charlotte E. Teunissen[f], Philip Scheltens[b], Wiesje M. Van der Flier[b,g], Henrik Zetterberg[a,h], Erik Portelius[a], Kaj Blennow[a,*]




➔ **Marked increase in CSF neurogranin in AD and prodromal AD (using several different assays and mass spec)**

➔ **High CSF neurogranin predict future rate of cognitive decline**

***Kvartsberg H et al, Alzheimers Dement 2015; Kvartsberg H et al, Alz Res Therapy 2015, De Vos A et al, Alzheimers Dement 2015; Portelius E et al, Brain 2015; Kester MI, JAMA Neurol 2015, Hellwig K et al, Alzheimers Dement 2015; Wellington H, Neurology 2016; Mattsson N, EMBO Mol Med 2016, Casaletto KB, Neurology 2017, Lista S, J Alzheimer Dis 2017; Portelius et al, Acta Neuropathol 2018***

# CSF neurogranin as an Alzheimer-specific biomarker

Acta Neuropathologica
https://doi.org/10.1007/s00401-018-1851-x

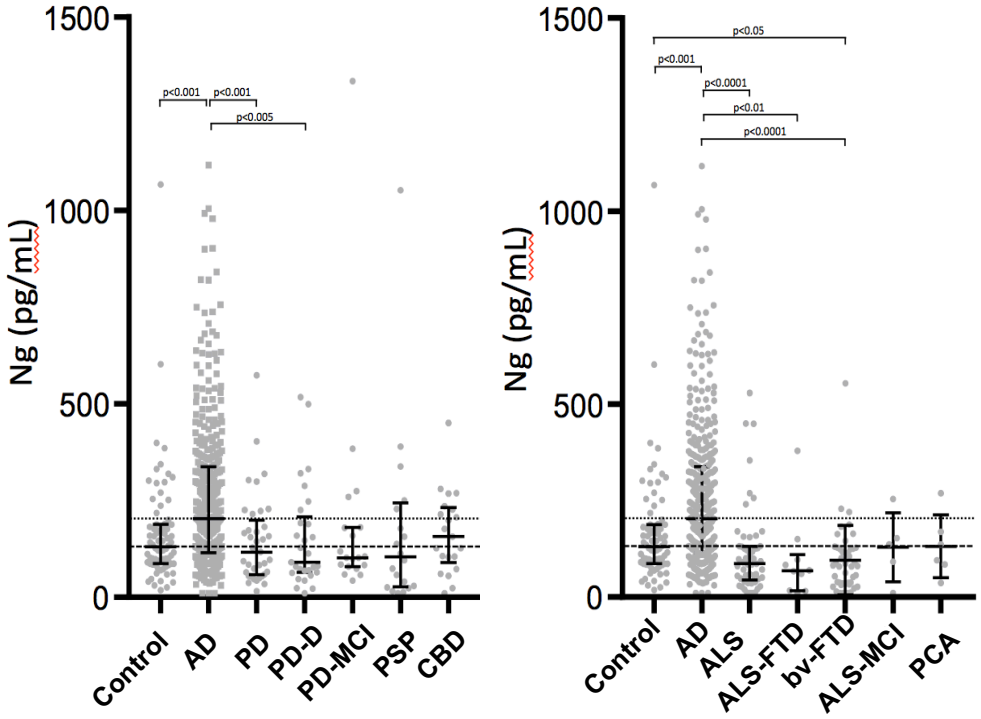
ORIGINAL PAPER

## Cerebrospinal fluid neurogranin concentration in neurodegeneration: relation to clinical phenotypes and neuropathology

Erik Portelius[1,2] · Bob Olsson[1,2] · Kina Höglund[1,2] · Nicholas C. Cullen[1] · Hlin Kvartsberg[1] · Ulf Andreasson[1,2] · Henrik Zetterberg[1,2,3,4] · Åsa Sandelius[1] · Leslie M. Shaw[5] · Virginia M. Y. Lee[5] · David J. Irwin[6] · Murray Grossman[6] · Daniel Weintraub[7,8] · Alice Chen-Plotkin[6] · David A. Wolk[6] · Leo McCluskey[6] · Lauren Elman[6] · Jennifer McBride[5] · Jon B. Toledo[5,9] · John Q. Trojanowski[5] · Kaj Blennow[1,2]

**Controls**
**+ AD, PD, PDD, PSP, CBD, ALS, FTD, PCA**

**>900 cases in total**




➔ **Increase CSF neurogranin seems to be specific for AD**

# CSF biomarkers to identify target engagement in man

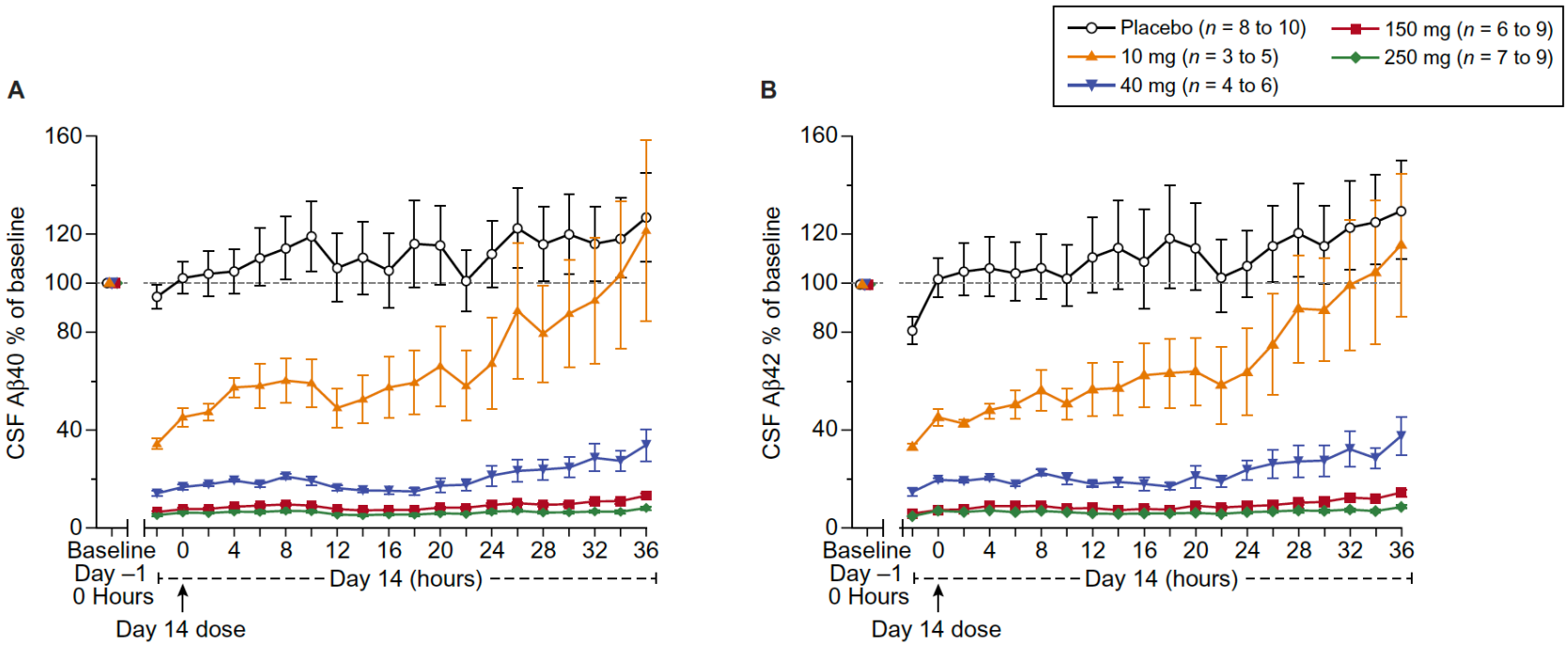
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

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]*




➔ **CSF biomarkers may be used to identify target engagement (and for dose finding)**

# EPOCH verubecestat BACE1 inhibitor study on mild-moderate AD

The NEW ENGLAND JOURNAL of MEDICINE

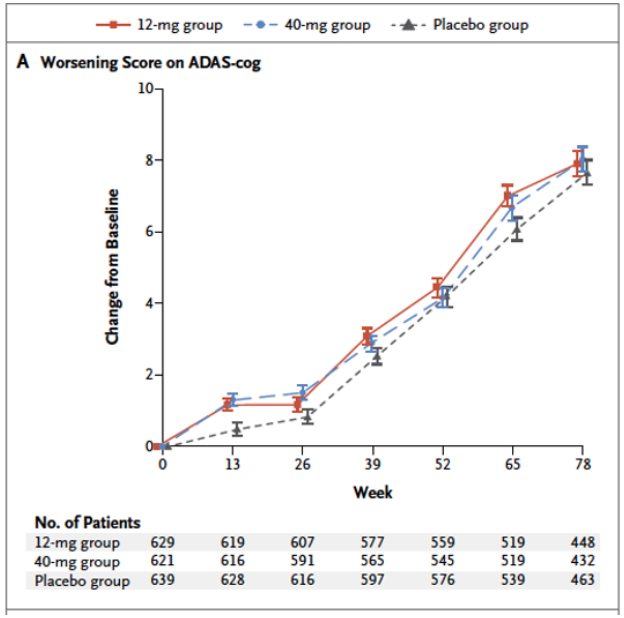
ORIGINAL ARTICLE

## 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.

**Verubecestat BACE inhibitor trial**

**Phase I showed 80% reduction in Aβ production**




| No. of Patients | | | | | | | |
|---|---|---|---|---|---|---|---|
| 12-mg group | 629 | 619 | 607 | 577 | 559 | 519 | 448 |
| 40-mg group | 621 | 616 | 591 | 565 | 545 | 519 | 432 |
| Placebo group | 639 | 628 | 616 | 597 | 576 | 539 | 463 |

**78 weeks: placebo, 12 and 40 mg**

**Terminated early for futility**

➔ **Target engagement on β-amyloid may not translate to disease-modifying effect / clinical benefit**

➔ **Downstream biomarker effects on neurodegeneration may be important indicators of disease-modification**

# Can CSF NFL be used to monitor drug effects on neurodegeneration ?

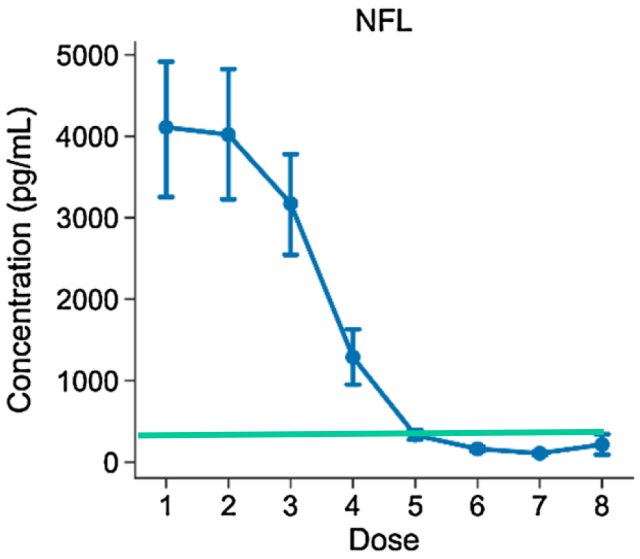
Journal of Neurology (2019) 266:2129–2136
https://doi.org/10.1007/s00415-019-09389-8

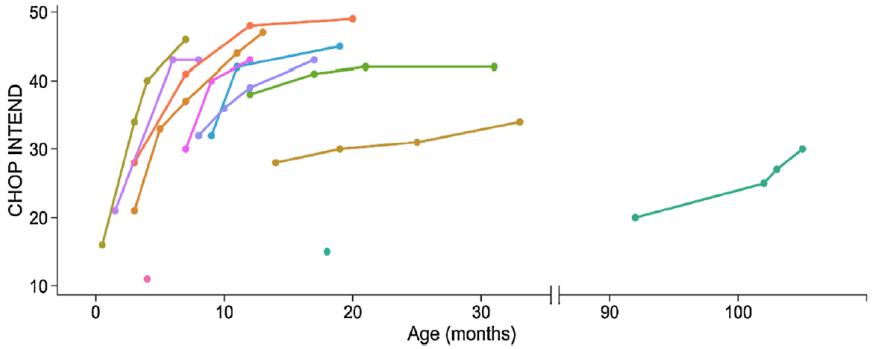
ORIGINAL COMMUNICATION

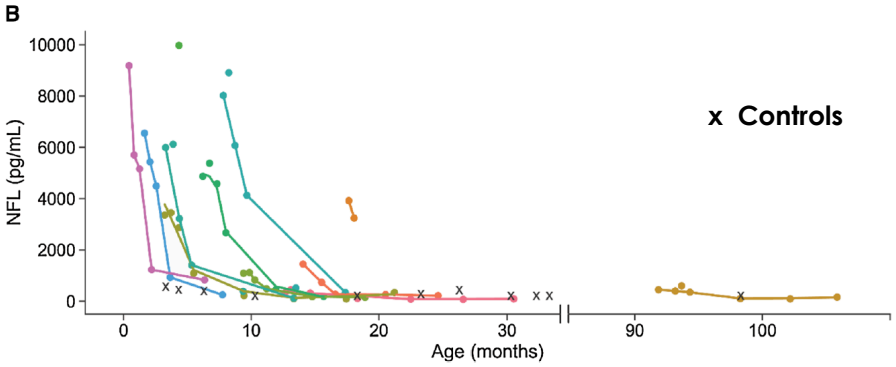
## NFL is a marker of treatment response in children with SMA treated with nusinersen

Bob Olsson[1,2] · Lars Alberg[3] · Nicholas C. Cullen[1,4] · Eva Michael[3,9] · Lisa Wahlgren[3,9] · Anna-Karin Kroksmark[3,5] · Kevin Rostasy[6] · Kaj Blennow[1,2] · Henrik Zetterberg[1,2,7,8] · Már Tulinius[3,9]

- Spinal muscular atrophy (SMA) 12 children
- Intrathecal nusinersen (Spinraza)
  - antisense oligonucleotide increasing CNS levels of survival motor neuron (SMN) protein
- CSF samples before each treatment




➔ Reduction in serum NFL with effective DMTs – correlates with clinical benefit

➔ Serum NFL may be useful to monitor downstream drug effects on intensity of neurodegeneration

# Thanks for listening !