DZNE
Deutsches Zentrum für Neurodegenerative Erkrankungen
in der Helmholtz-Gemeinschaft

UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

Predictice molecular diagnosis of Alzheimer´s Dementia: towards new clinical models for preventive treatment

Prof. Dr. Jens Wiltfang

3rd Intern. Conf. on Alzheimer´s Disease & Dementia, Toronto, August 31, 2015

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current needs in neurodegenerative disease research

- treatment of Alzheimer´s Disease (AD) starts too late and critical time windows are missed

- need for novel preventive treatments

- need to identify subphenotypes of multi-genetic (sporadic) AD responding differentially to treatment interventions

- need to identify novel treatment targets;
  molecular biomarker research is not only promising to improve the early and differential diagnostics of dementias, but it also points to novel molecular treatment targets

alzheimer's association®

the compassion to care, the leadership to conquer

NEW CRITERIA AND GUIDELINES FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE PUBLISHED FOR FIRST TIME IN 27 YEARS

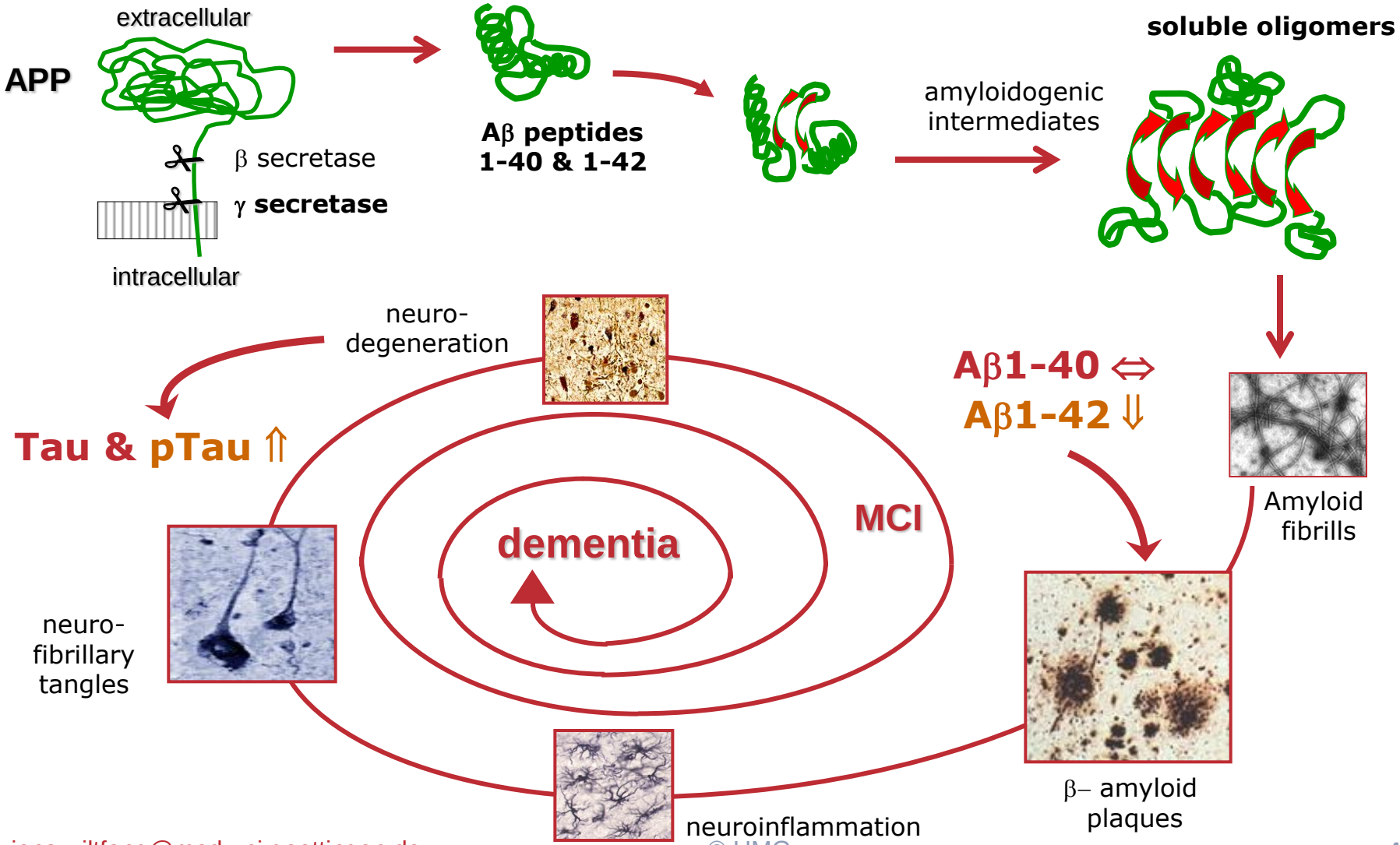
– Research Agenda Suggested for Detecting Pre-Symptomatic Alzheimer's –
– New Alzheimer's Definition Moves Researchers Closer to Early Detection and Intervention –

CHICAGO, April 19, 2011 – For the first time in 27 years, new criteria and guidelines for the diagnosis of Alzheimer's disease have been published by three expert workgroups spearheaded by the Alzheimer's Association and the National Institute on Aging (NIA) of the National Institutes of Health (NIH).

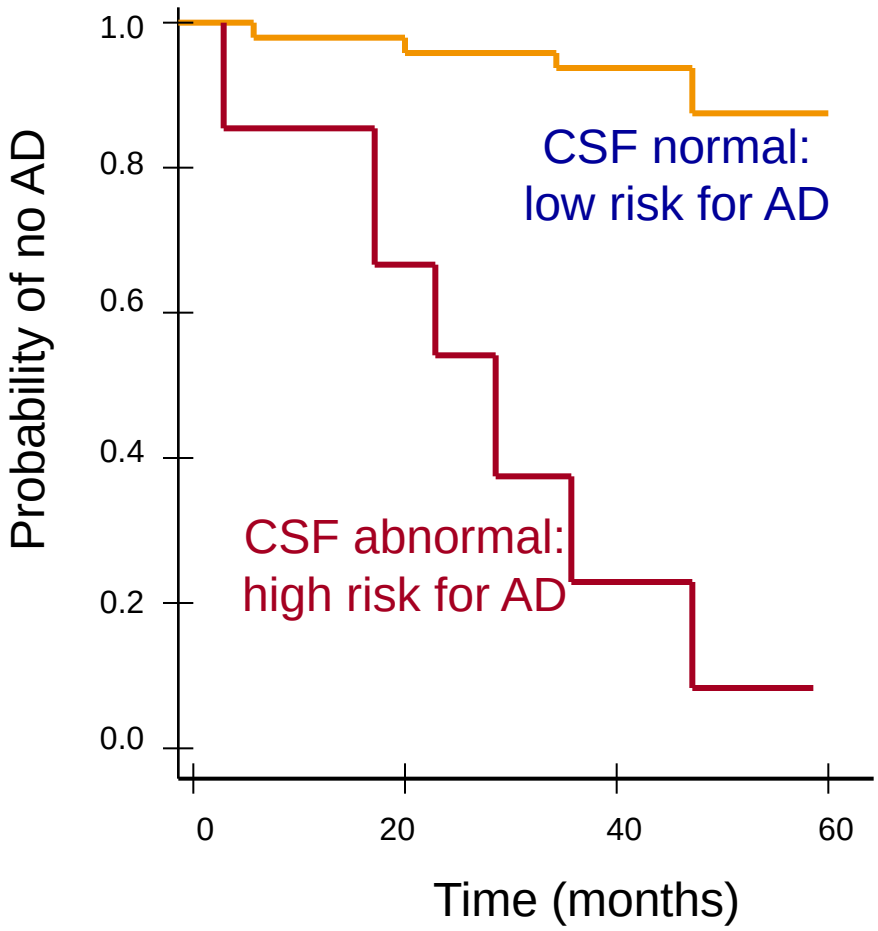
novel concepts of clinical-molecular phenotyping call for biomarker-guided diagnosis

Amyloid cascade hypothesis of Alzheimer´s Dementia

A. Alzheimer



CSF dementia biomarker and time to AD (Aβ1-42, total-Tau, & phosho-Tau181)



CSF-NDD of AD

- Validated by autopsy controlled studies
- Meta-analysis: specificity & sensitivity appr. 85%
- Evidence validated on S3 level of national diagnostic guidelines (DGN/DGPPN 2010)
- Meanwhile, an EU wide research initiatives has been launched to improve the diagnostic reliability and validity of CSF-NDD (e.g. BIOMARK-ADP)

Hansson (2007) Lancet Neurology

Prognostic value of CSF AD biomarkers

Cerebrospinal Fluid Levels of β-Amyloid 1-42, but Not of Tau, Are Fully Changed Already 5 to 10 Years Before the Onset of Alzheimer Dementia

Peder Buchhave, MD, PhD; Lennart Minthon, MD, PhD; Henrik Zetterberg, MD, PhD; Åsa K. Wallin, MD, PhD; Kaj Blennow, MD, PhD; Oskar Hansson, MD, PhD

Conclusions: Approximately 90% of patients with MCI and pathologic CSF biomarker levels at baseline develop AD within 9 to 10 years. Levels of Aβ42 are already fully decreased at least 5 to 10 years before conversion to AD dementia, whereas T-tau and P-tau seem to be later markers. These results provide direct support in humans for the hypothesis that altered Aβ metabolism precedes tau-related pathology and neuronal degeneration.

Arch Gen Psychiatry. 2012;69(1):98-106

Prognostic value of CSF AD biomarkers

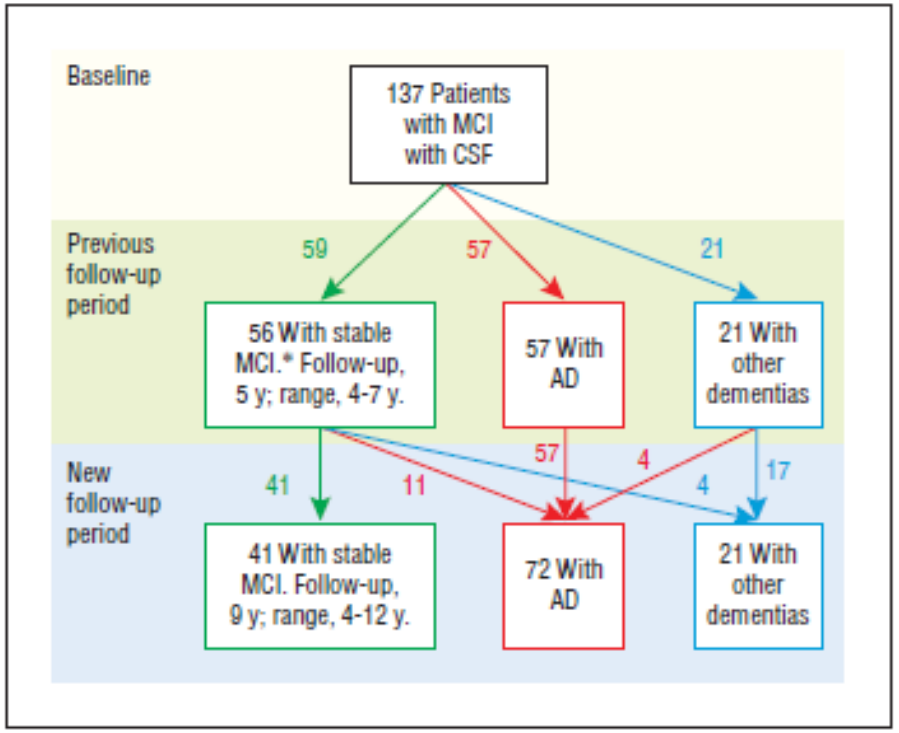
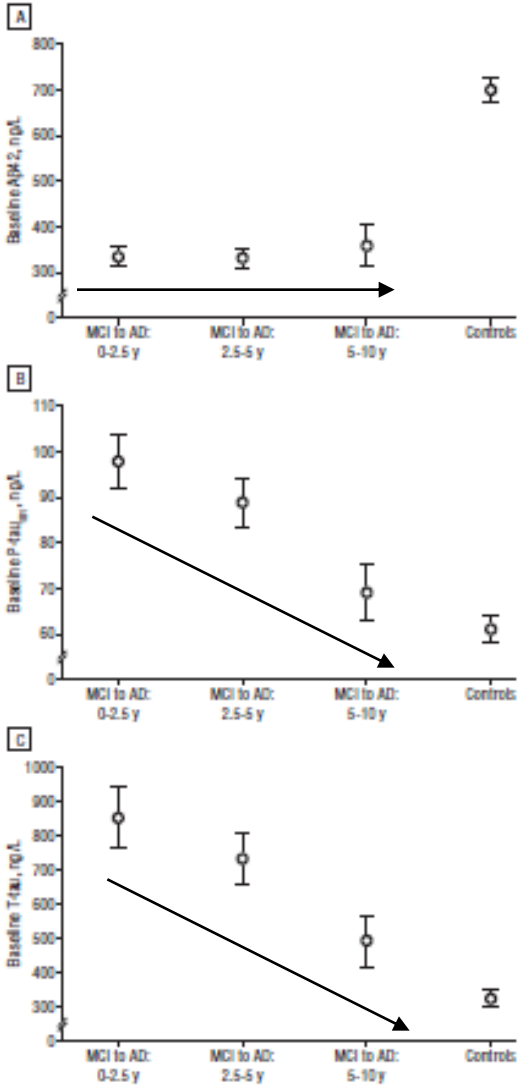
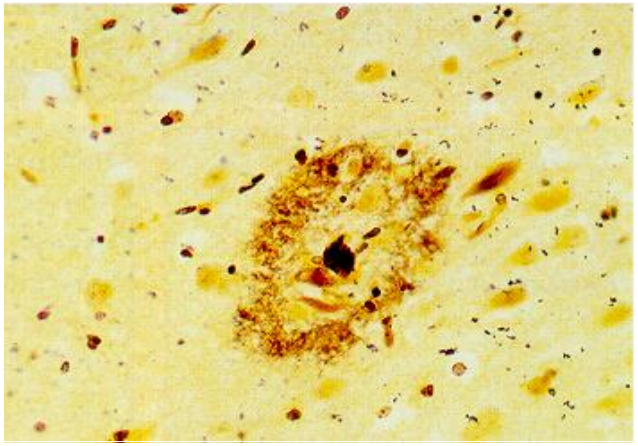


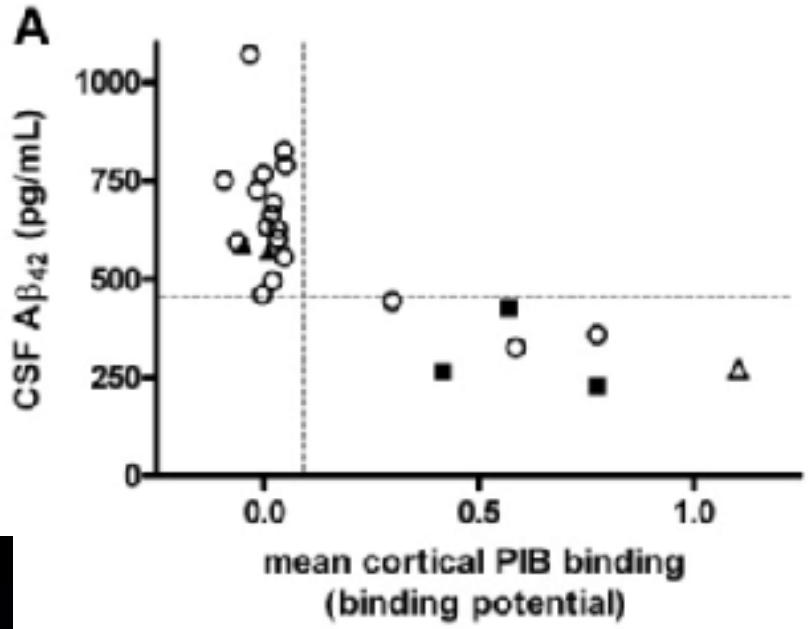
Figure 1. The 137 patients with mild cognitive impairment (MCI) at baseline and the diagnostic outcomes after the previous and new (extended) follow-up periods. During clinical follow-up of the study, 41 patients remained cognitively stable after median follow-up of 9.2 years (range, 4.1-11.8 years), whereas 72 patients with MCI developed Alzheimer disease (AD) and 21 developed other types of dementia. *Three patients with stable cognition at the previous follow-up were excluded because they died before sufficient follow-up (<4 years). Because of uncertainty about their cognitive stability, they were excluded from the study. CSF indicates cerebrospinal fluid.



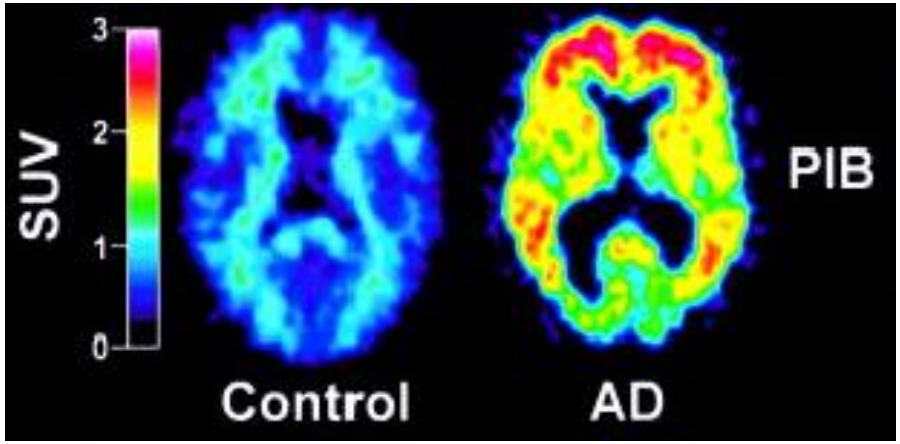
Arch Gen Psychiatry. 2012;69(1):98-106

Amyloid-PET





Fagan et al 2006



Klunk et al., 2004

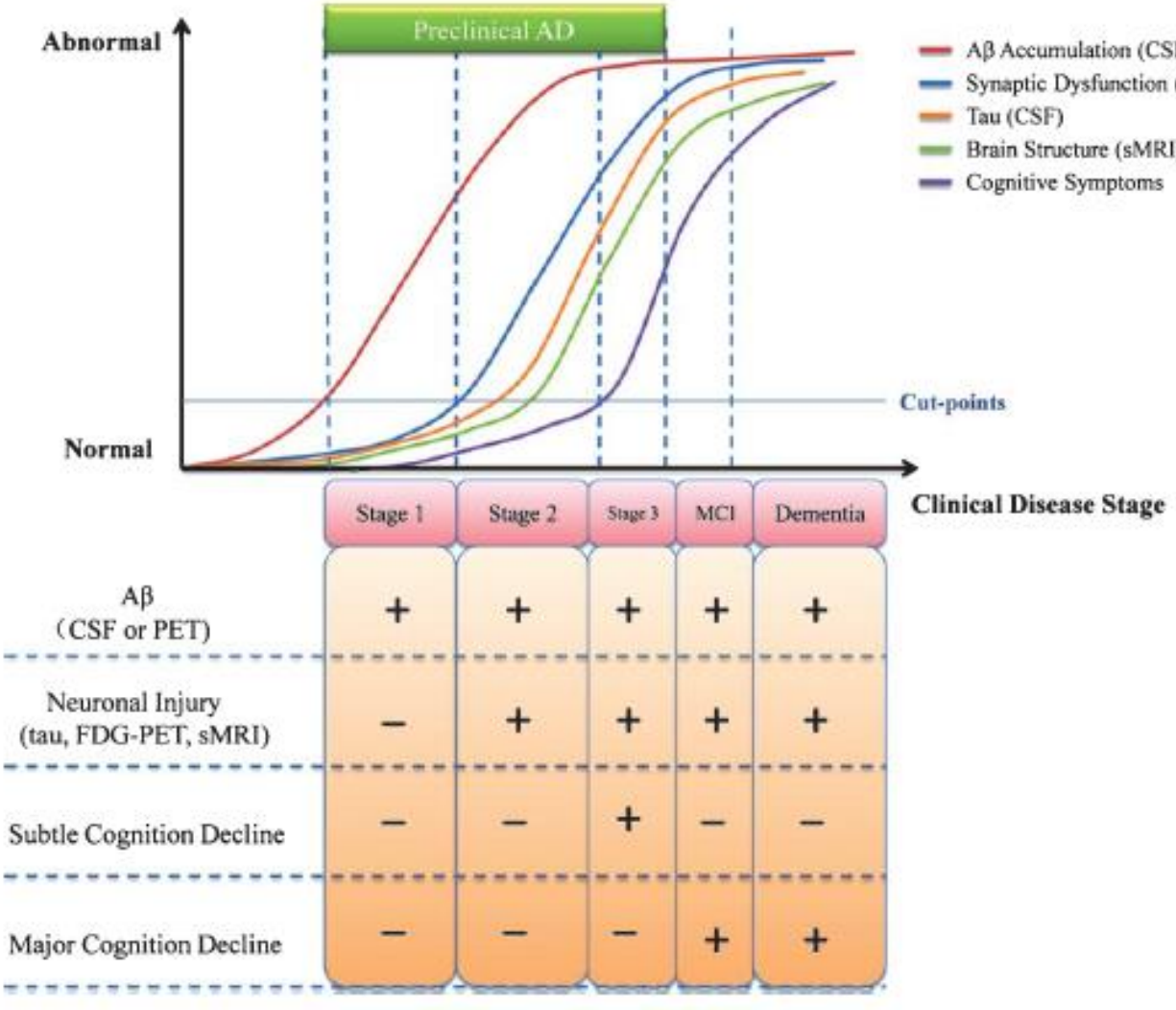
Meanwhile several ^{18}F-Amyloid PET tracers are available which allow multicenter studies

- Differential diagnosis within the group of primary neurodegenerative dementias is significantly improved by combined *in-vivo/in-vitro* clinical phenotyping by Amyloid-PET & CSF dementia biomarkers

Etiology of cognitive deficit	Amyloid deposition
MCI due to AD	+ or ++
AD (mild)	++
AD (moderate)	++
DLB	+ or –
FTD	–
SD	–
PSP	–
CBD	–
VAD	–

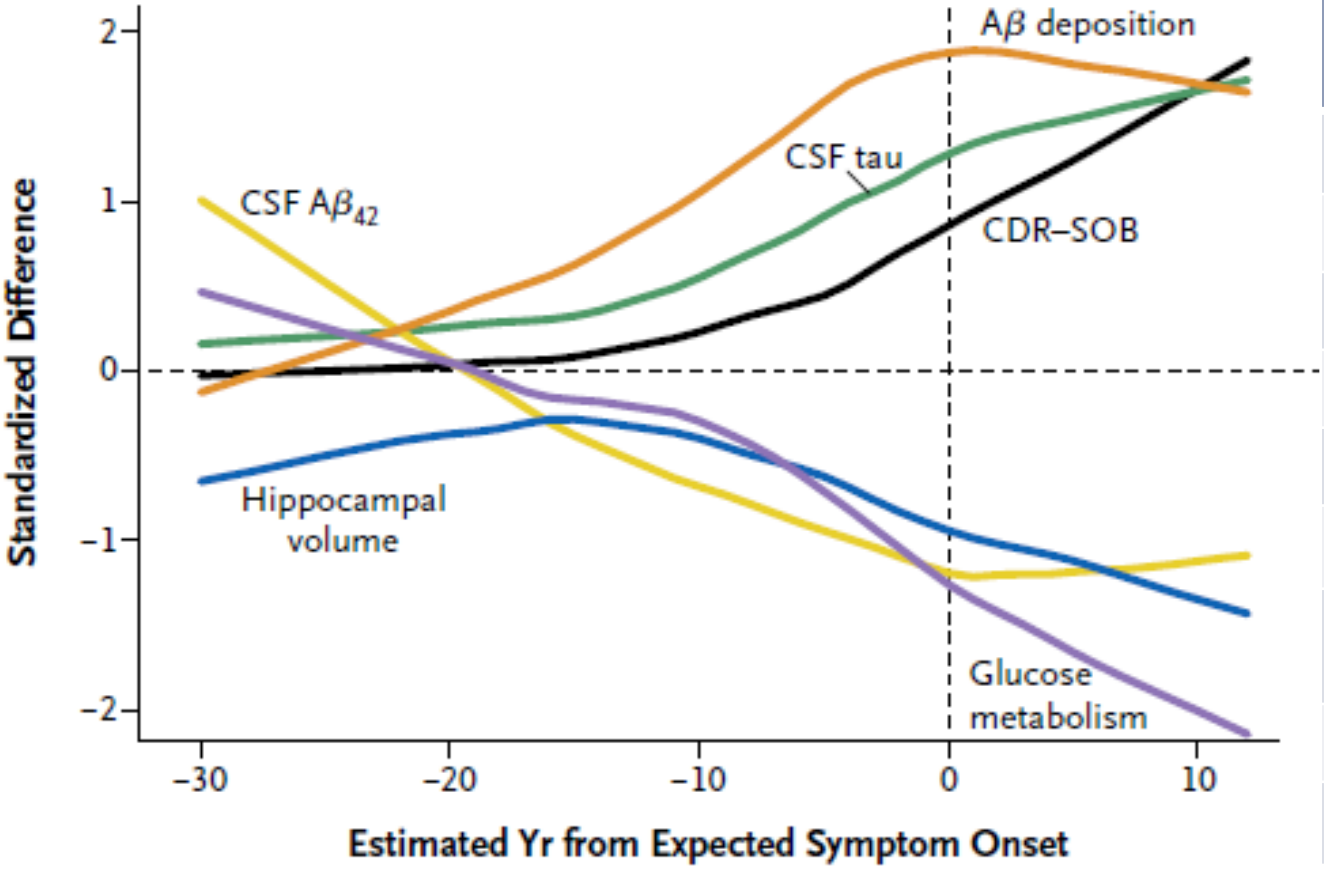
MCI: Mild Cognitive Impairment
AD: Alzheimer´s Disease/Dementia
DLB: Dementia with Lewy bodies
FTD: Frontotemporal Dementia
SD: Semantic Dementia
PSP: Progressive Supranuclear Palsy
CBD: Corticobasal Degeneration
VaD: Vascular Dementia

Ishii 2014, Am J Neuroradiol



Tan et al., JAD, 2014; Jack et al., Lancet Neurol. 2010

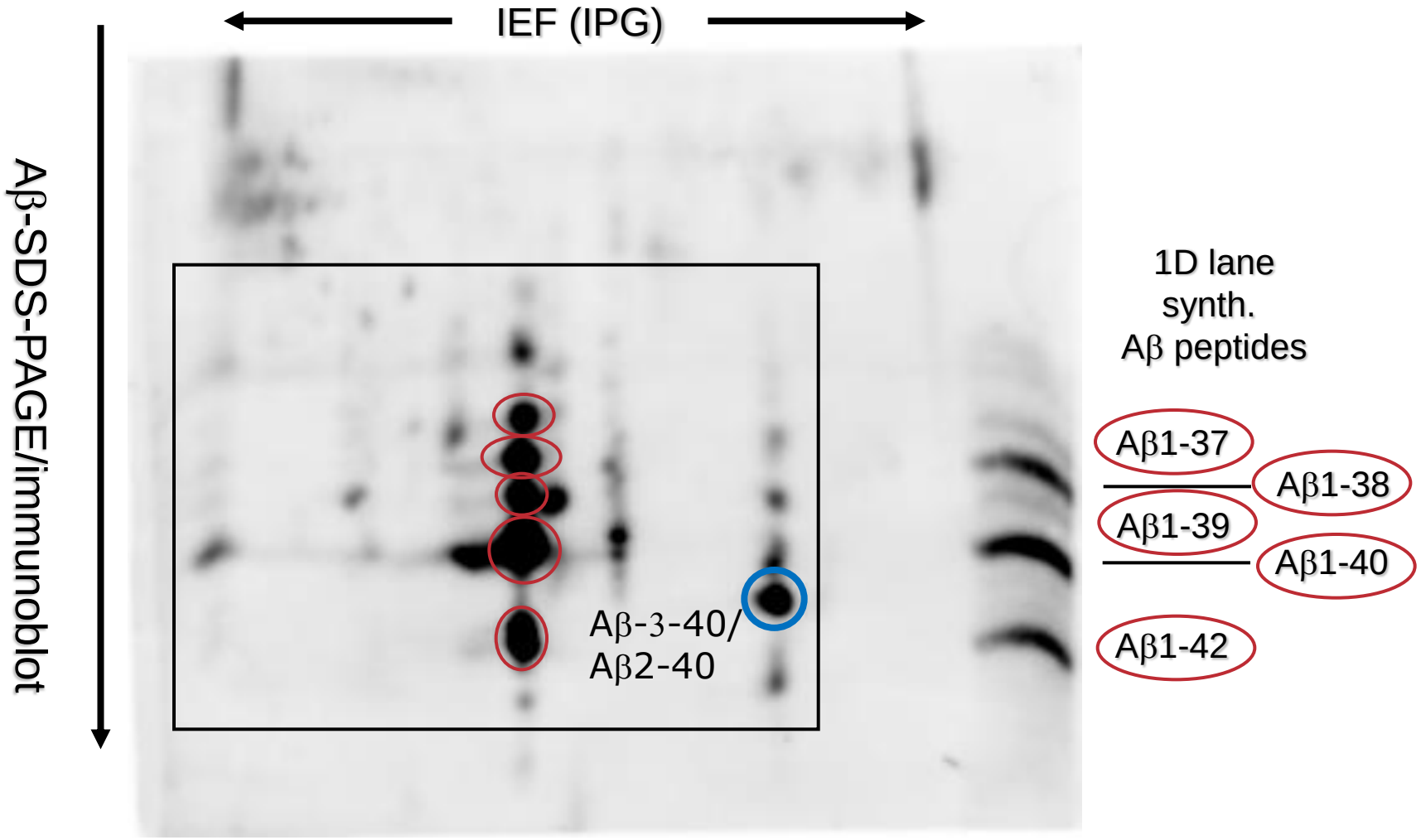
Biomarker cascade in dominantly inherited AD



Biomarker	Decline prior to estimated dementia onset (years)
CSF Abeta1-42	25
PIB-PET	15
CSF Tau	15
Brain atrophy	15
FDG-PET	10
Episodic memory	10
Global cognitve impairment	5
CDR	5
Dementia Diagnosis	3

Bateman et al., NEJM, 2012

Urea-based 2D-Abeta-WIB for blood Aβ peptides

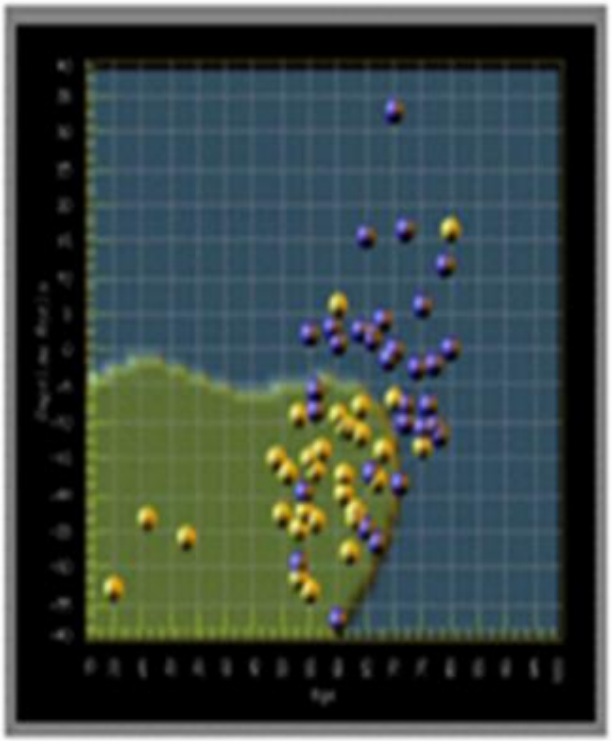


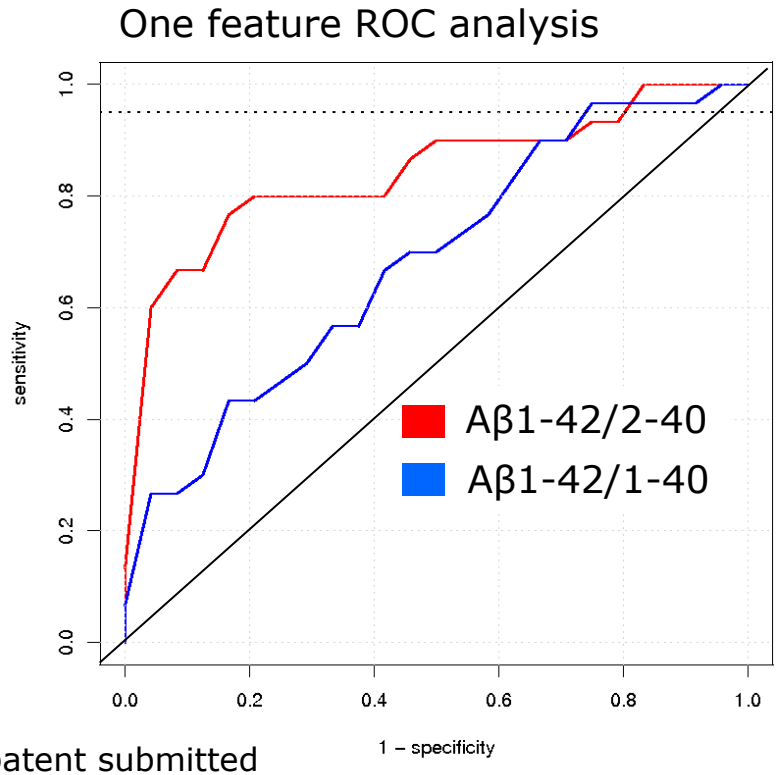
Maler JM, et al., Wiltfang J (2007) Proteomics

N-modified Aβ peptide species for AD blood assay ?

80% of early AD/high risk MCI patients versus controls (n=64) can be classified correctly accoding to their blood plasma ratio Aβ1-42/Aβ-3-40

Aβ1-42/Aβ-3-40 is significantly superior to the conventional ratio Aβ1-42/Aβ1-40.
In contrast to Aβ1-42/Aβ1-40 the new ratio is correlated to CSF biomarkers (Tau, Abeta) and neuroimaging (data not shown)





Quantitative mass spec of human blood plasma Abeta peptides

No. 9] Proc. Jpn. Acad., Ser. B 90 (2014) 353

Novel plasma biomarker surrogating cerebral amyloid deposition

By Naoki KANEKO,[*1] Akinori NAKAMURA,[*2] Yukihiko WASHIMI,[*3] Takashi KATO,[*2,*3] Takashi SAKURAI,[*3] Yutaka ARAHATA,[*3] Masahiko BUNDO,[*3] Akinori TAKEDA,[*3] Shumpei NIIDA,[*4] Kengo ITO,[*2,*3] Kenji TOBA,[*3] Koichi TANAKA[*1] and Katsuhiko YANAGISAWA[*2,†]

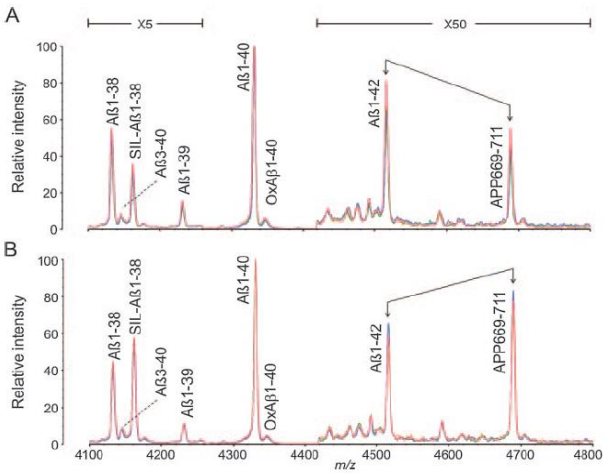
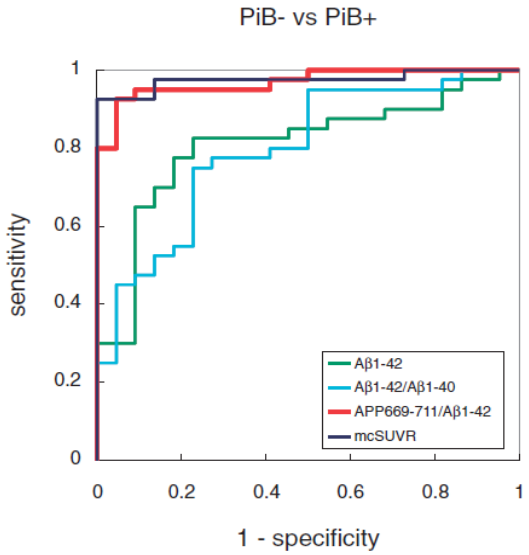


Fig. 1. MALDI-TOF mass spectra of plasma Aβs and AβAPs. Representative mass spectra obtained by IP-MS of plasma samples from the HC– (A) and AD (B) subjects are shown. In addition to Aβ1-40 and Aβ1-42, AβAPs including Aβ1-38, Aβ3-40, Aβ1-39 and APP669-711 were simultaneously measured by MALDI-TOF MS. Four mass spectra (represented in red, blue, green and orange) were obtained from one immunoprecipitation. The levels of Aβs and AβAPs were calculated by averaging the four intensity ratios of Aβs and AβAPs peak to SIL-Aβ1-38 peak. The arrows represent the difference in signal intensity between Aβ1-42 and APP669-711.



High correlation of Abeta1-42/-3-40 ratio with 18F-Amyloid plaque load

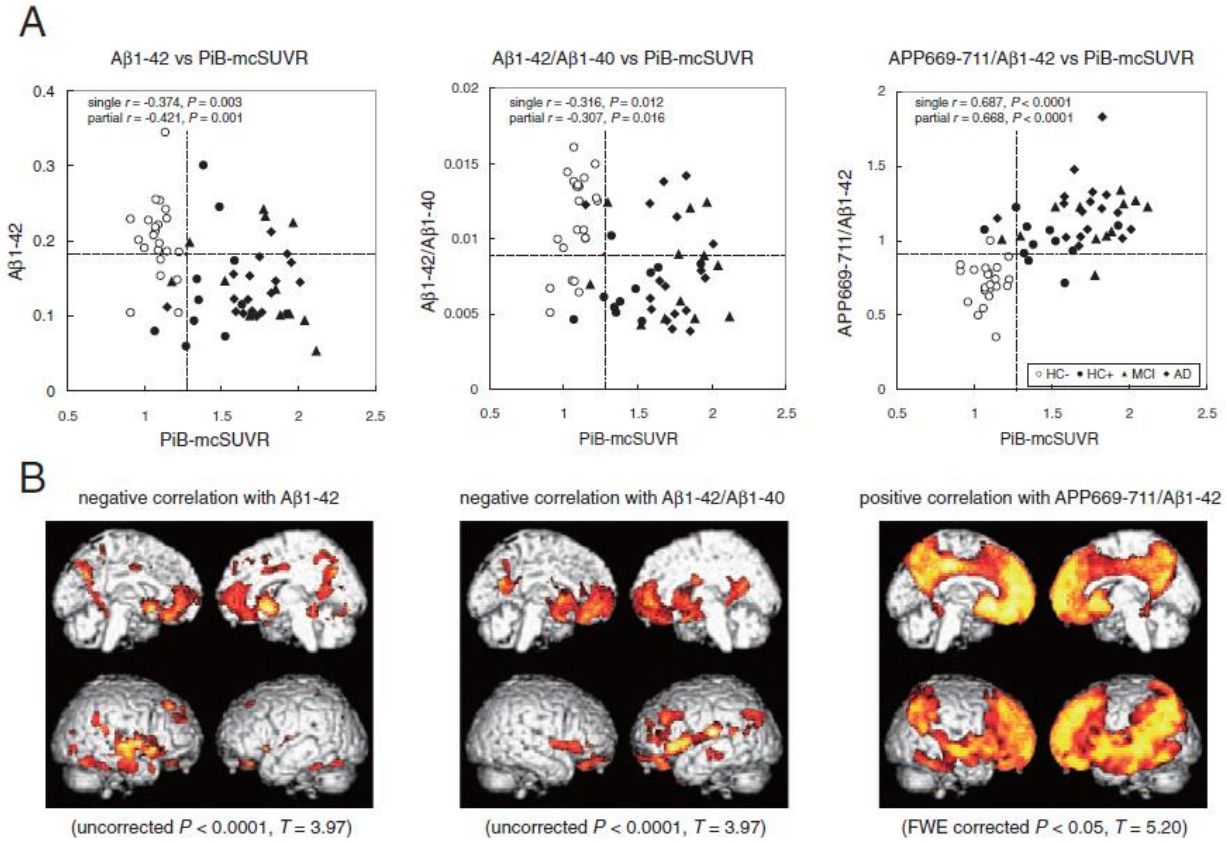
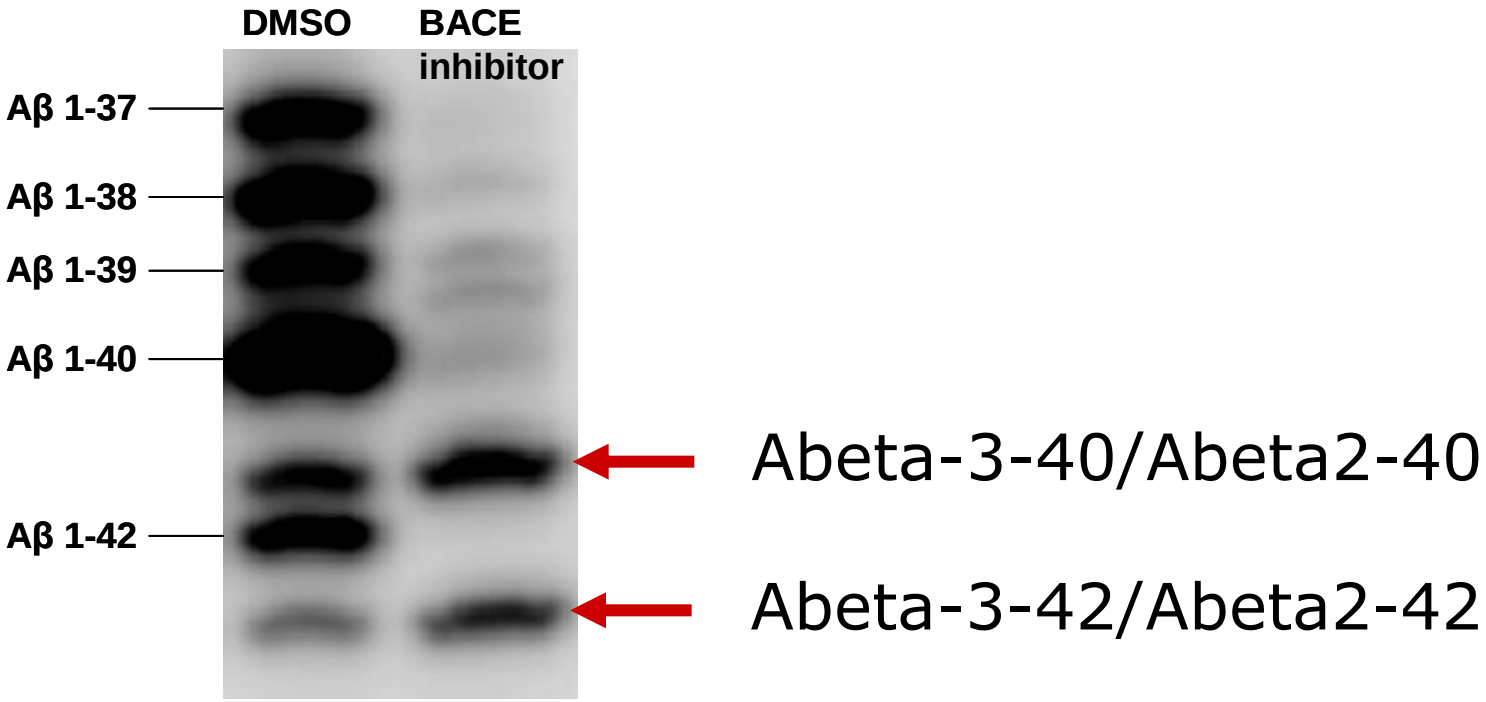


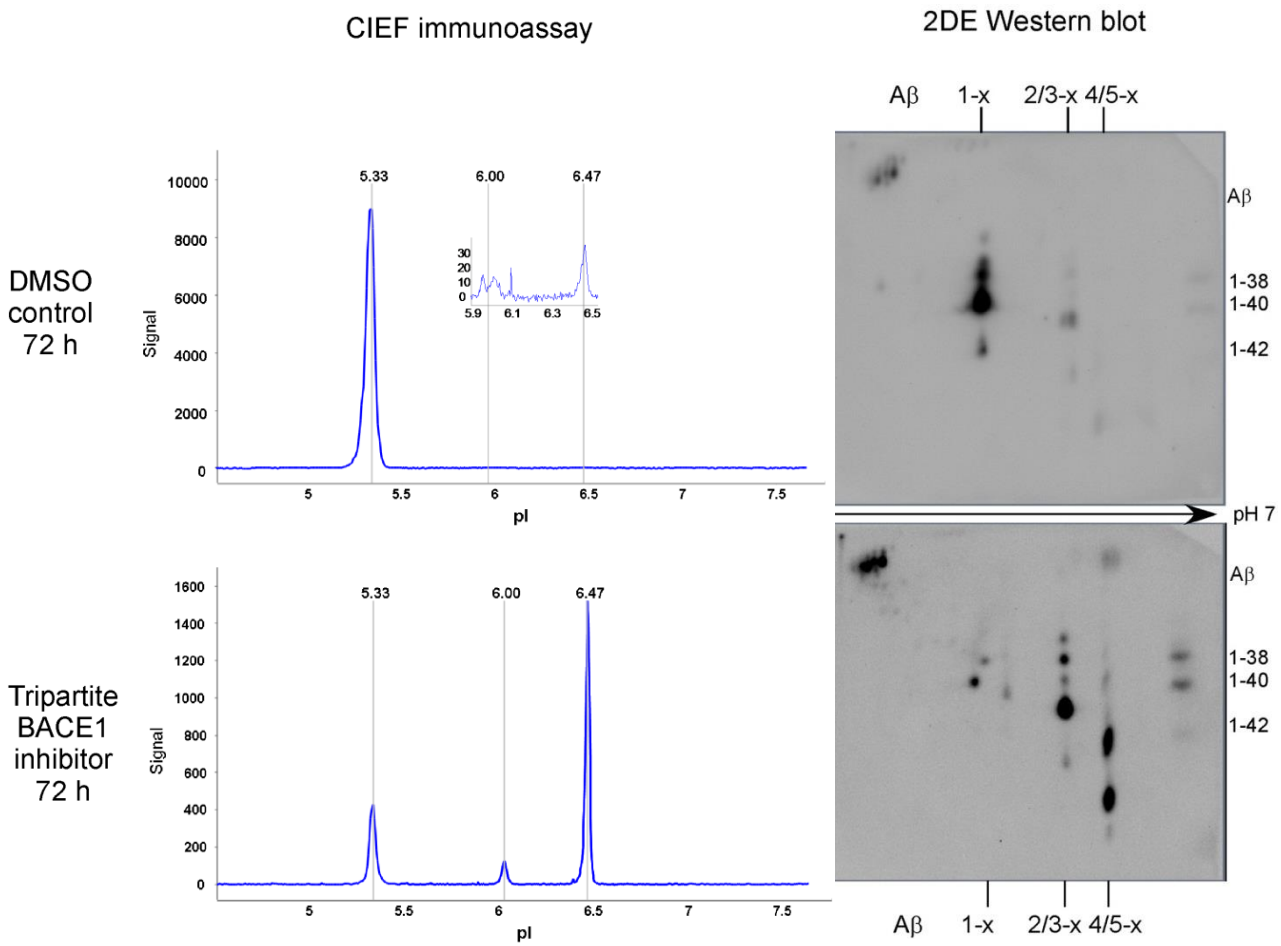
Fig. 4. Correlations between plasma biomarkers and PiB-mcSUVR. A) Scatter plots for biomarkers and PiB-mcSUVR. The open and closed symbols in the scatter plots indicate PiB− and PiB+ groups, respectively. The dashed lines represent cut-off values estimated by the ROC analyses as shown in Fig. 3 and Table 2. B) Regression analysis of PiB-SUVR images for each biomarker adjusted for age. Brain areas that showed statistically significant correlation between regional PiB retention and each biomarker are visualized. Please note that the height threshold of APP669-711/Aβ1-42 is different from the others. The extent thresholds of all are the same ($k = 200$ voxels).

Specific beta amyloid peptide variants appear to be procuded independently of BACE-1



SY5Y APPwt cell culture supernatants after 72 h treatment with membrane-anchored BACE inhibitor or DMSO (control)

Haußmann *et al.*, Anal Chem, 2013, 85(17), 8142-9



After BACE1 inhibitor treatment of SH-SY5Y cells overexpressing wildtype APP, the majority of Aβ peptides is amino-terminally modified

SH-SY5Y cells overexpressing APPwt were incubated for 72 h with either 100 nM tripartite BACE1 inhibitor or 0.1% DMSO (vehicle control). IP (mAb 6E10) of Aβ peptides from cell culture supernatants with mAb 6E10 and analyzed by CIEF immunoassay or 2D western blot

Haußmann *et al.*, Anal Chem, 2013, 85(17), 8142-9

Clinical significance of N-terminally modified Abeta peptides

- N-terminally modified Abeta species are highly abundant in human AD brain (Wiltfang et al.; JBC 2001)

  Transgenic animal models of AD and human AD brains differ dramatically regarding their relative abundance of N-terminally modified species (Schieb et al., Jahn, Wiltfang, Klafki; JBC 2011).

- N-terminally modified Abeta peptides are among the first species to precipitate within beta-amyloid plaque maturation and they may accelerate seeded Abeta oligomerization

Science 2009: Evidence for distinct gamma-secretase complexes with functional relevance for distinct APP processing

ScienceExpress Report

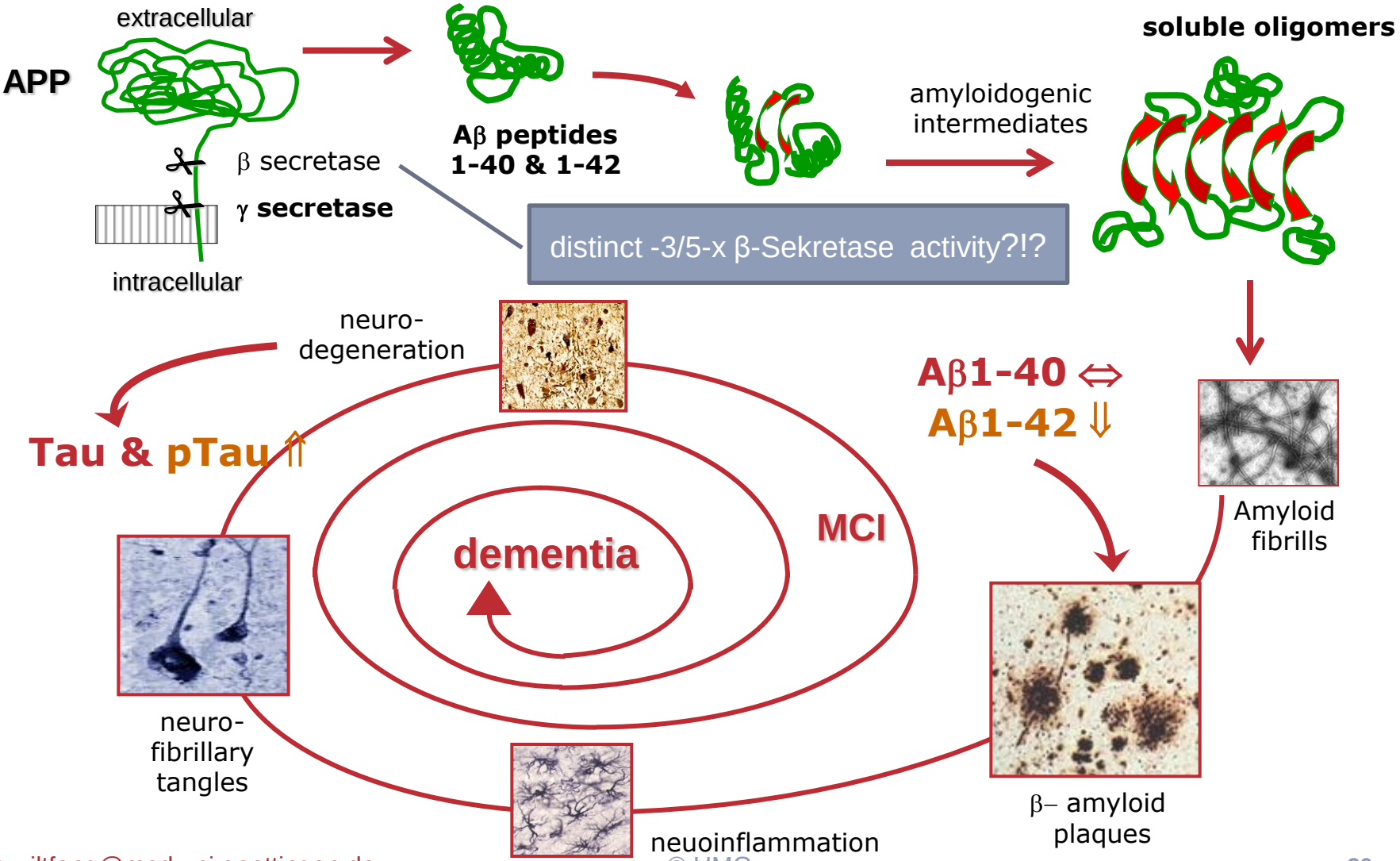
γ-Secretase Heterogeneity in the Aph1 Subunit: Relevance for Alzheimer's Disease

Lutgarde Serneels,[1,2*] Jérôme Van Biervliet,[1,2*] Katleen Craessaerts,[1,2] Tim Dejaegere,[1,2] Katrien Horré,[1,2] Tine Van Houtvin,[1,2] Hermann Esselmann,[3,4] Sabine Paul,[3,4] Martin K. Schäfer,[5] Oksana Berezovska,[6] Bradley T. Hyman,[6] Ben Sprangers,[7] Raf Sciot,[8] Lieve Moons,[9] Mathias Jucker,[10] Zhixiang Yang,[11] Patrick C. May,[11] Eric Karran,[12†] Jens Wiltfang,[3,4] Rudi D'Hooge,[13] Bart De Strooper[1,2‡]

Also evidence for distinct beta-secretase (BACE) activity with functional relevance for distinct APP processing ??

Amyloid cascade hypothesis of Alzheimer´s dementia

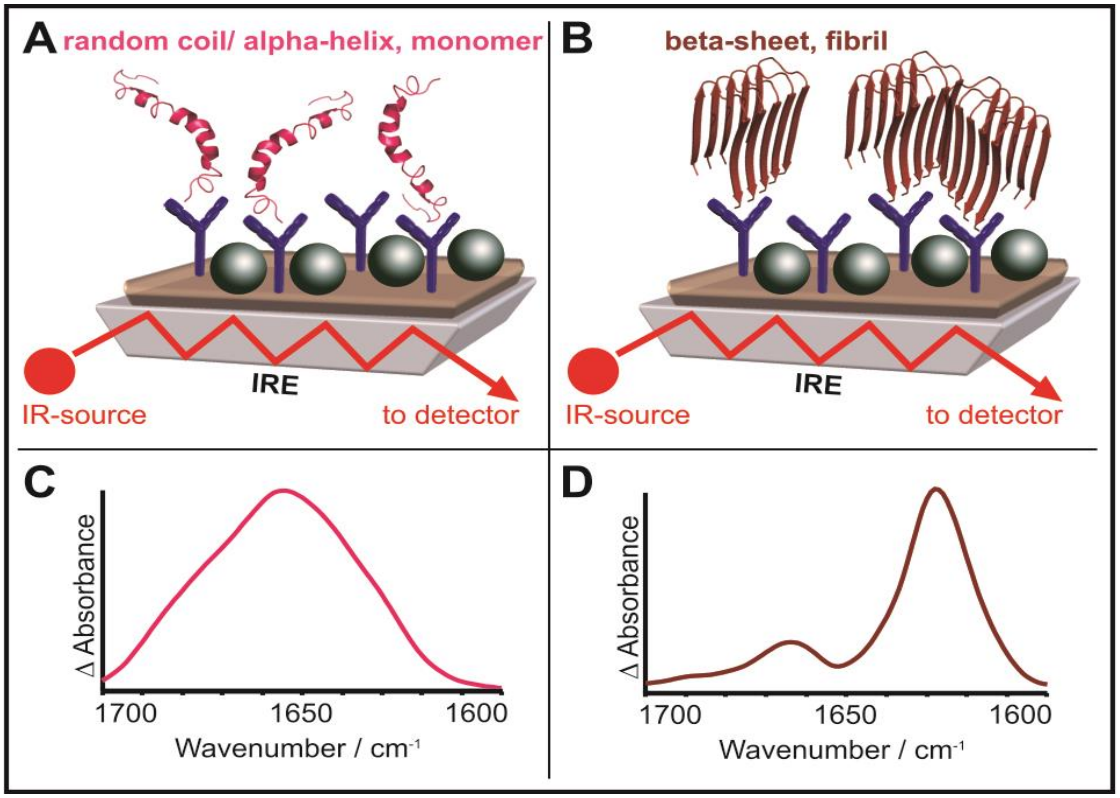
A. Alzheimer



Molecular Imaging by Fourier-transformed Near Infrared Spectroscopy as a novel biomarker for protein misfolding diseases

Nabers, et al., Wiltfang et al., Journal of Biophotonics, 2015;
patent pending

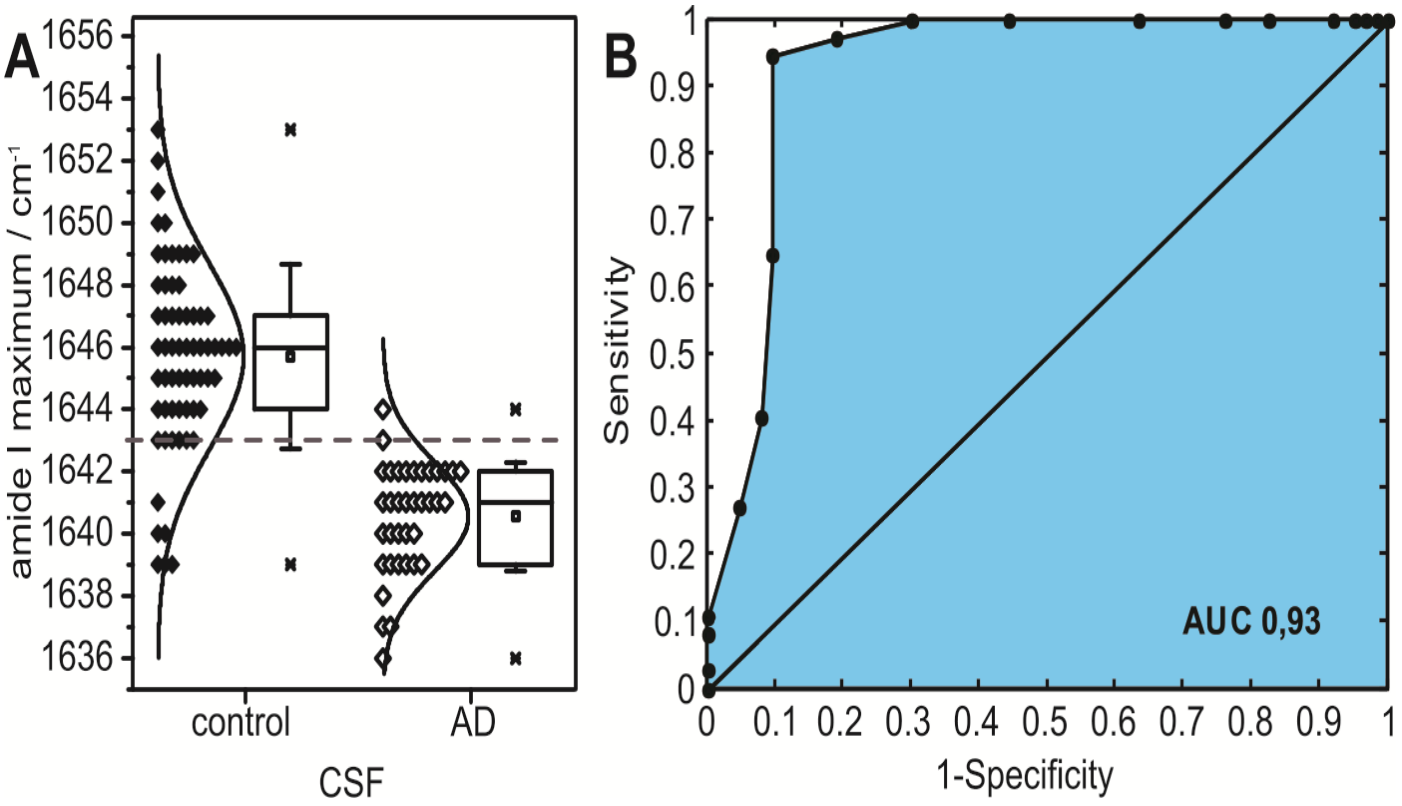
ATR-FTIR spectroscopic immuno sensor for neurochemical diagnosis of early AD



A. Nabers, et al., Wiltfang et al., Journal of Biophotonics, 2015; patent pending

Schematic representation of the immuno-ATR-FTIR spectroscopic setup. The IR-beam is multiple total reflected in the IRE (A,B) and generates thereby an evanescent wave at the boundary layer. Thus monomeric (C) or beta-sheet enriched fibrillar Abeta peptides (D) could be detected after antibody-based capture from biological samples. The scheme exemplarily depicts the detection of different synthetic Abeta(42) conformations.

ATR-FTIR spectroscopic immuno sensor for neurochemical diagnosis of early AD



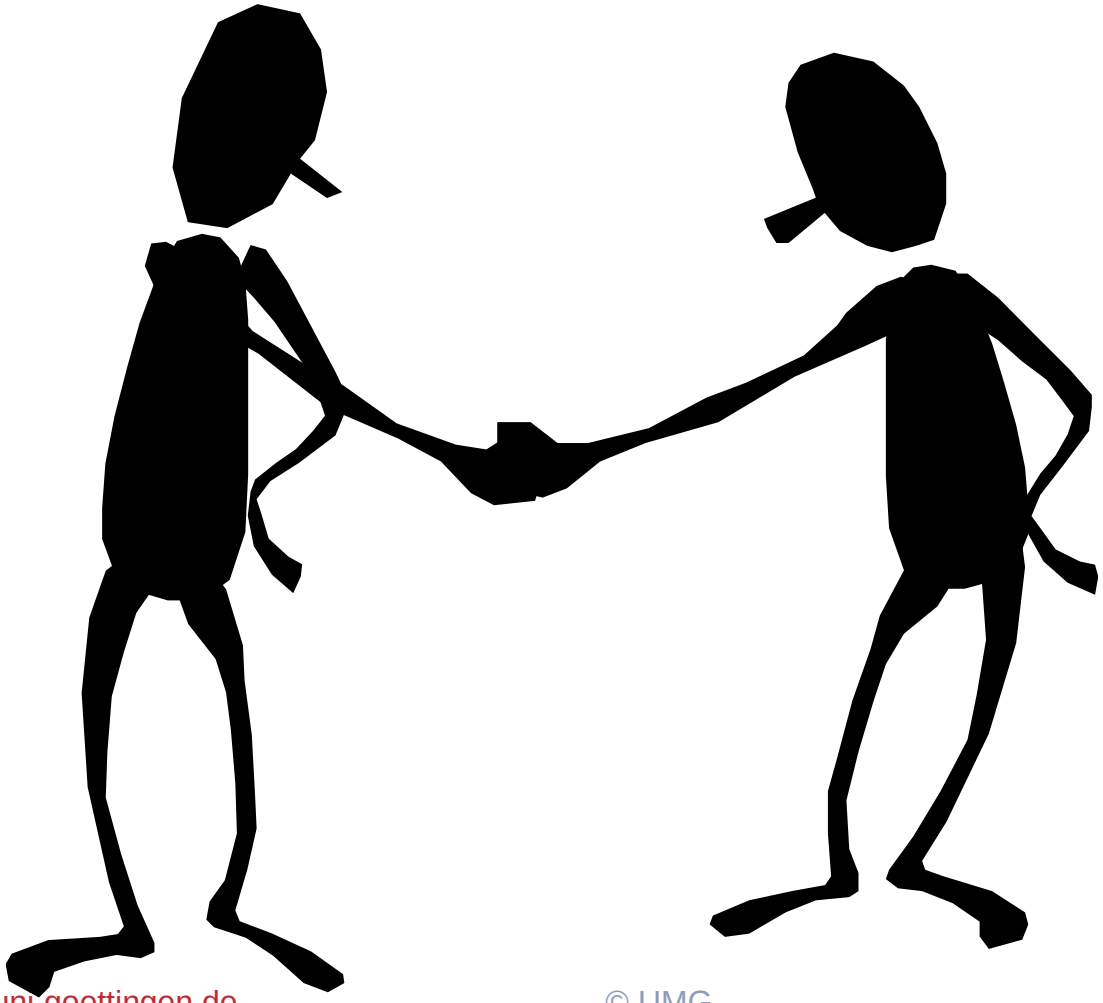
Legend: The averaged and normalized amide I band maxima recorded of control and AD patient CSF (A) samples indicate a higher frequency in control samples, synonymous to a higher alpha-helical or random coil content, than the Abeta fraction in AD patients.

Patent pending, unpublished patient data; A. Nabers et al., J. Wiltfang, paper under review

Summary

- The molecular pathophysiology of Alzheimer´s Disease is launched more than 10 years before cognitive brain deficits of Alzheimer´s Dementia become overt as amnestic MCI
- beta-amyloid mediated neuropathology with neurotoxic soluble oligomer species preceedes Tau-mediated neuronal damage. Moreover, there is strong evidence for a Prion-like disease propagation.
- A gain of endoproteolytic function in rare autosomal-dominant genetic AD is well documented. However, in sporadic AD (99% of cases) scientific evidence points more to a loss of catabolic clearance function
- In case of multigenetic (sporadic) AD the final molecular cause has not been validated yet but Abeta & and Tau are at least highly correlated surrogate marker
- Biomarkers (CSF, Amyloid/Tau-PET) can identify preclinical AD, which allows to validate promising preventive treatment strategies
- N-terminally modified Abeta peptide species are likely to be generated by non-BACE secretase activity, and they may offer new diagnostic and therapeutic molecular targets

Thank you for your attention



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