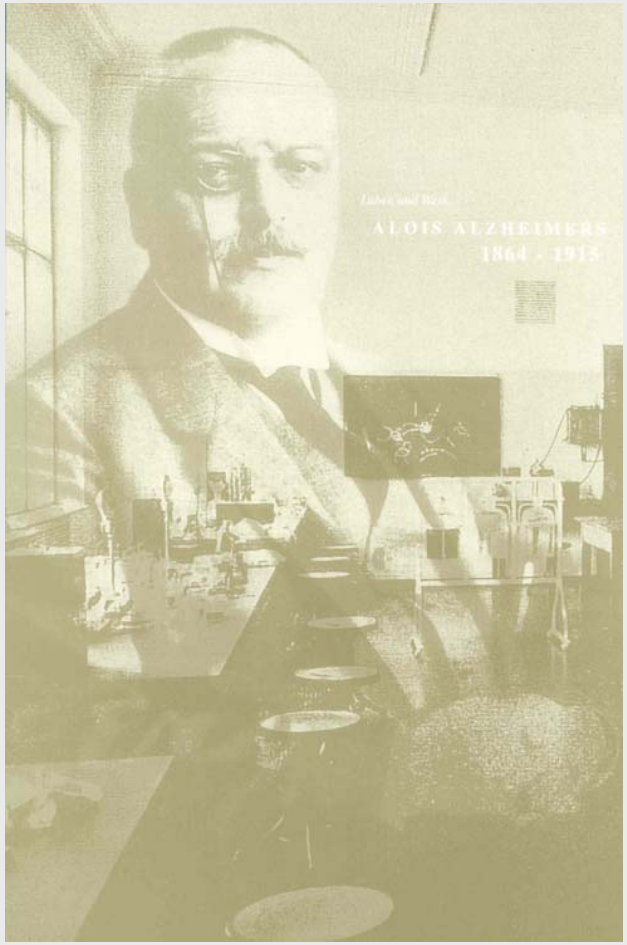
Alzheimer‘s disease
Target population and development of biomarkers



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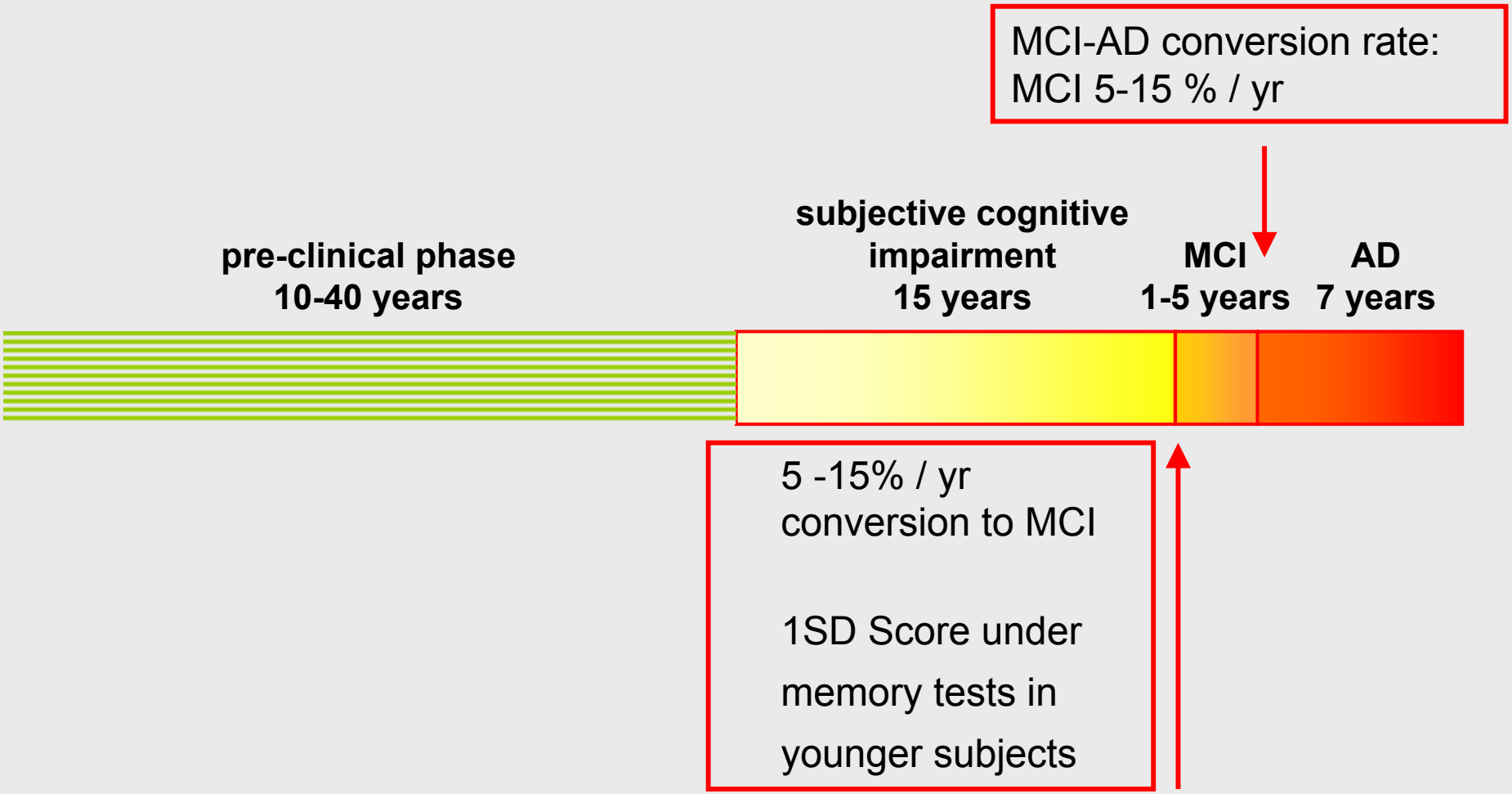
from molecules to mind

Open regulatory issues

„AD is still an open research field“

- Which **population** do we study?
- How valid and reliable are **biochemical markers**?
- Focus on value regarding early characterisation, detection & prediction
- Potential role for enrichment of trial populations
- Current use as endpoints in proof of concept studies or confirmatory clinical trials

Precsymptomatic and clinical continuum of AD



IPA Expert Conference on MCI - Gauthier et al. (2006) The Lancet; PCP: Braak und Braak (1991); SMI: Reisberg und Saeed (2004); MCI: Peterson und Morris (2005)

Alzheimer's disease (AD)

Target population I: (mild) - moderate – (severe) AD as reference

- **Clinical diagnosis**: dementia syndrome and criteria for severity (mild moderate, severe) are defined in DSM-IV-TR and in ICD-10 (F00-F03)
- Use of **Screening** test for degree of cogntive impairment (MMSE)
- **Probablility assessment** of AD: history, progressive course, exclusion of other diagnosable causes of dementia
- **Subtype diagnosis** can be further specified using NINCDS-ADRDA criteria
- **Diagnostic criteria need revision and updating:**
- Sensitivity has been shown very good to excellent, specificity has been much lower (optimised assessment and use of biomarkers)
- **Revised criteria** are being discussed in the APA DSM-V and WHO ICD-11 working groups
- Potential implementation of operationalised **neurobiological criteria** (using laboratory methods & neurochemical information) may aid to an earlier and more accurate characterisation of AD

Hampel et al. (2008) Alzheimer's & Dementia; Broich (2007) International Psychogeriatrics

Alzheimer's disease (AD)

Target population II: early AD and prodromal stages

- **Very early AD and prodromal stages**
  - **MCI** is proposed as a transitional stage to AD and a nosological entity in elderly patients with mild cognitive deficits
  - **Concept** is in evolution and suffers limitations:
  - **Prevalence rates vary** greatly depending on criteria used (high proportion returns to normal and up to 12%/a progress to dementia)
  - MCI is not considered as a homogeneous clinical entity (role of **subtypes** such as **aMCI** and assessment tools need to be refined)
  - Clinical research demonstrates that characterisation of an at risk population such as aMCI and prediction of clinical AD may be substantially supported by use of biochemical markers in the CSF & APOE genotyping
  - recent evidence supporting characterisation of even earlier presymptomatic at risk groups with CSF markers

Biological markers in AD

- Biomarkers can play a critical role at all stages of the drug discovery / development process

Development of biological markers

AD presents difficulties in distinct areas (phase II-III trials)

- diagnosis (*early identification of homogenous populations when treatment would have the greatest effect - fixed marker*)
- classification *(enhancing specificity)*
- prognosis / prediction *(in trials with decline and conversion to dementia as endpoint)*
- progression *(natural or pathological history)*
- biological activity *(mechanisms of action)*
- surrogate *(predicts clinical endpoints – dynamic marker)*

NIH Biomarker Definitions Working Group (2001) Clin Pharmacol
Hampel et al. (2008) in press

Criteria of an *ideal* diagnostic biomarker of AD

- detects a fundamental feature of AD pathology
- is validated in neuropathologically confirmed cases
- sensitivity > 80 % (> 85 %)
- specificity > 80 % (> 75 %)
- reliable
- reproducible
- relatively inexpensive
- simple to perform

Consensus Report (1998) Neurobiol Aging

ELSEVIER

Neurobiology of Aging 24 (2003) 521–536

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Rapid communication

Biological markers for therapeutic trials in Alzheimer's disease Proceedings of the biological markers working group; NIA initiative on neuroimaging in Alzheimer's disease

Richard A. Frank [a,*], Douglas Galasko [b,1], Harald Hampel [c,2], John Hardy [d,3], Mony J. de Leon [e,4], Pankaj D. Mehta [f,5], Joseph Rogers [g,6], Eric Siemers [h,7], John Q. Trojanowski [i,8]

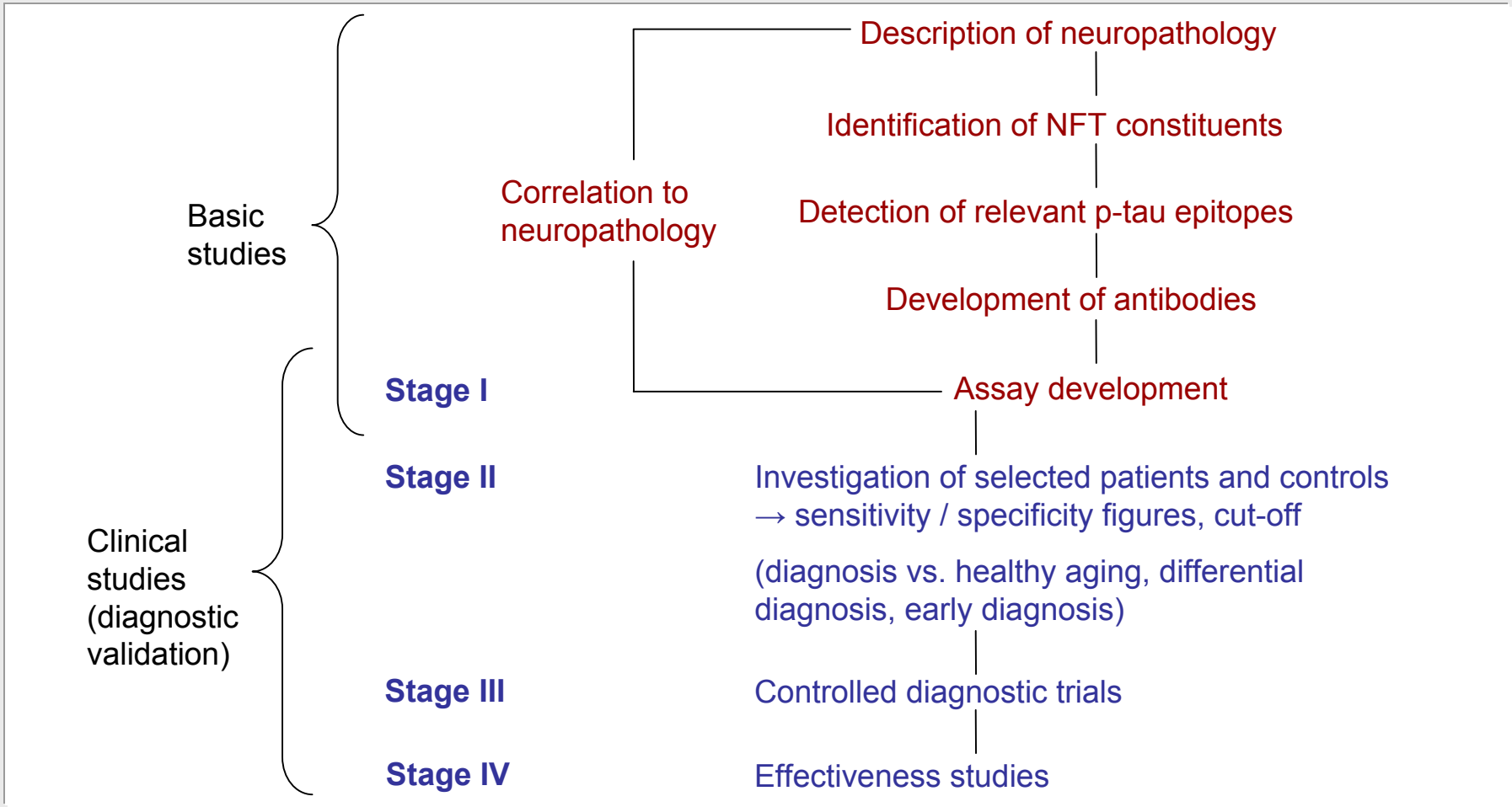
1) Feasibility:

- validated assay
- properties including high precision & reliability
- reagents and standards well described

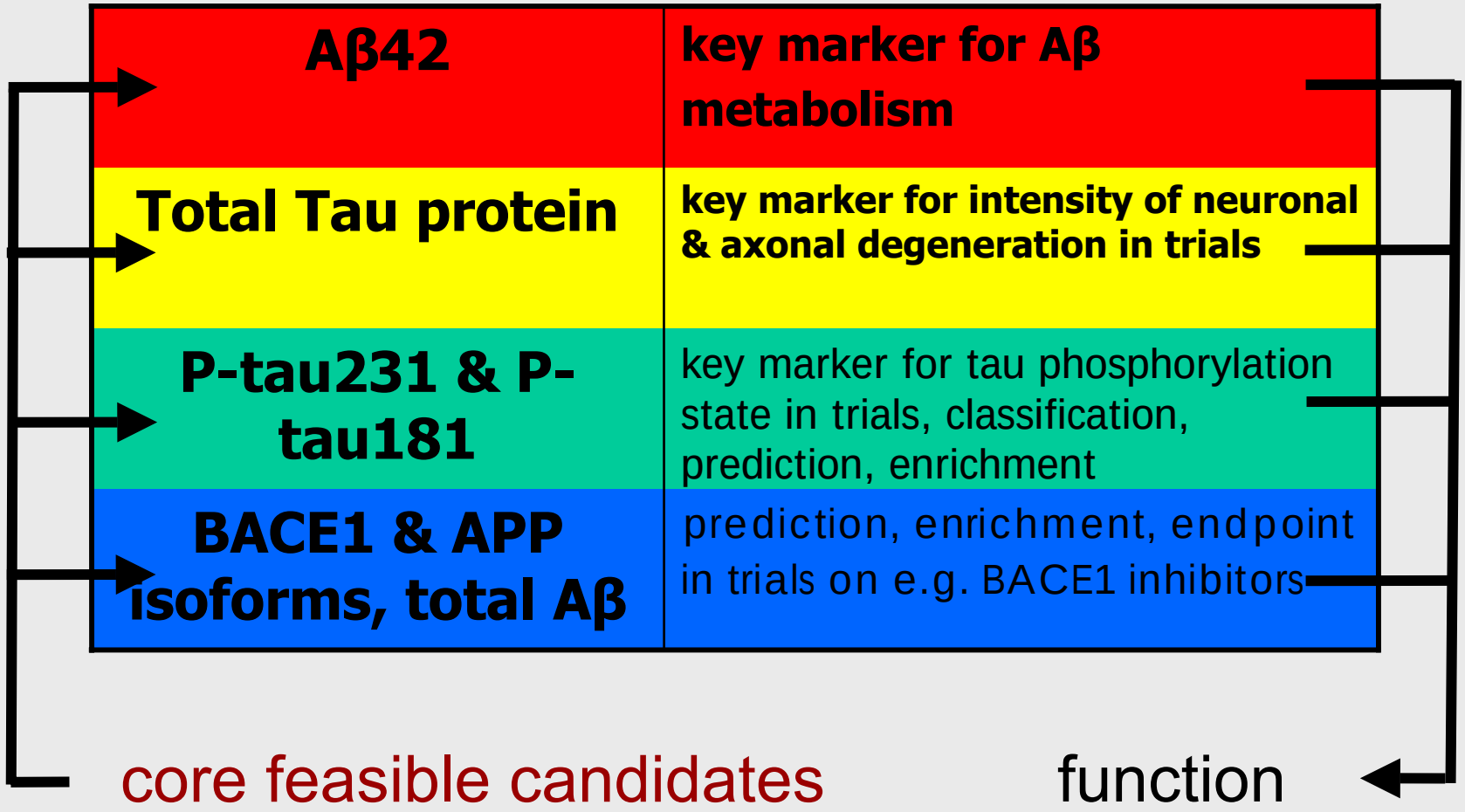
2) Core analyte:

- evidence of association with key mechanisms of pathology

Development of a biomarker for AD
e.g. p-tau (> 15 years so far)

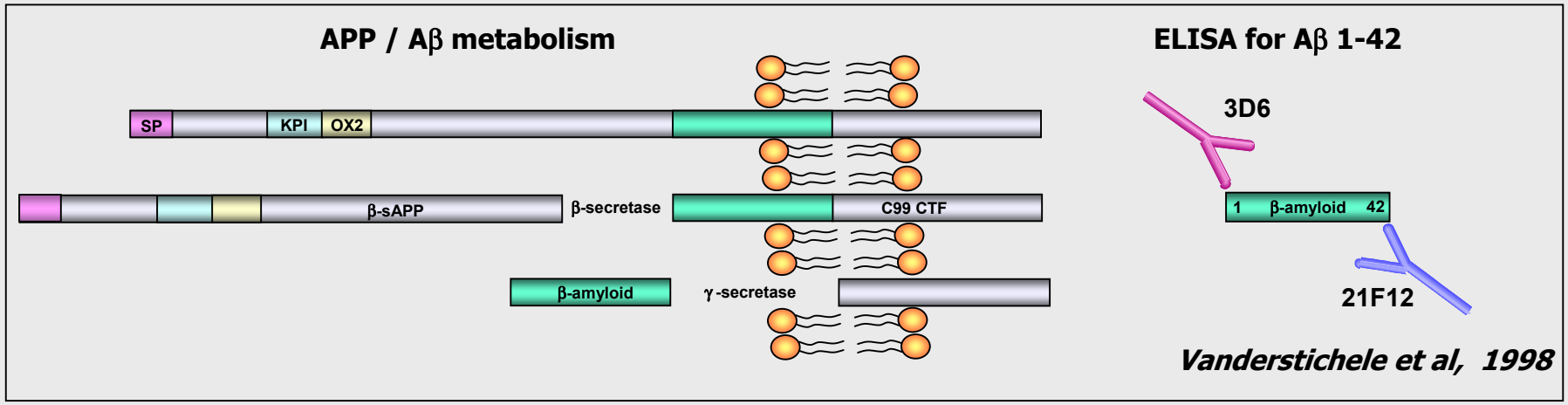


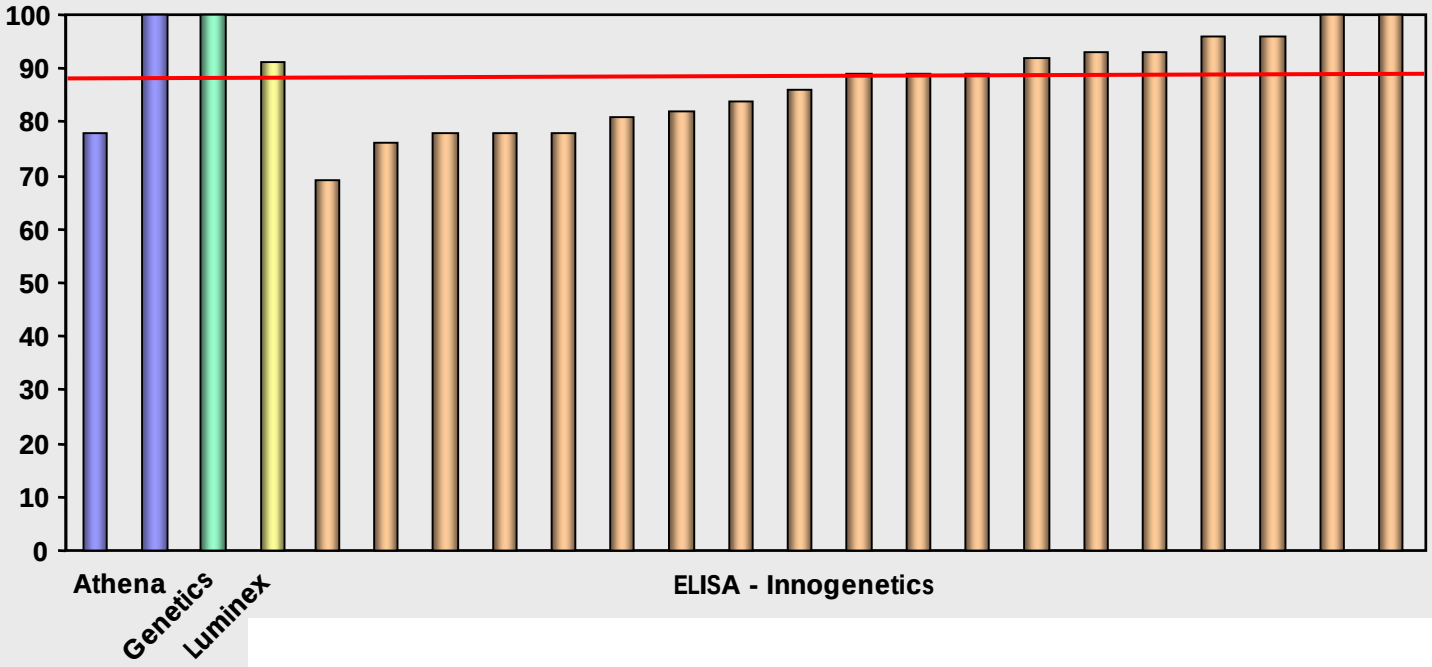
Core feasible AD biochemical CSF marker candidates



Hampel et al. (in press)

Candidate CSF biomarker for AD: Aβ42



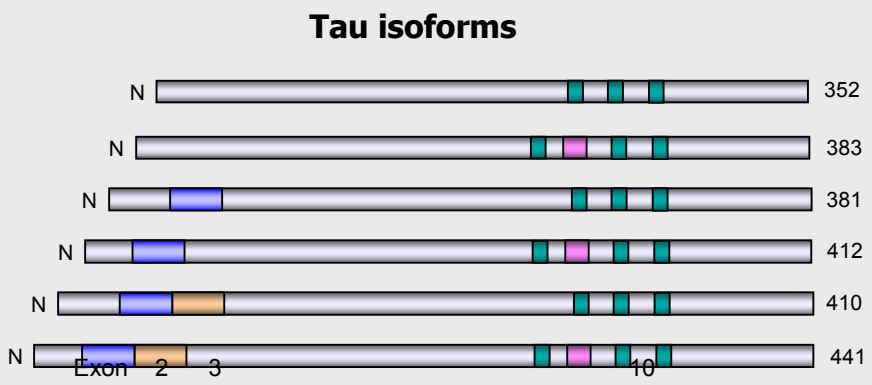


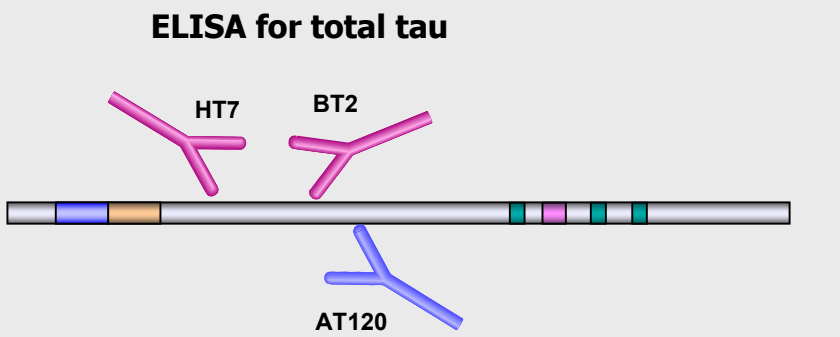
Mean decrease:
50% of controls

Studies (n)	21
AD cases	1163
Controls	819
Mean sens	88 %
Mean spec	87 %

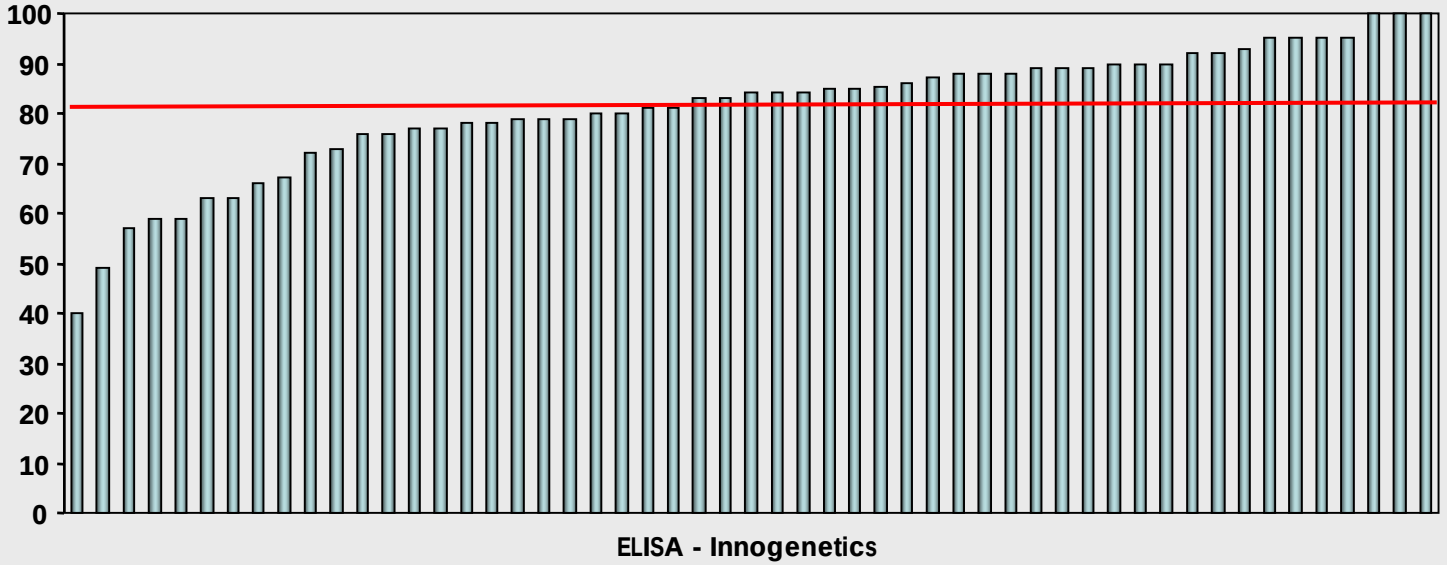
Blennow & Hampel (2003) Lancet Neurology; Blennow updated (2006)

Candidate CSF biomarker for AD: total tau





Blennow et al, Mol Chem Neuropathol 1995;26:231

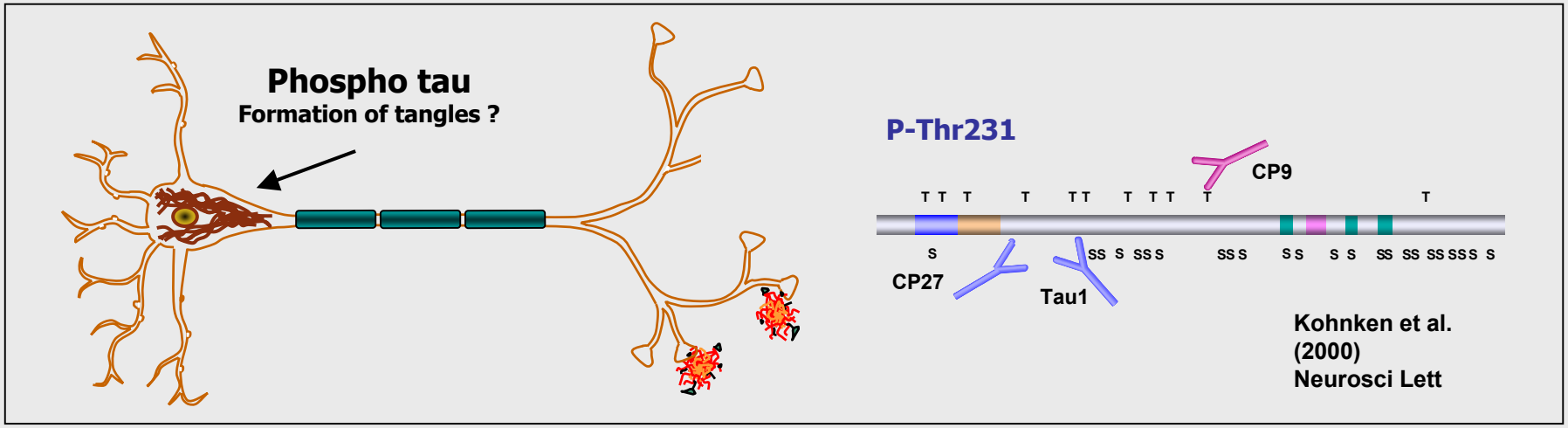


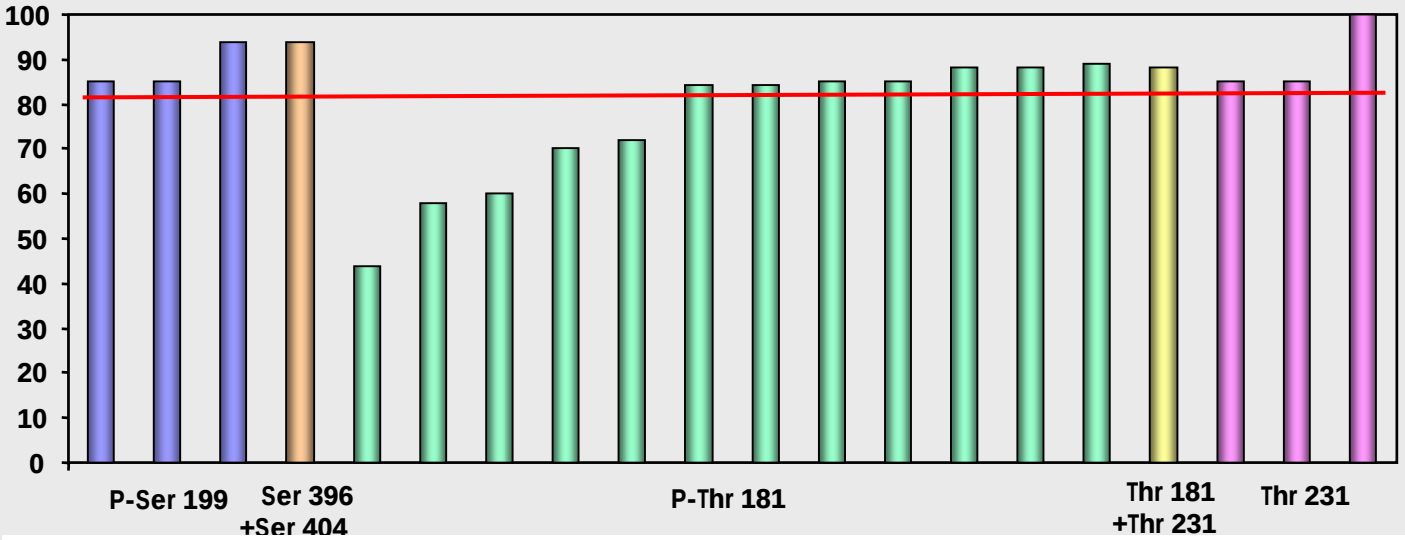
Mean increase:
320% of controls

Studies (n)	52
AD cases	3255
Controls	1955
Mean sens	81 %
Mean spec	90 %

Blennow & Hampel (2003) Lancet Neurology; updated (2006)
Hampel et al. (2008) Alzheimer's & Dementia

Candidate CSF biomarker for AD: phospho tau





Mean increase:
300% of controls

Studies (n)	20
AD cases	1214
Controls	655
Mean sens	81 %
Mean spec	88 %

Blennow & Hampel (2003) Lancet Neurology; updated (2006)
Hampel et al. (2008) Alzheimer's & Dementia

Comparative study: phosphorylated tau protein

diagnostic and classificatory accuracy [%] for group comparisons (ROC-analysis)

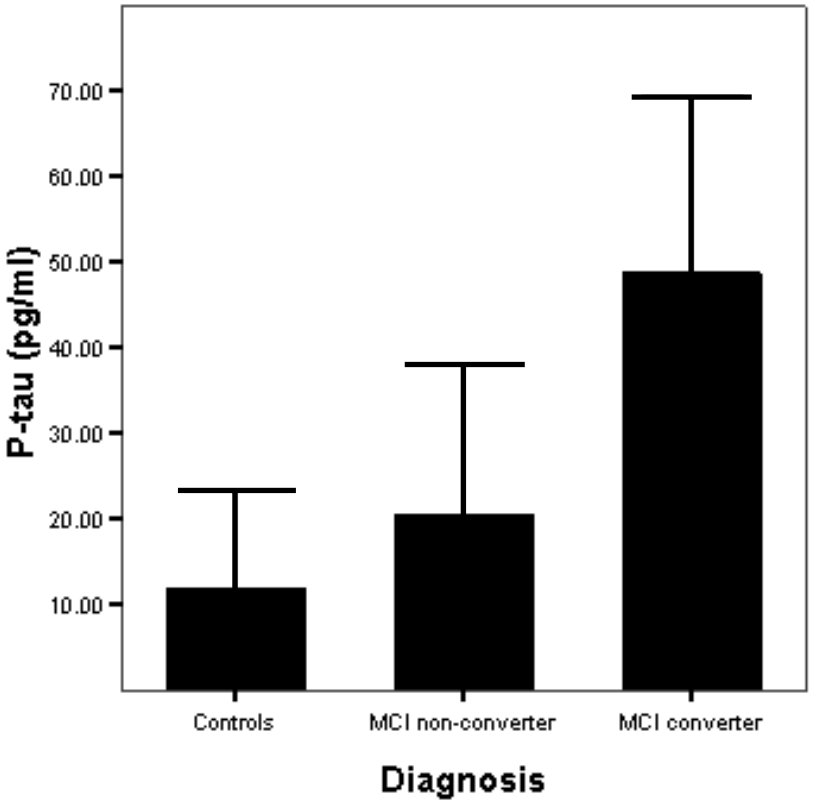
	p-tau 231 **[pg/ml]**			p-tau 181 **[pM]**			p-tau 199 **[fmol/ml]**		
AD vs.	**Sens**	**Spec**	**CAC**	**Sens**	**Spec**	**CAC**	**Sens**	**Spec**	**CAC**
non-AD	**86**	**85**	**85**	**87**	**80**	**84**	**72**	**83**	**77**
HC	**98**	**91**	**97**	**87**	**91**	**88**	**77**	**100**	**81**
OND	**96**	**91**	**95**	**90**	**86**	**89**	**88**	**86**	**88**

Negative predictive value: 87 % (negative test rules out AD with over 87 % probability)
Positive predictive value: 76 %

Hampel et al. (2004) Arch Gen Psychiatry

European multicenter trial
short-term predictive value of p-tau$_{231}$ in incipient AD

4 centers, n: 144 - 56 HC, 88 MCI (43 conv / 45 non-conv)

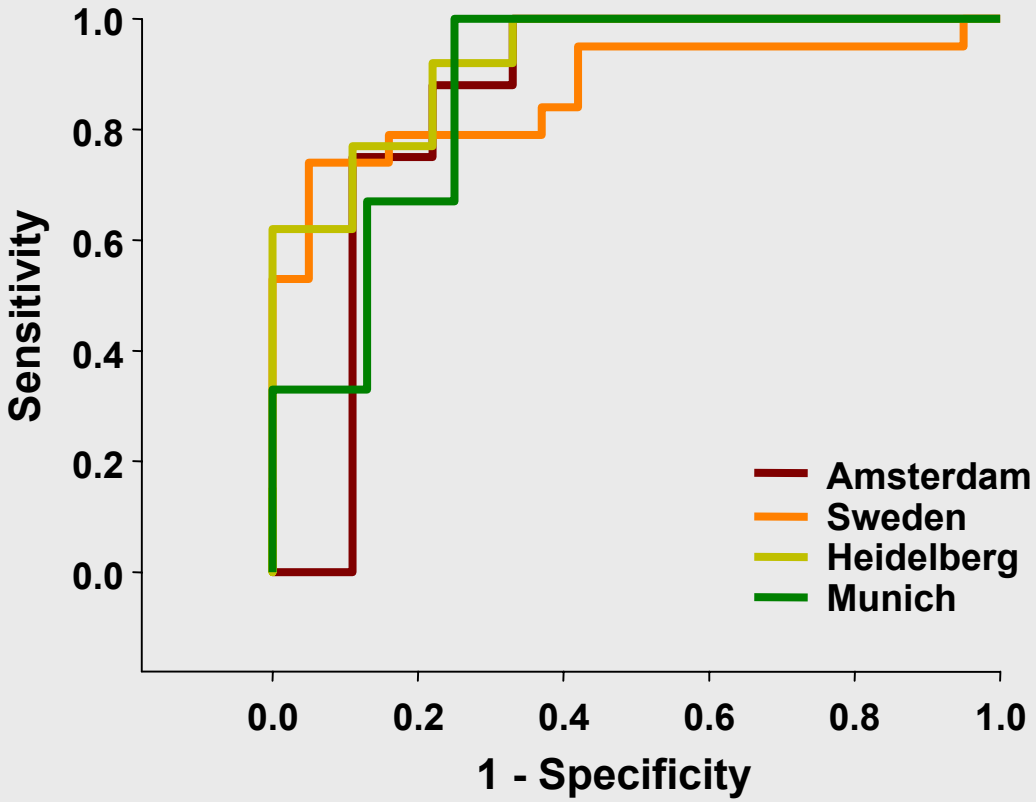


Baseline analysis & short follow-up interval: 1.5 years

Ewers et al. (2007) Neurology

Prediction of conversion from MCI to AD is stable across centres using CSF P-Tau (ROC-analysis)

4 European centers, n: 144 - 56 HC, 88 aMCI (43 conv / 45 non-conv)



A priori defined cut-off
(27.3 pg/ml of 1 reference center)

Sensitivity: 87.5%
Specificity: 73.0%

Classification accuracy: 80.0%

Variable cut-off
Sensitivity: 81.1%
Specificity: 79.8 %

Classification accuracy: 80.5%

A priori cut-off point = 27.32 pg/ml determined based on the Göteborg center

Ewers et al. (2007) Neurology

Improving prediction of incipient AD in MCI subjects combining three core CSF biomarker candidates

Study design: **Follow-up study over 4 - 6 years of aMCI and non-aMCI subjects**

MCI n= 134

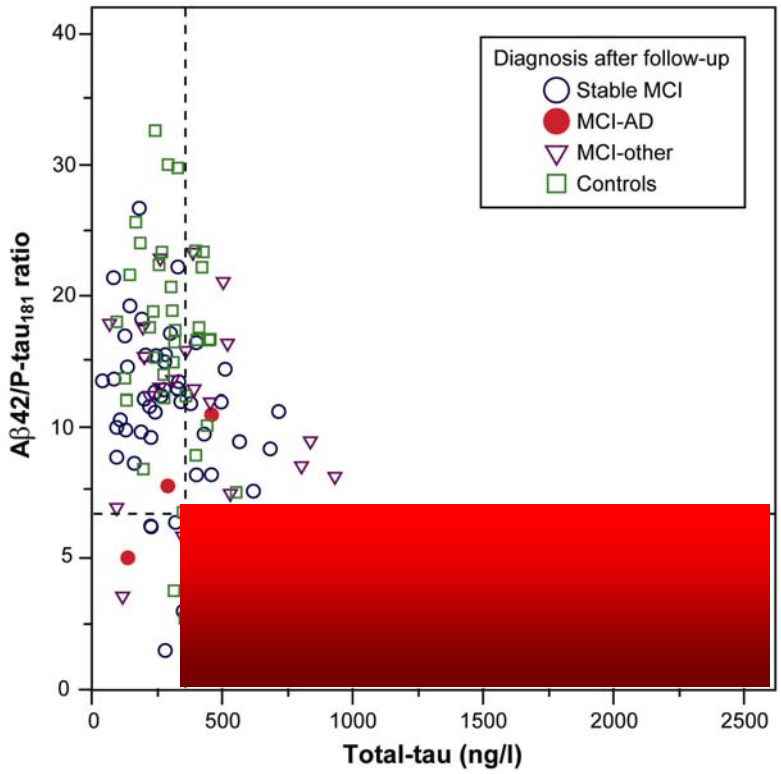
57 MCI → AD
56 MCI → MCI
21 MCI → other dementias

Healthy controls n= 39
cognitively stable for 3 years

T-tau > 350 pg/mL +
Aβ42 / P-tau ratio < 6.5

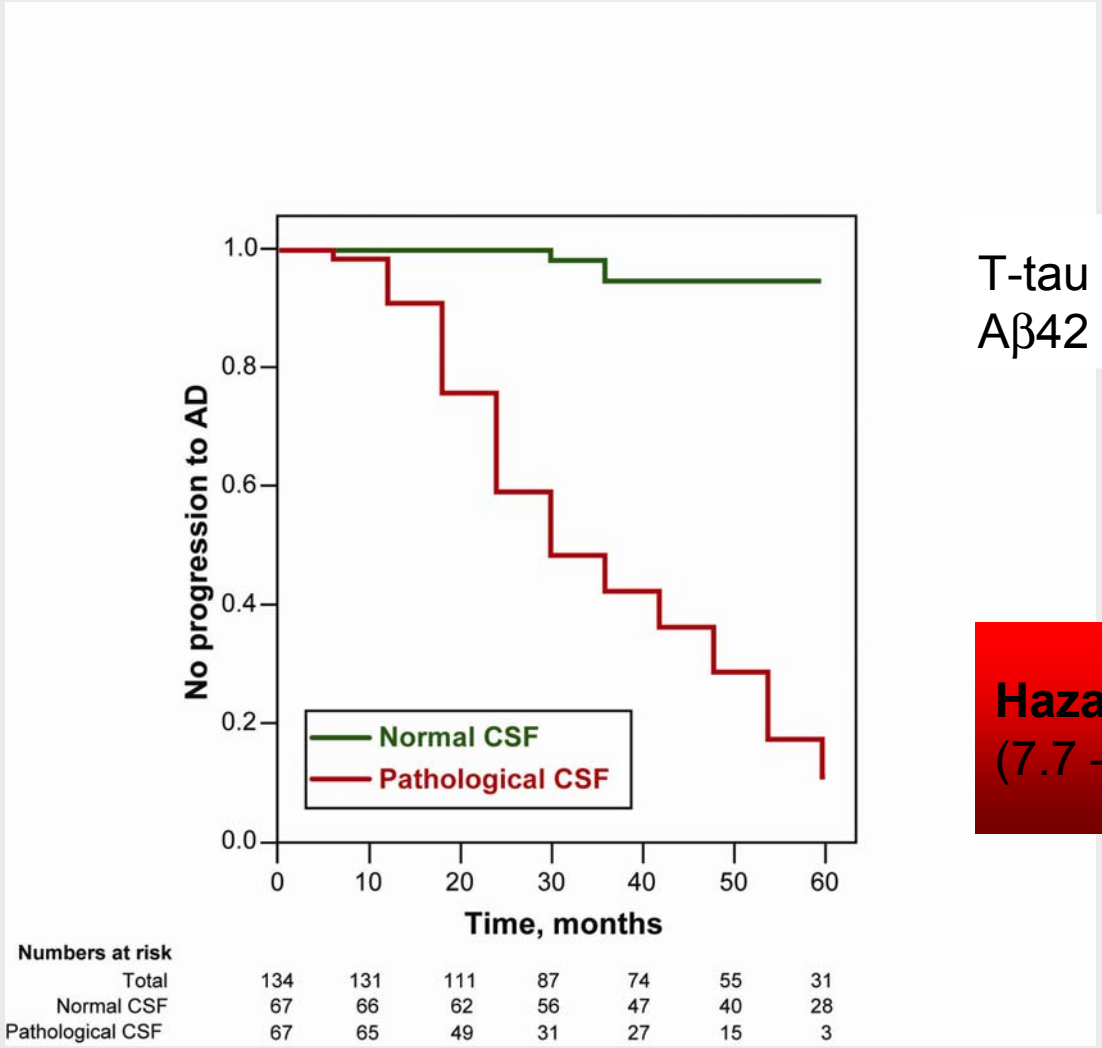
Sens MCI ⇒ AD 95 %

Spec MCI ⇒ MCI + other 87 %



Hansson et al. (2006) Lancet Neurol

Increased risk of AD in MCI subjects with pathological CSF
Potential stratification & enrichment of MCI trials



T-tau > 350 pg / mL +
Aβ42 / P-tau ratio < 6.5

Hazard ratio : 25.5
(7.7 – 84.9)

Hansson et al. (2006) Lancet Neurol

BACE1 & ApoE predict conversion from MCI to AD

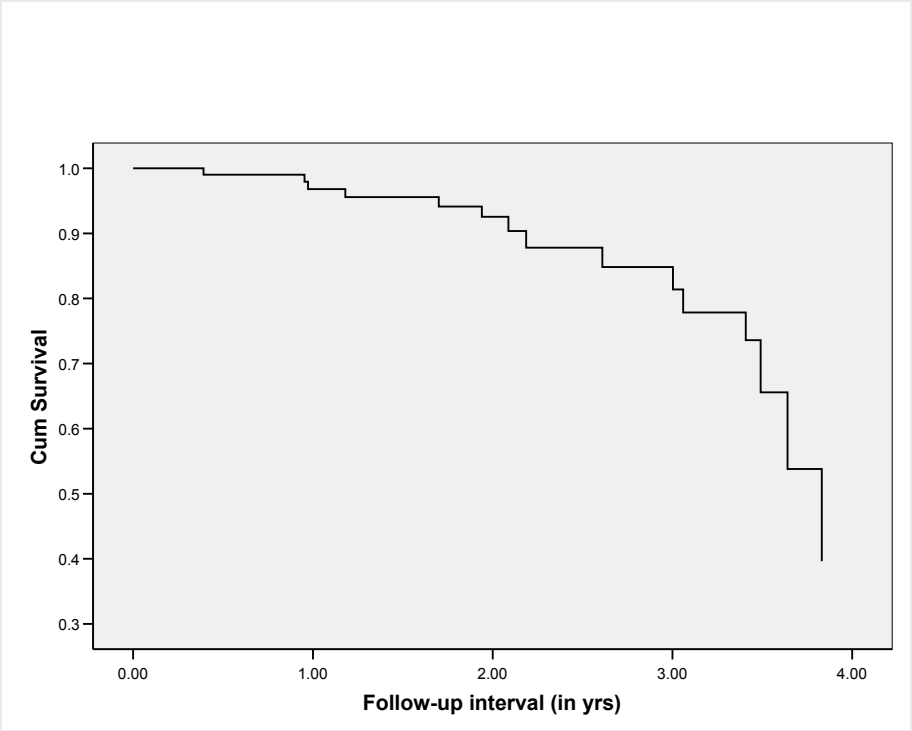
Cumulative survival

in ApoE & BACE model

MCI converter vs.

MCI Non converter

follow-up 2.5 yrs



- **Intitial multimodal prediction set:**
  - **CSF: BACE1 protein, total tau, p-tau(181), abeta1-42**
  - **Neuropsychology: free recall, recognition, naming, word fluency (CERAD)**
  - **ApoE genotype**

Ewers et al. (*accepted*)

CSF core feasible biomarker candidates altered in presymptomatic and preclinical AD

- Same CSF marker phenotype as established in advanced clinical AD:
- decreased abeta42 predicts **cognitive decline** among older women without MCI & dementia, Prospective Population Study; (*Gustafson et al. (2007) J Neurol Neurosurg Psychiatry)*
- aβ42 & P-Tau combination predicted later **subjective cognitive impairment** & decline in quality of life in healthy elderly subjects; (*Stomrud et al. (2007) Dement Geriatr Cogn Disord)*
- tau/abeta42 ratio predicts later **cognitive decline** in non-demented adults in a community setting *(Fagan et al. (2007) Arch Neurol)*
- tau/abeta42 ratio predicts later **cognitive decline** in normal controls at risk for MCI (*Li et al. (2007) Neurology)*

Current stages of multimodal development of (bio- and imaging) markers in AD (after basic studies)

Stage I

- **Methodological study**
- **Establishing technical characteristics**

- blood markers
- proteome analysis
- abeta oligomers
- APP isoforms
- total abeta
- ....

Stage II

- **Selected patients**
- **Determining sensitivity and specificity**
- **Determining norm values**

- BACE 1
- abeta 42/40-ratio
- abeta-Ab
- ...

Stage III

- **Controlled dx trials (multicenter initiatives)**
- **Intent to diagnose population**
- **Determining prevalence and positive/negative predictive values**
- **Validate norm values**
- **Determination of added value of diagnostic methods (multimodal marker set)**

- t-tau
- phospho-tau 181, 231
- $abeta_{1-42}$

Conclusion: current biochemical marker research is a dynamic field

- core feasible candidates are currently beeing validated in prospective, well controlled clinical studies
- using multi-institutional teamwork through large collaborative groups (ADNI trials)
- already established intra-individual stability (longitudinal CV), characteristics of the immunoassays (within-day and between-day CV)
- current validation of within-lab repeatability and between-lab reproducibility and of multicenter diagnostic and predictive performance (sensitivity, specificity, PPV, NPV)
- multi-center validation time frame ends within next 2-5 years

CSF biomarkers as endpoints in clinical trials on anti-Aβ compounds

Safety monitoring

• CSF poly- / mononuclear cells	General indicators of CNS inflammation
• Albumin ratio	Blood-brain barrier function / damage
• IgG index	Intrathecal IgG production
IgG oligoclonal bands	
• IgM index	Intrathecal IgM production
IgM oligoclonal bands	
• T-tau	Neuronal / axonal damage?
Neurofilament protein	Damage to white-matter axons?
Glial fibrillary acidic protein	Damage to glial cells / gliosis?

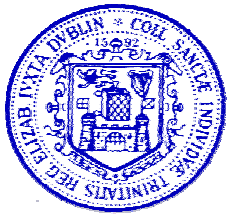
CSF biomarkers

• Aβ42	Primary efficacy measure
• Aβ40	Primary efficacy measure
• other Aβ isoforms	Optional efficacy measures
• sAPPα	Effect on non-amyloidogenic APP processing
• BACE1 act., sAPPβ	Effect on amyloidogenic APP processing
• Total tau	Downstream biomarker for effect on neurodegeneration
• Phospho-tau	Downstream biomarker for effect on tau phosphorylation

Open regulatory issues discussion: *role of biochemical markers*

- as the development of such biochemical markers has been improved considerably there is still the question of how they should be used in clinical trials:

- **for early characterisation, detection & prediction**
- **enrichment & stratification of trial populations**
- **endpoints** in **proof of concept studies** or confirmatory **clinical trials**



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