Strategies to develop trial-relevant biomarkers in AD

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Disclosures

Commercial partners:

- Quanterix, ADx Neurosciences, Roche AG, Health-Holland.

Contract research partners:

- Eisai, FujiFilm-Toyama, Vivoryon, Brainstorm-Cell, Roche, AC Immune.

Grant funding:

- European Union Marie Sklodowska Curie program, EU-JPND, ZonMW, Alzheimer Association, Alzheimer Nederland, Health~Holland Top Sector Life Sciences & Health, Weston Brain Institute.

Prof Teunissen receives no personal compensation from any of the above or others except the Amsterdam UMC.

Contents

- Proteomics to identify clusters for stratification in AD trials
- Strategies to accelerate biomarker development

The need for biomarkers

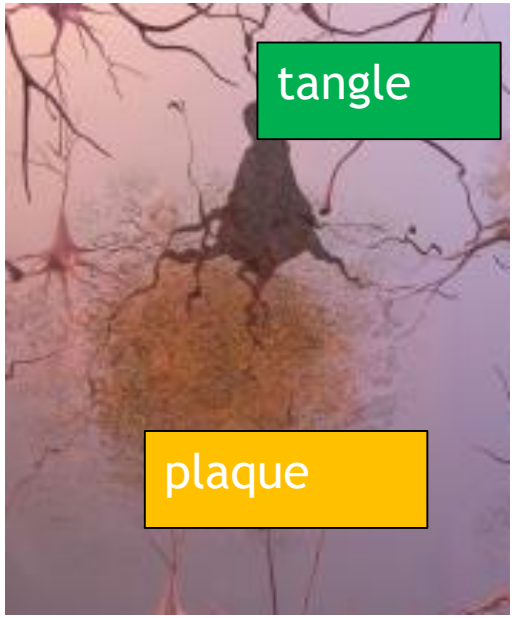
The need for biomarkers

The need for biomarkers

1. Early diagnosis
2. Prognosis
3. monitoring

20 years

The Alzheimer Biomarkers



(p)Tau

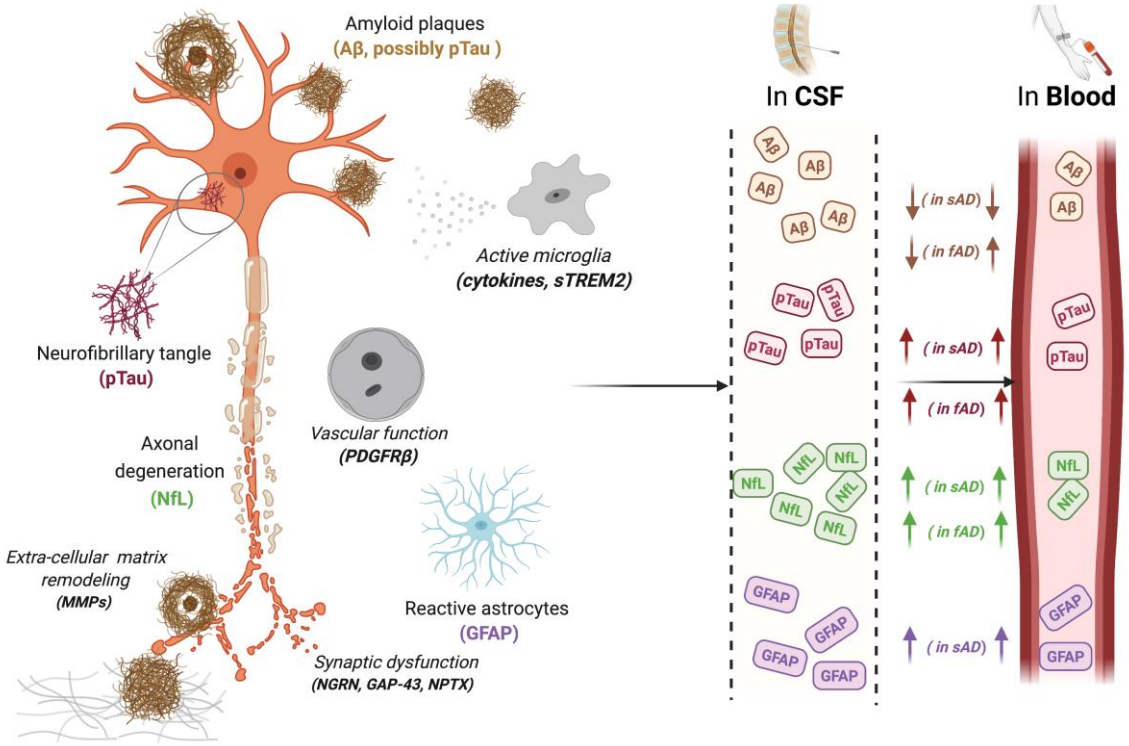
Amyloid beta

PET

Need for novel biomarkers in AD?

- capture the full complexity of mechanisms involved

- stratification

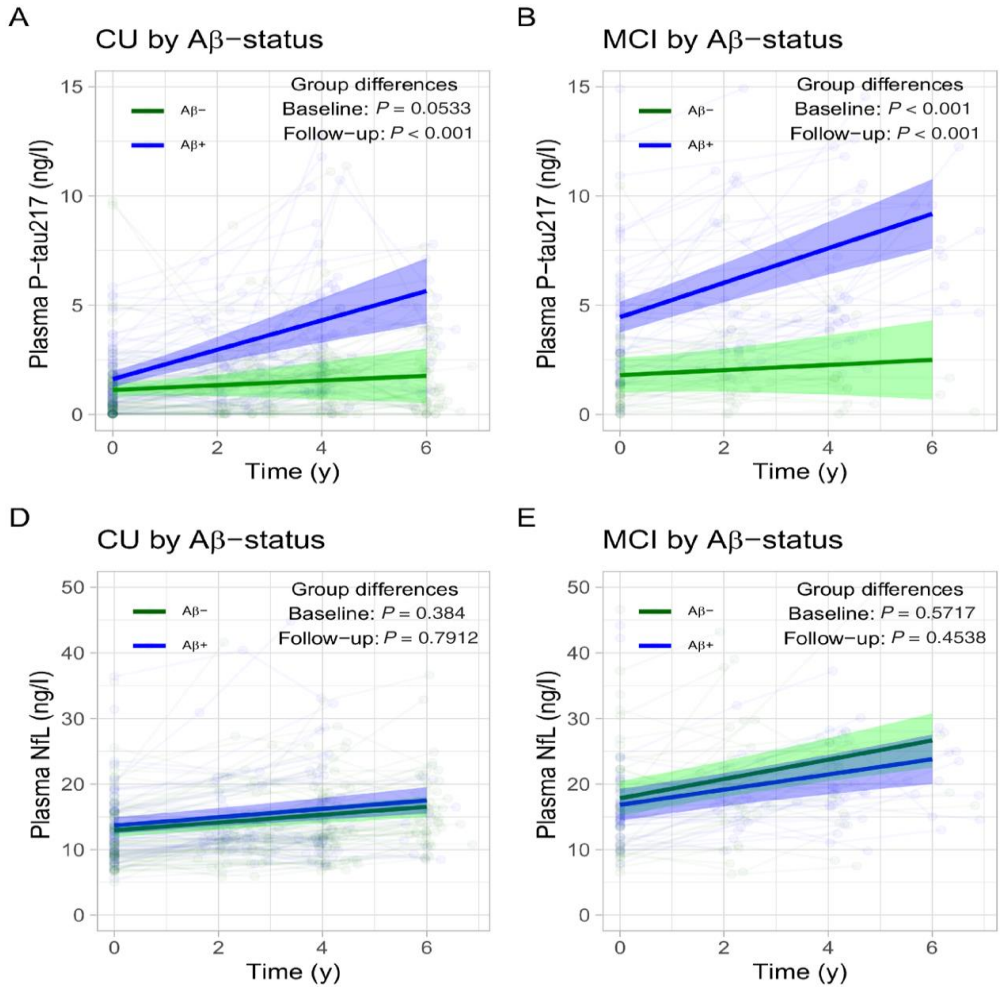


Teunissen et al., Lancet Neurology, in press

Inclusion and effect monitoring by plasma p-tau217 (Lilly) and NfL across the AD stages

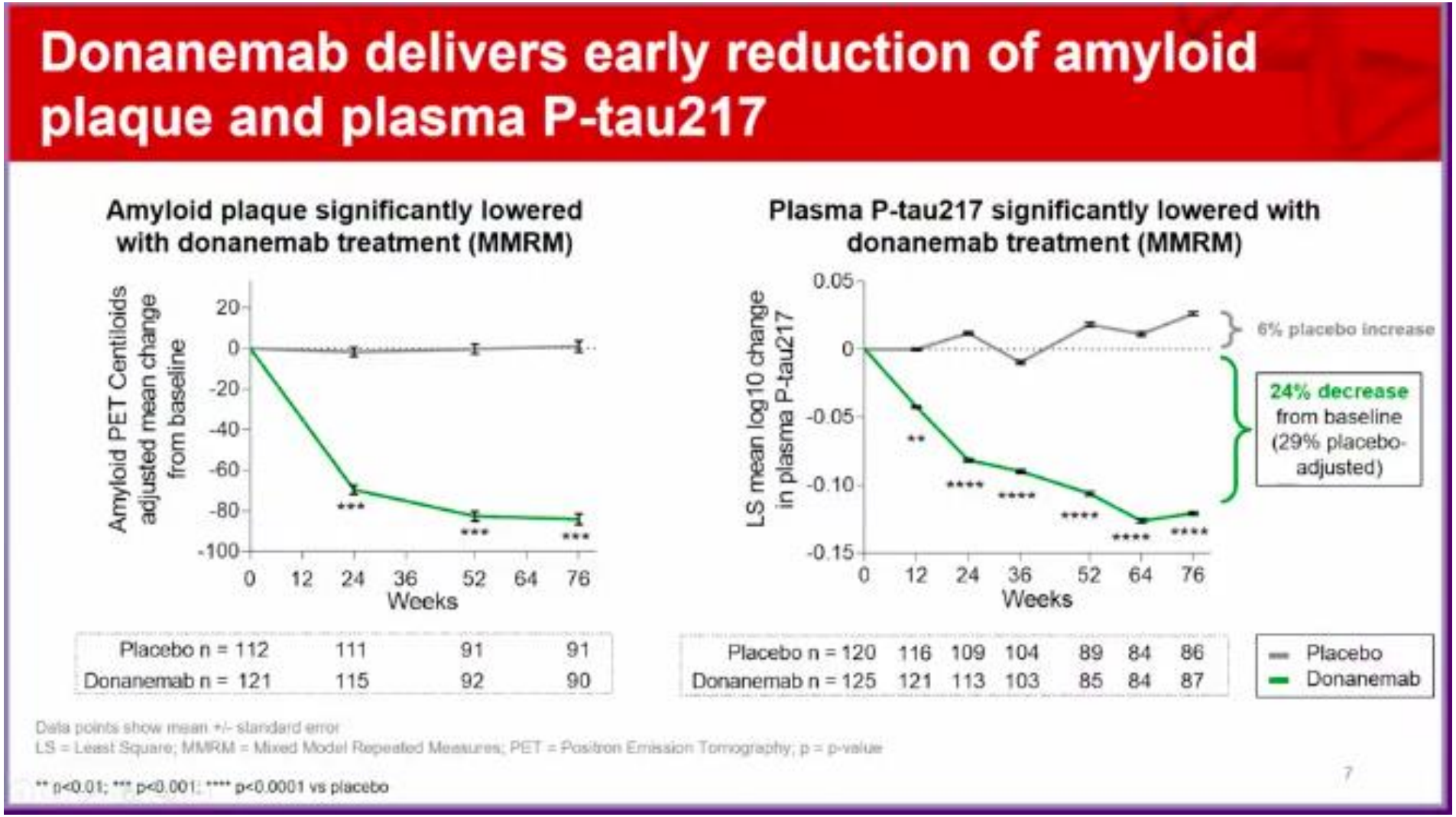
Detect reduction in pTau slope

N=109 per arm to for CU
N=71 per arm for MCI



Mattsson-Carlgren et al, 2020 Brain

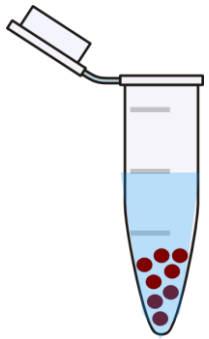
Outcome measure

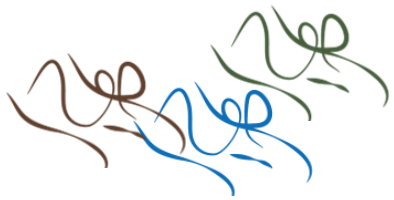


Mintun, AAIC 2021 oral presentation

CSF proteomic subtypes in AD -> stratification

556 of 708 proteins measured with TMT by Gobom, Zetterberg & Blennnow





proteins

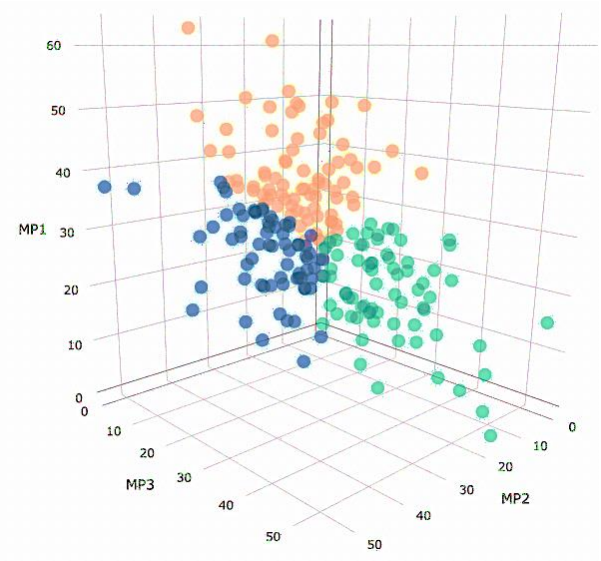
Non-negative matrix factorisation

subjects

228 AD individuals across clinical spectrum from the EMIF-AD MBD study (*Bos et al., 2018 Alz Res & Ther*)

Proteins

Individuals



Tijms et al., *Brain 2020*

CSF proteomic subtypes in AD

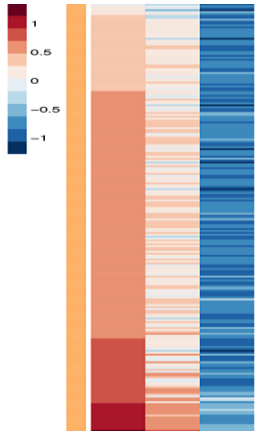
556 Proteins

- Every row = 1 protein
- Each column = subtype
- Colour indicates Z score average within subtype
- Scaled to control group (normal cognition and normal abeta & tau CSF levels)

Tijms et al., *Brain 2020*

CSF proteomic subtypes in AD

556 Proteins



Subtype 1
Increased proteins associated with neuronal plasticity related processes

Increased in subtype 1

Decreased in subtype 3

Tijms et al., *Brain 2020*

CSF proteomic subtypes in AD

556 Proteins

Subtype 1
Increased proteins associated with neuronal plasticity related processes

Subtype 2
Increased proteins associated with innate immune system (e.g., complement activation)

Increased in subtype 2

Tijms et al., *Brain 2020*

CSF proteomic subtypes in AD

556 Proteins

Subtype 1
Increased proteins associated with neuronal plasticity related processes

Subtype 2
Increased proteins associated with innate immune system (e.g., complement activation)

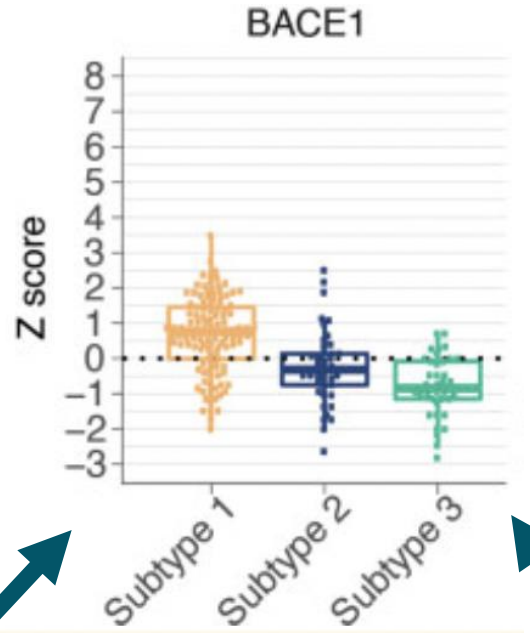
Increased in subtype 3

Subtype 3
Blood brain barrier?
Albumin;
Immunoglobulin G

Tijms et al., *Brain 2020*

Implications for trials – target-stratification

BACE1 activation



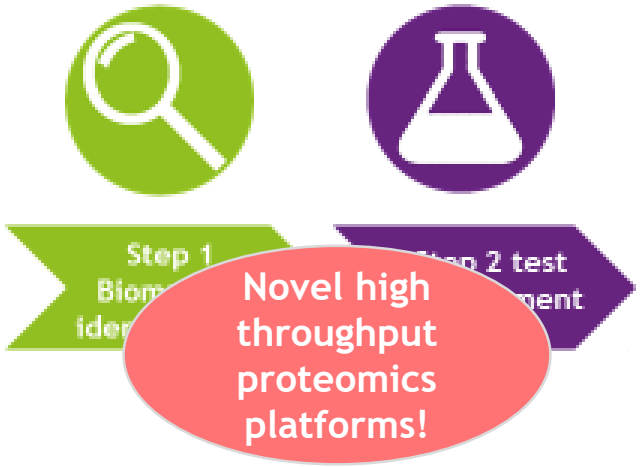
Inhibitors may work for subtype 1 only?

Inhibition not a good idea for subtypes 2&3?

Tijms et al., *Brain 2020*

Challenges for implementation of novel biomarkers

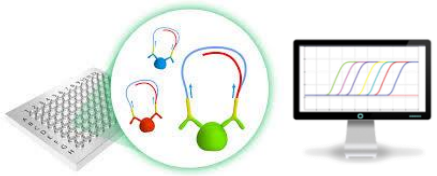
Biomarker identification by novel screening methods



Smooth translation discovery findings

Discovery		Validation
Mass spectrometry	→	Immunoassay
Immunoassay	→	Immunoassay

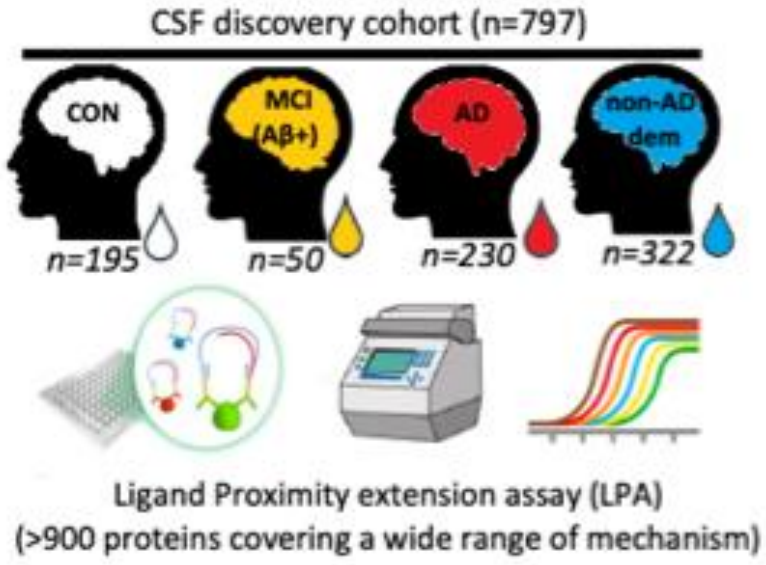
Proximity Ligand Assay (antibody/qPCR):



>900 proteins covering a wide diversity of mechanisms

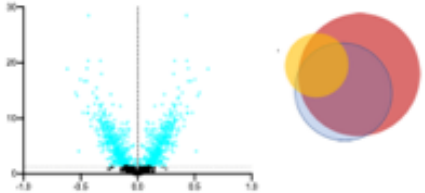
Olink

Goal: understand the CSF proteome changes in AD
-> mechanisms + clinical panels



PART 1

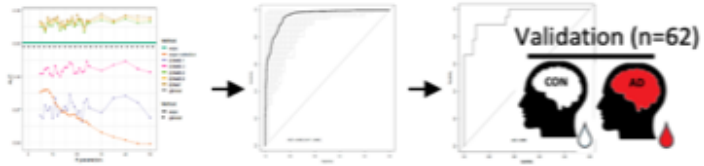
Differential protein abundance



→ Mechanisms

PART 2

Translatable classification models

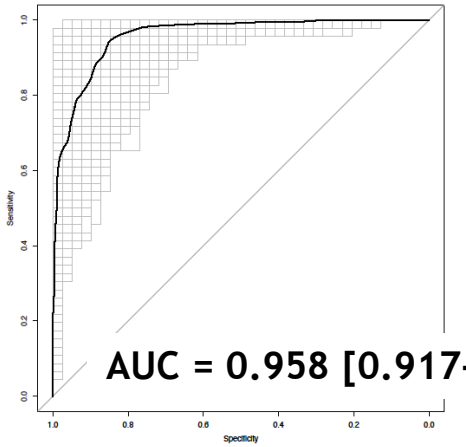


→ Panels

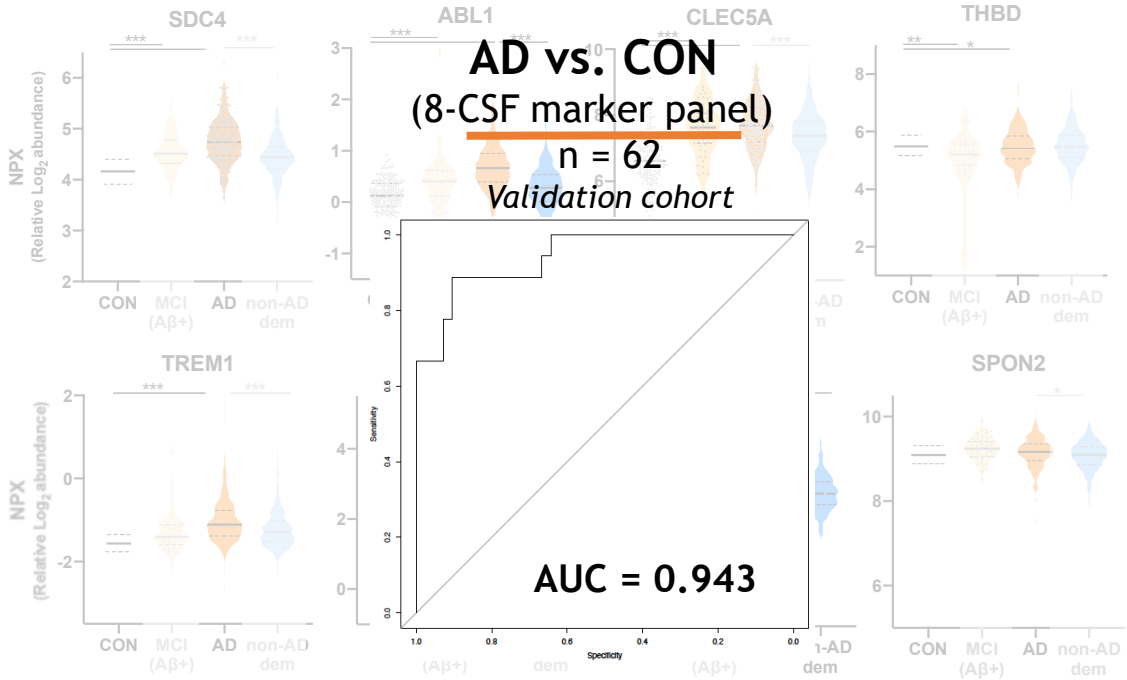
Can we identify translatable CSF panels (max. 21 markers)?

AD vs. CON
(8-CSF marker panel)

n = 425



AUC = 0.958 [0.917-0.988]



	CSF biomarker panels			
	MCI(Aβ+) vs. CON		CON vs. AD	
Differentiated groups	*AUC*	*95% CI*	*AUC*	*95% CI*
MCI(Aβ+) vs CON	0.991	0.969-1	0.869	0.744-0.972
AD vs CON	0.867	0.797-0.93	**0.958**	**0.917-0.988**
AD vs non-AD dem.	0.736	0.65-0.816	0.798	0.719-0.870

Del Campo et al, under review

Succesful Ella assays

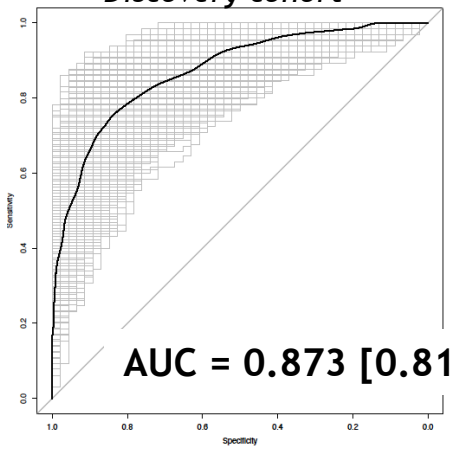
Can we identify translatable CSF panels (max. 21 markers)?

AD vs. non-AD dementias

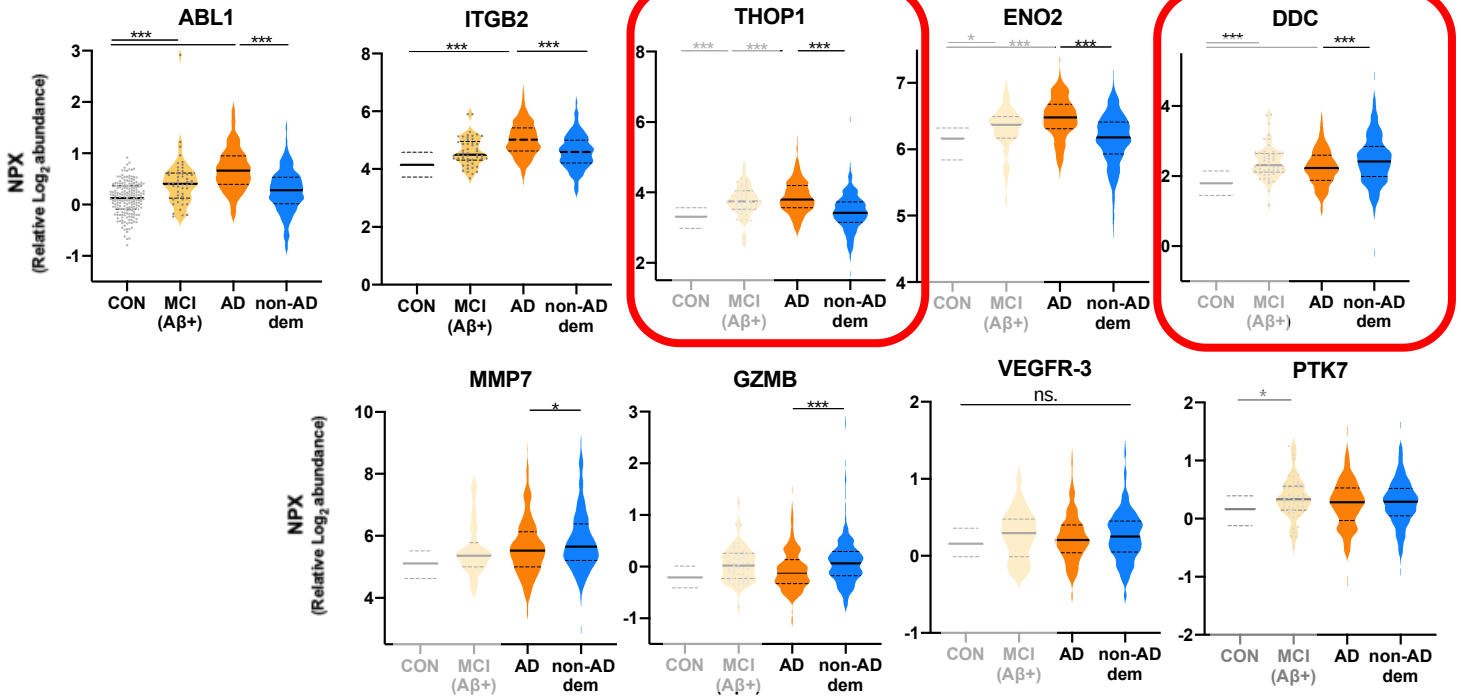
(9-CSF marker panel)

n = 552

Discovery cohort



AUC = 0.873 [0.812-0.927]



CSF biomarker panels

	MCI(Aβ+) vs. CON		CON vs. AD		AD vs. non-AD dem	
Differentiated groups	*AUC*	*95% CI*	*AUC*	*95% CI*	*AUC*	*95% CI*
MCI(Aβ+) vs CON	0.991	0.969-1	0.869	0.744-0.972	0.800	0.667-0.921
AD vs CON	0.867	0.797-0.93	0.958	0.917-0.988	0.866	0.795-0.928
AD vs non-AD dem.	0.736	0.65-0.816	0.798	0.719-0.870	**0.873**	**0.812-0.927**

Del Campo et al, under review

Summary

- Different subtypes/biological profiles within the AD population can be identified using CSF proteomics strategies

- Novel proteomics strategies (Olink, mass spect improvements) and multiplexing ultrasensitive technologies enable acceleration of fluid biomarker development for neurological diseases

You never work alone…….

NL, Dept of Clinical Chemistry

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Betty Tijms
Philip Scheltens