THE bPRIDE PROJECT

blood Proteins for early Discrimination of dEmentias

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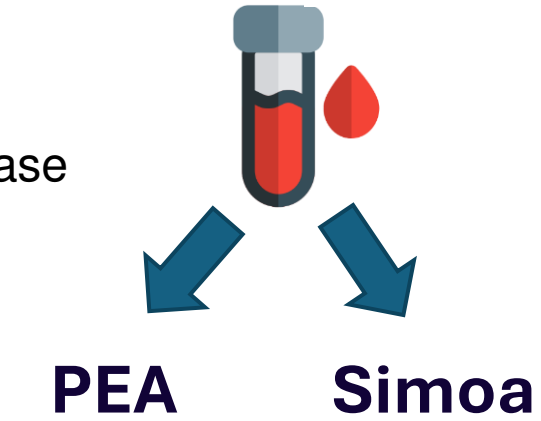
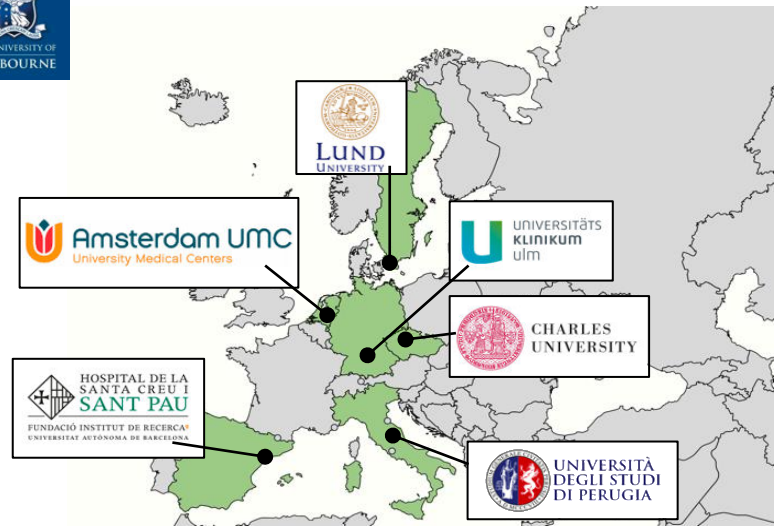
Aims:

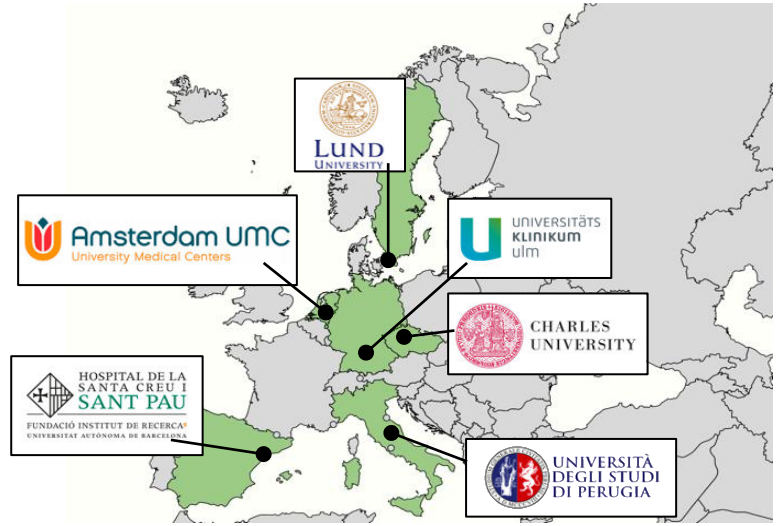
- ❑ Generate and validate blood tests for early, specific diagnosis of AD, LBD, and FTD.
- ❑ Use novel technologies to analyze >1000 blood proteins across >1000 patients at different disease stages.



PEA **Simoa**



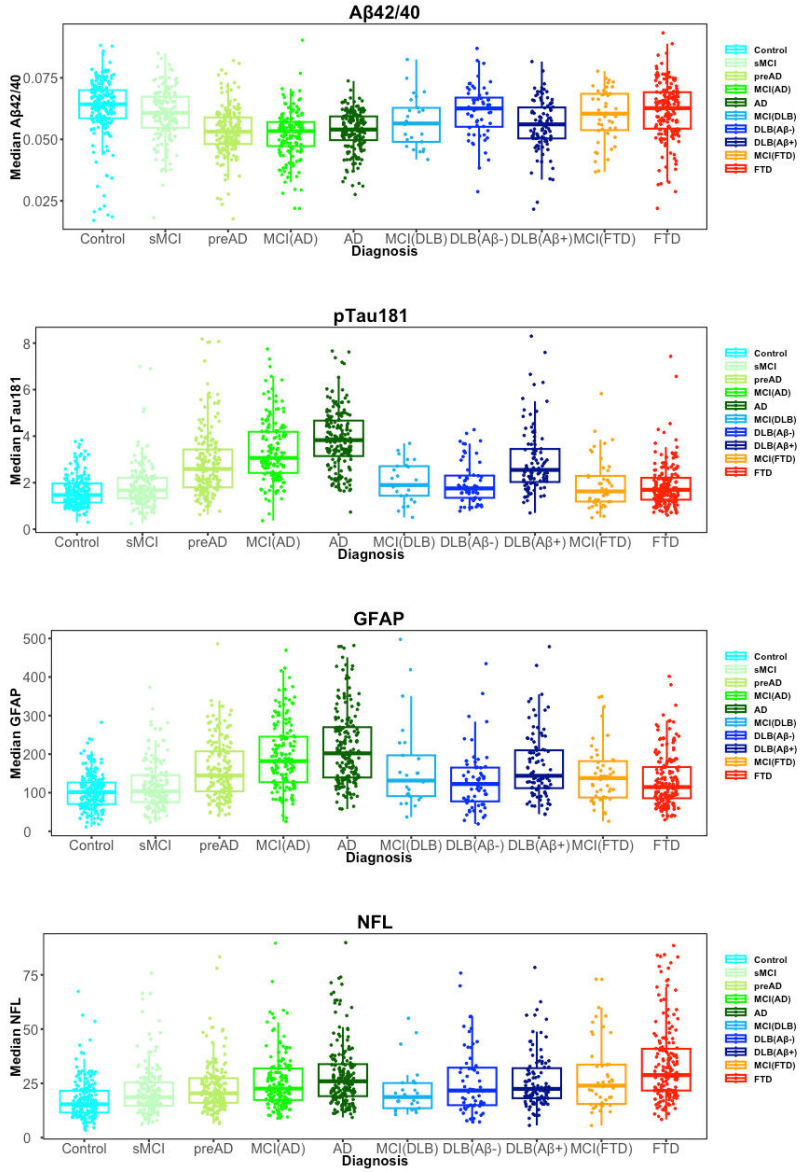
bPRIDE multicentre cohort



Group	subgroup	N	Age (y)	% Males	Edu (y)	MMSE	Aβ pos. (%)
CTRL	SCD	362	70±8	37%	12±6	29±2	0%
	sMCI	154	69±13	50%	11±6	27±3	0%
AD	preAD	183	72±9	33%	12±6	29±2	100%
	MCI-AD	157	72±8	43%	11±6	26±3	100%
	AD-dem	175	72±10	38%	10±8	21±6	100%
LBD	MCI-DLB	25	72±9	60%	7±2	26,5±3	47%
	DLB	167	72±8	70%	6±3	23±6	49%
FTD	MCI-FTD	45	68±8	64%	9±5	26±3	15%
	FTD-dem	163	68±13	57%	11±7	24±8	5%

SIMOA-based biomarkers of AD

Diagnostic performance of plasma Aβ42/40 ratio, pTau181, GFAP, and NFL along the continuum of Alzheimer's disease and non-AD dementias



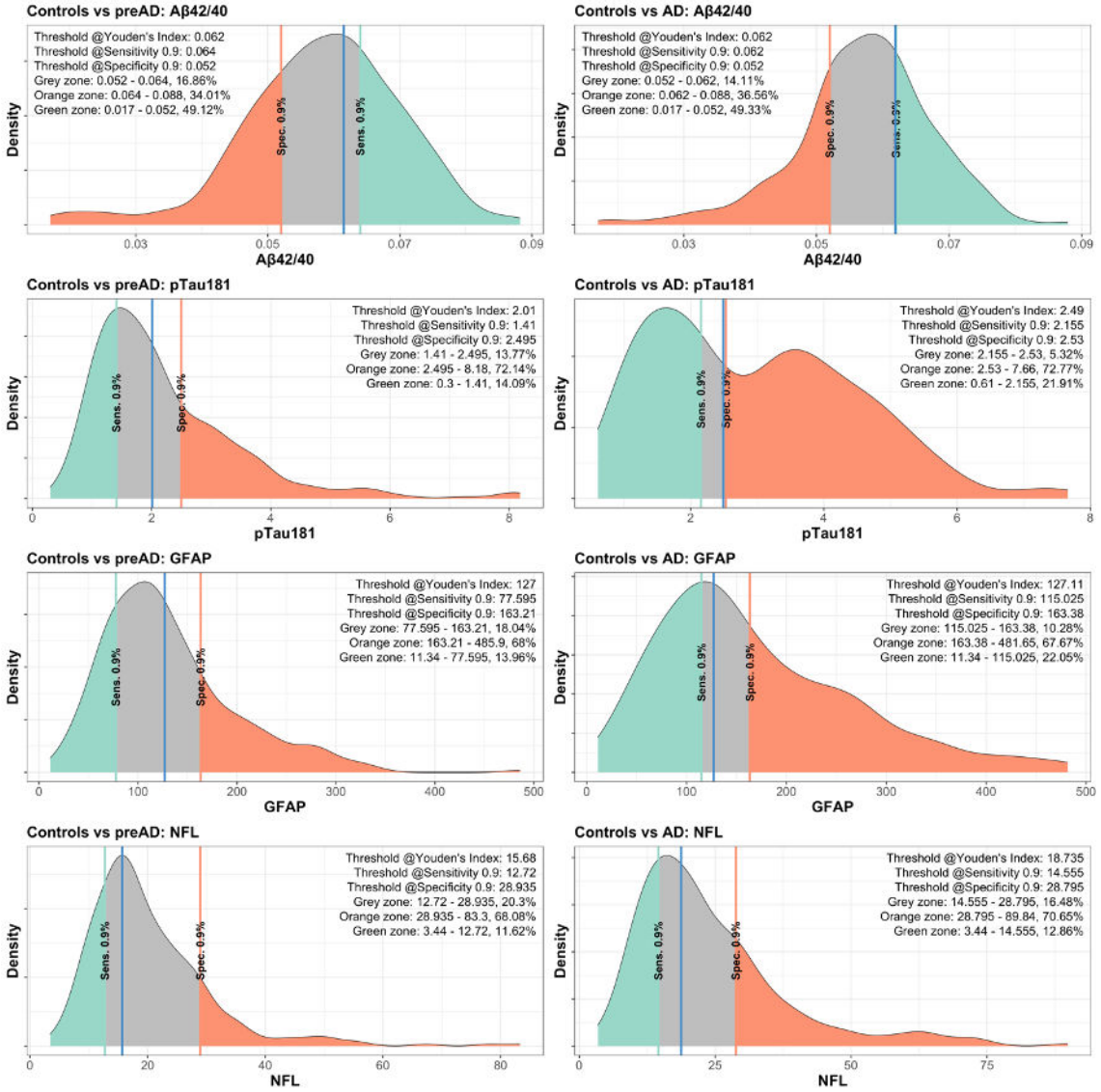
Group	Biomarker	AUC (95%CI)
Controls vs preAD		
	Aβ42/40	0.81 (0.76 - 0.86)
	GFAP	0.78 (0.72 - 0.84)
	NFL	0.66 (0.58 - 0.74)
	pTau181	0.82 (0.73 - 0.91)
	pTau181/Aβ42	0.84 (0.76 - 0.92)
Controls vs MCI (AD)		
	Aβ42/40	0.83 (0.78 - 0.88)
	GFAP	0.86 (0.80 - 0.92)
	NFL	0.76 (0.71 - 0.81)
	pTau181	0.90 (0.87 - 0.93)
	pTau181/Aβ42	0.92 (0.88 - 0.96)
MCI(AD) vs AD		
	Aβ42/40	0.60 (0.53 - 0.67)
	GFAP	0.52 (0.48 - 0.56)
	NFL	0.54 (0.47 - 0.61)
	pTau181	0.61 (0.56 - 0.66)
	pTau181/Aβ42	0.59 (0.53 - 0.65)
Controls vs AD		
	Aβ42/40	0.83 (0.77 - 0.89)
	GFAP	0.91 (0.89 - 0.93)
	NFL	0.81 (0.77 - 0.85)
	pTau181	0.94 (0.92 - 0.96)
	pTau181/Aβ42	0.96 (0.93 - 0.99)
AD vs other dementia		
	Aβ42/40	0.71 (0.69 to 0.73)
	GFAP	0.71 (0.68 to 0.74)
	NFL	0.61 (0.56 to 0.66)
	pTau181	0.87 (0.84 to 0.90)
	pTau181/Aβ42	0.90 (0.87 to 0.93)

Cross validated AUC (95%CI)

0 0.25 0.5 0.75 1

Lower Higher

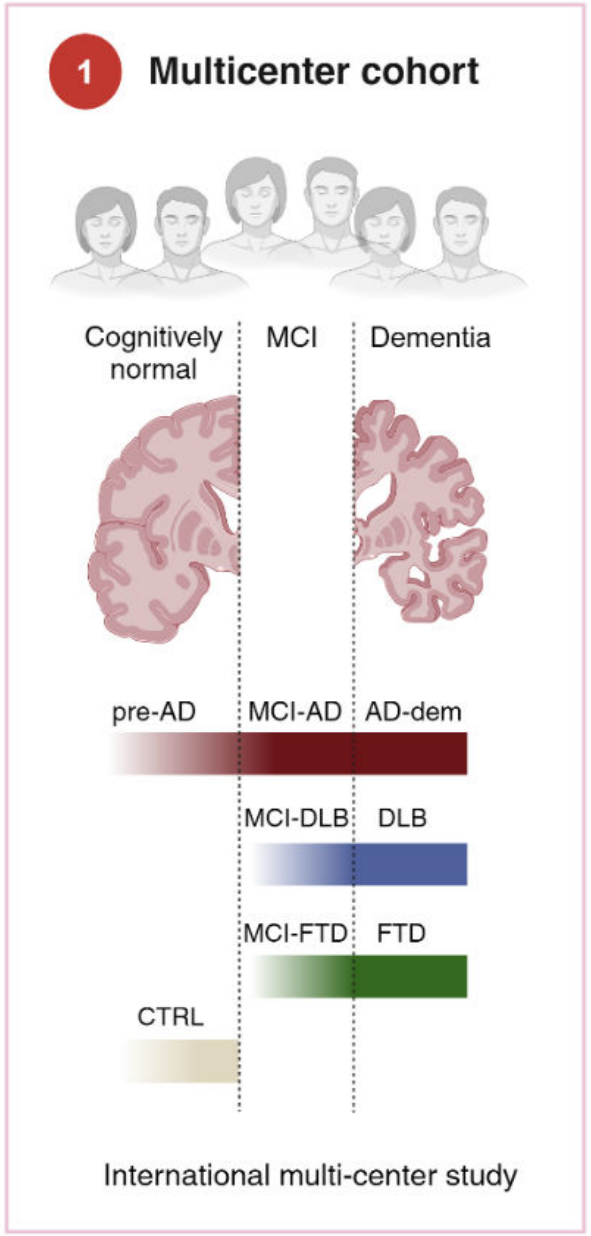
James D. Doecke et al. manuscript in revision *Alz & Dem*

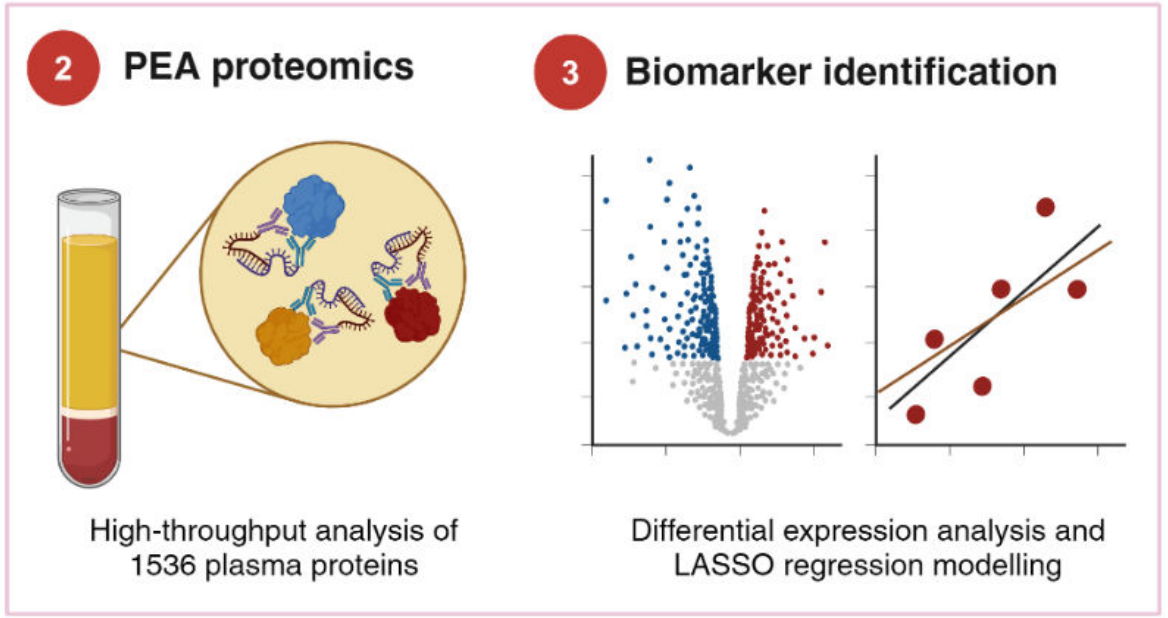


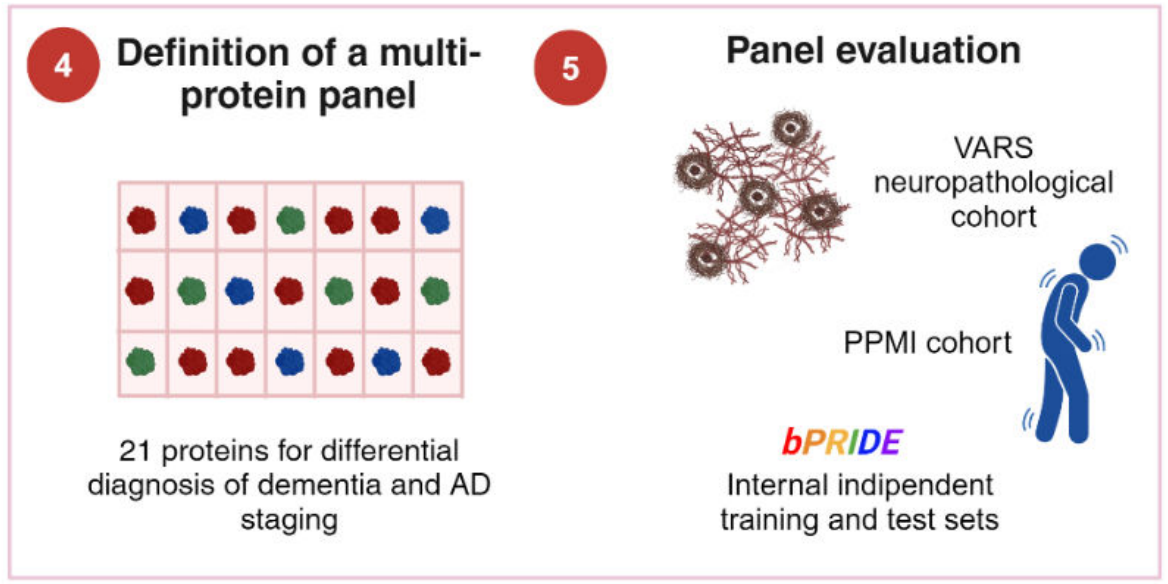
External validation

		AUC (95%CI)		
Group	Biomarker	UNIPG*[ι]	ALFA+[ι]	BIODEGMAR[ι]
Controls vs preAD	Aβ42/40	0.83 (0.69 - 0.97)	0.6 (0.55 - 0.64)	0.65 (0.59 - 0.71)
	pTau181	0.6 (0.41 - 0.78)	0.64 (0.59 - 0.69)	0.71 (0.64 - 0.78)
	GFAP	0.73 (0.57 - 0.9)	0.64 (0.59 - 0.69)	0.74 (0.67 - 0.81)
	NFL	0.67 (0.49 - 0.84)	0.57 (0.53 - 0.62)	0.57 (0.52 - 0.62)
Controls vs MCI(AD)	Aβ42/40	0.61 (0.46 - 0.75)		0.73 (0.66 - 0.8)
	pTau181	0.79 (0.66 - 0.93)		0.74 (0.66 - 0.81)
	GFAP	0.77 (0.63 - 0.91)		0.75 (0.68 - 0.82)
	NFL	0.68 (0.53 - 0.83)		0.58 (0.52 - 0.64)
Controls vs AD	Aβ42/40	0.76 (0.6 - 0.92)		0.65 (0.59 - 0.71)
	pTau181	0.86 (0.72 - 0.99)		0.72 (0.64 - 0.79)
	GFAP	0.86 (0.73 - 0.98)		0.74 (0.67 - 0.81)
	NFL	0.82 (0.68 - 0.96)		0.58 (0.52 - 0.64)

- ❑ pTau181 best marker for AD continuum vs controls and FTD but not for AD/DLB due to AD co-pathology in DLB.
- ❑ Combinations with Ab42/40 and GFAP improve performance
- ❑ Need of centre-specific thresholds



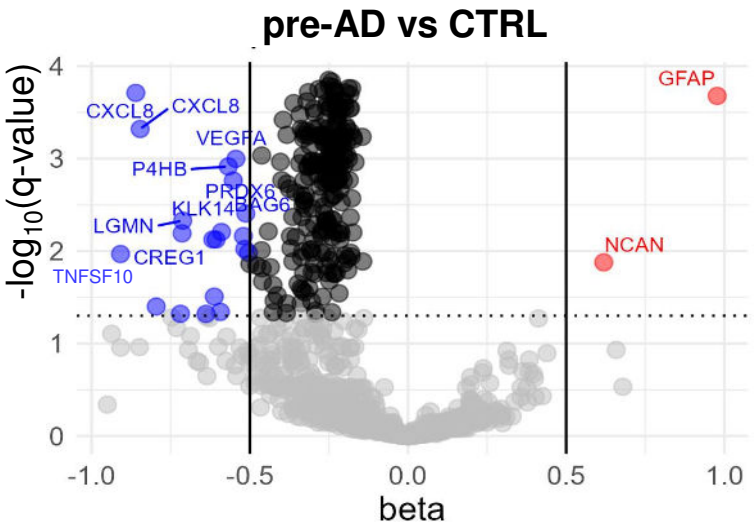


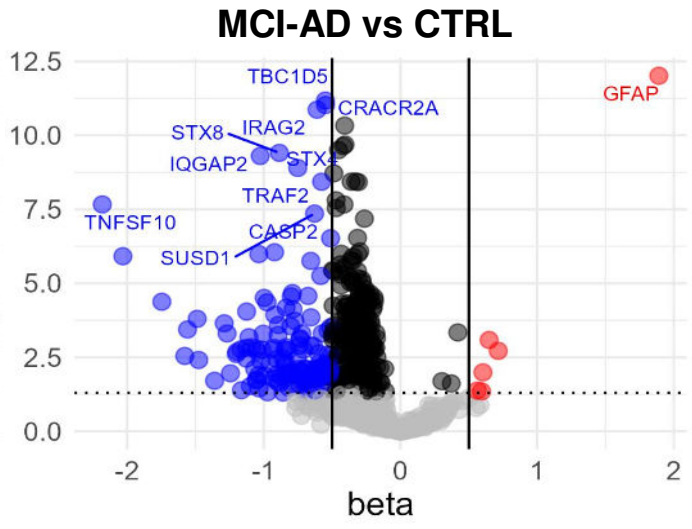


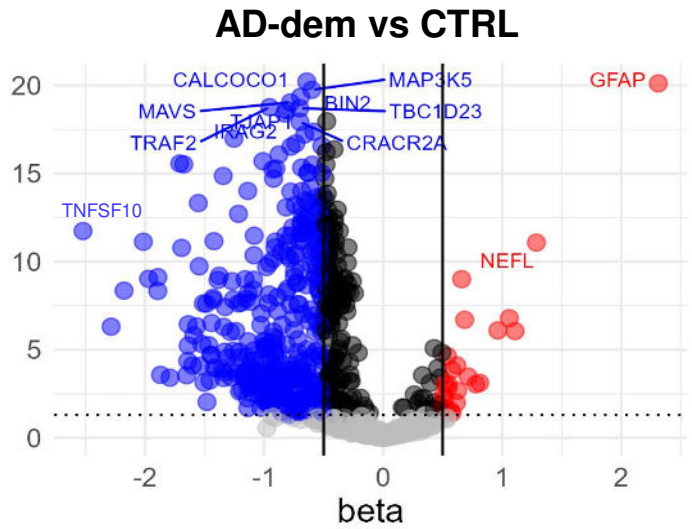
Looking for biomarkers for the differential diagnosis and molecular staging of neurodegenerative diseases leading to dementia by proximity-extension assay proteomics

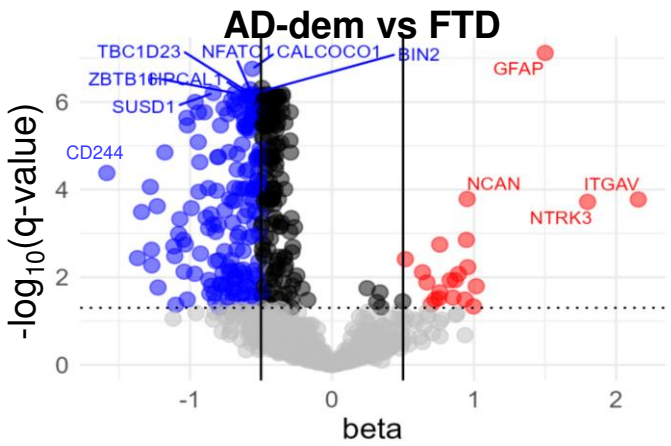
(Manuscript in preparation)

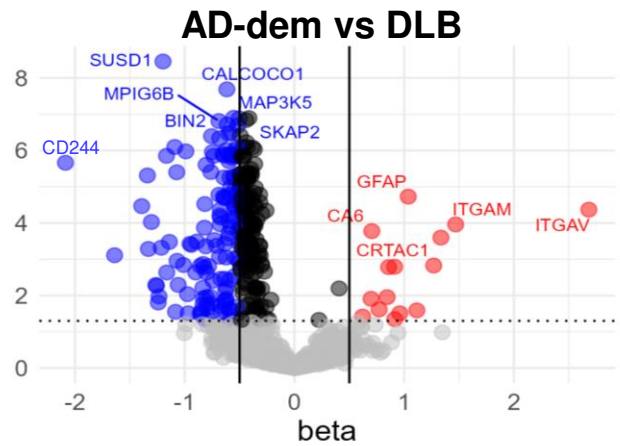
Most specific biomarkers for AD

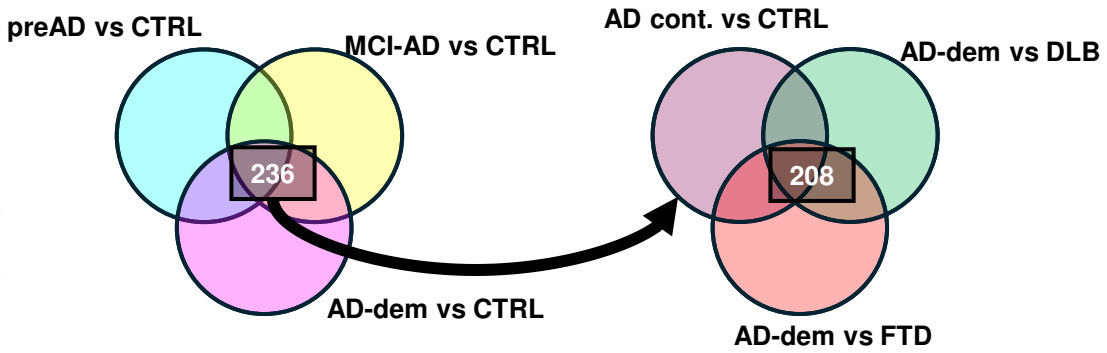






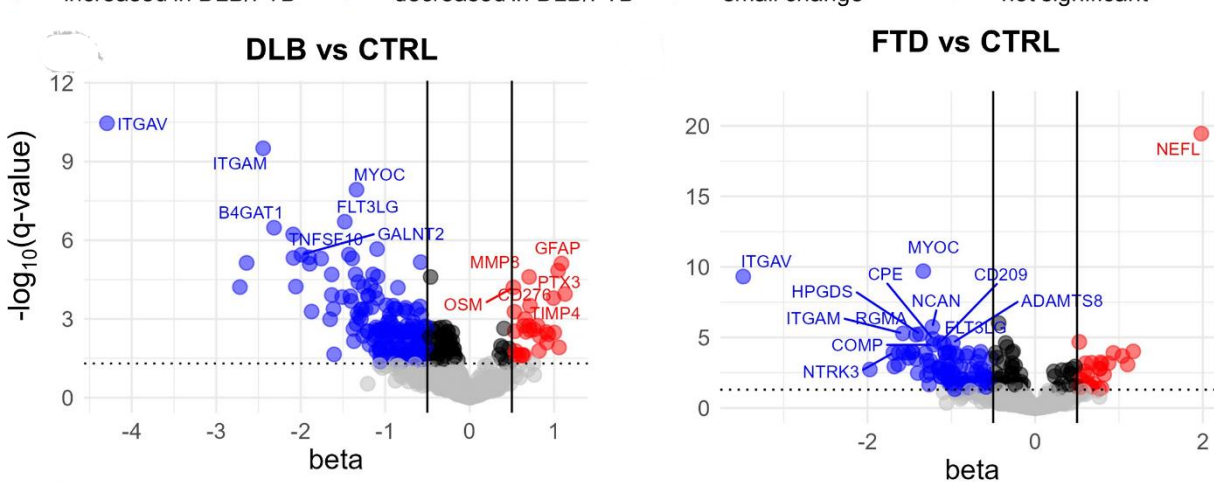


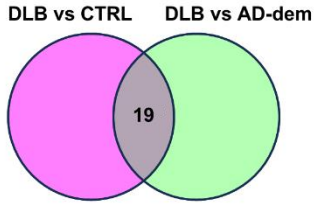


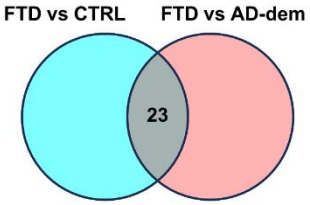


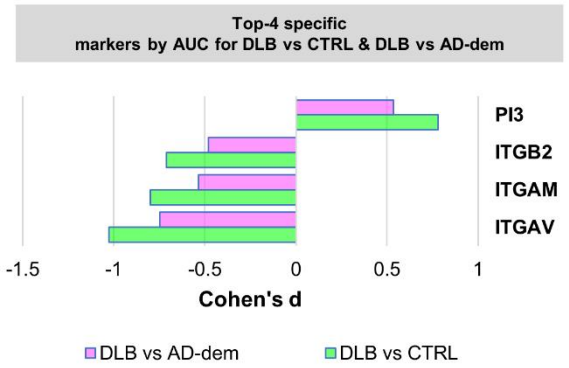
protein	↑/↓ in AD	preAD vs CTRL	MCI-AD vs CTRL	AD-dem vs CTRL	AD-dem vs FTD	AD-dem vs DLB
GFAP	↑	0.68	0.78	0.83	0.76	0.70
CALCOCO1	↓	0.62	0.70	0.80	0.71	0.74
MAP3K5	↓	0.60	0.71	0.79	0.68	0.74
BIN2	↓	0.61	0.70	0.79	0.68	0.72

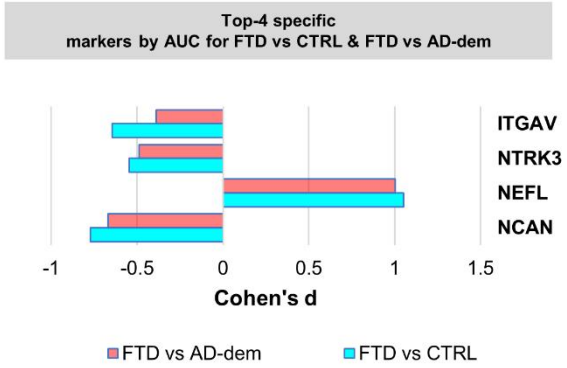
Most specific biomarkers for DLB and FTD

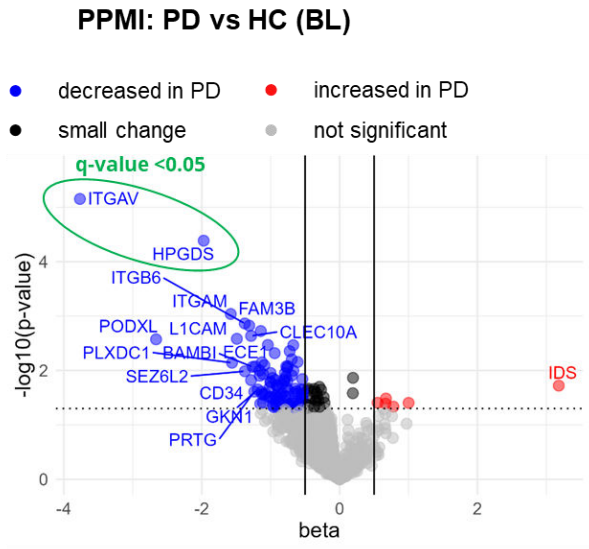


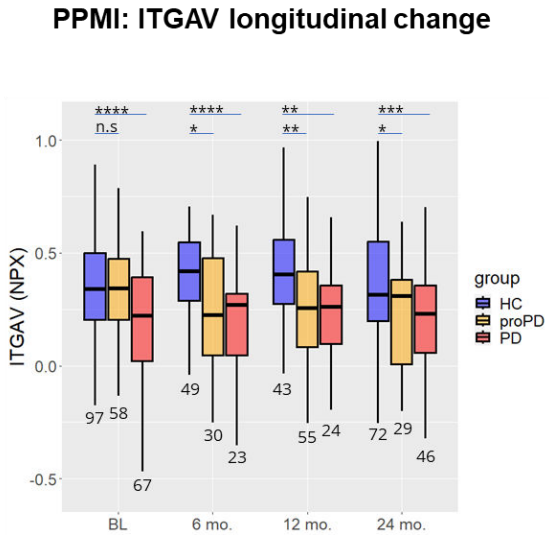


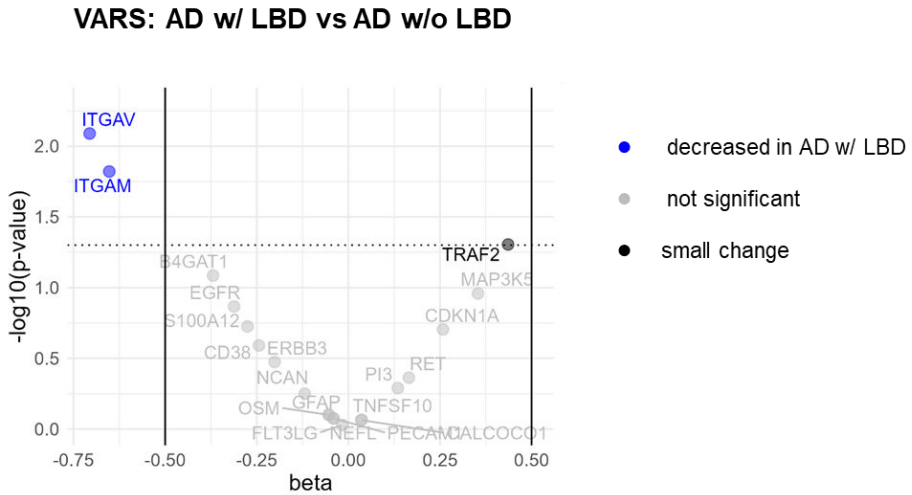






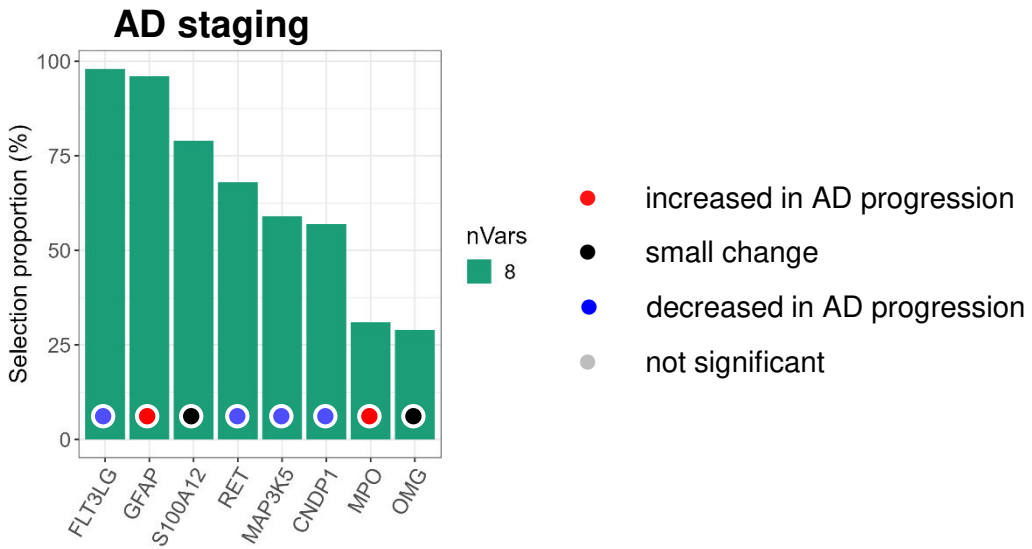






Variable selection

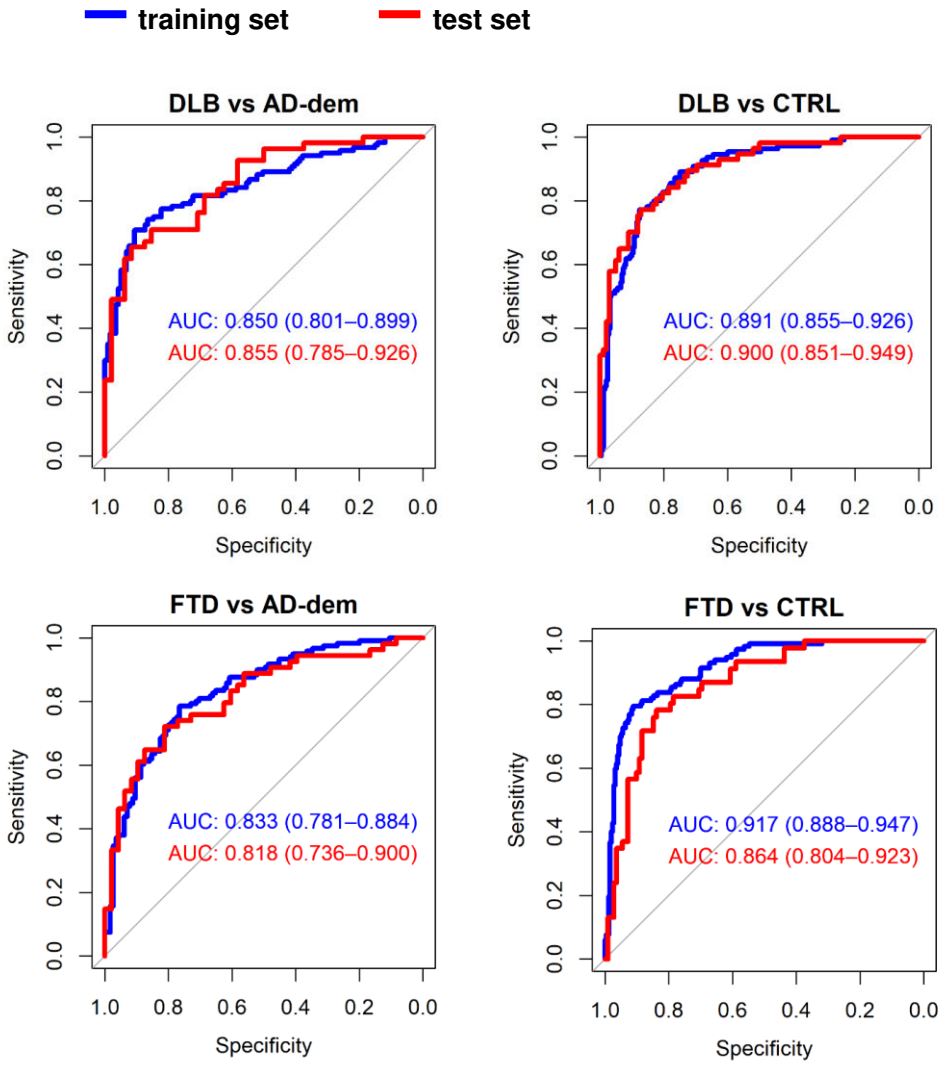
Database splitting 70/30% (training/test)
100-fold CV LASSO regression
in training set
selection of top-5 proteins by selection proportion
in 5-variable models + proteins highlighted in univ.
analysis and 2 proteins for MCI-FTD vs CTRL

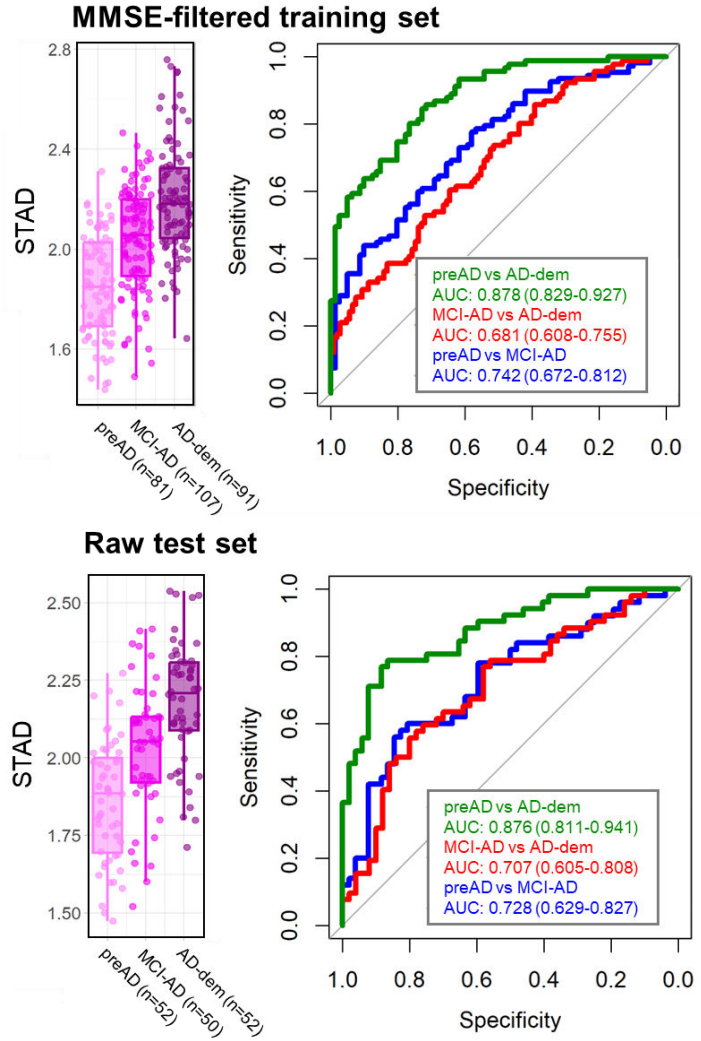


Top proteins by selection proportion

Assay name	Uniprot	OID	Olink Explore panel	Standard plasma dilution in Explore
1	PI3	P19957	OID20326	Cardiometabolic
2	FLT3LG	P49771	OID20661	Inflammation
3	OSM	P13725	OID20574	Inflammation
4	NEFL	P07196	OID20871	Neurology
5	B4GAT1	O43505	OID21127	Neurology
6	ITGAM	P11215	OID21071	Neurology
7	CD38	P28907	OID21316	Oncology
8	ITGAV	P06756	OID21416	Oncology
9	GFAP	P14136	OID21247	Oncology
10	MAP3K5	Q99683	OID21253	Oncology
11	CALCOCO1	Q9P1Z2	OID21387	Oncology
12	ERBB3	P21860	OID20705	Inflammation
13	NCAN	O14594	OID21055	Neurology
14	PECAM1	P16284	OID21131	Neurology
15	TNFSF10	P50591	OID20611	Inflammation
16	RET	P07949	OID21346	Oncology
17	NTRK3	Q16288	OID21057	Neurology
18	EGFR	P00533	OID20319	Cardiometabolic
19	TRAF2	Q12933	OID20507	Inflammation
20	CDKN1A	P38936	OID21319	Oncology
21	S100A12	P80511	OID21374	Oncology

bPRIDE models





Summary PEA data

1. Among more than 1400 markers analysed by Olink, GFAP exhibit the best performance in differentiating AD from CTRL.
2. Although PEA markers do not outperform Simoa ones for AD vs CTRL, they may allow differential diagnosis vs DLB and FTD
3. We made a robust selection of 21 markers to be included in a custom panel for AD differential diagnosis, DLB and FTD identification, and AD staging
4. DLB-associated markers show associations to neuropathology and work also for PD
5. The models derived from the panel perform well in internal training and test sets

Thank you!

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