

Novel Plasma Biomarkers Associated with Amyloid PET Positivity and Tau PET Staging across the Alzheimer’s Disease Continuum



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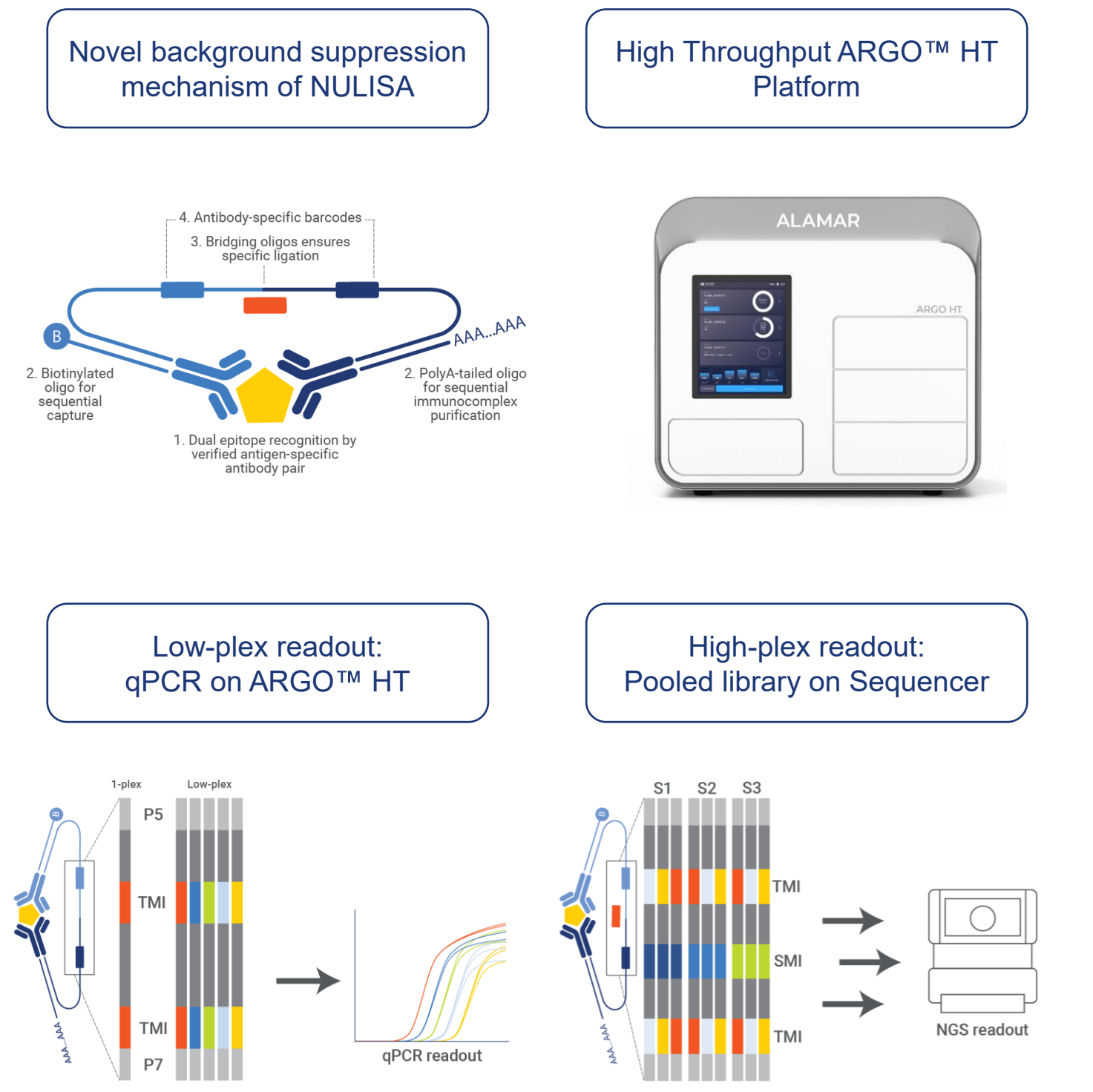
Study Objective and Cohort

Background: Blood-based biomarkers (BBMs) are transforming Alzheimer’s disease (AD) diagnosis and staging. While pTau-217 emerging as the lead BBM for identifying AD pathology, additional biomarkers are needed to fully implement diagnostic and staging frameworks. Here, we employed ultrasensitive NULISA (Nucleic acid-Linked Immuno-Sandwich Assay)¹ technology to analyze a well-characterized Korean cohort to identify novel proteins along the AD progression continuum.

Methods: We developed the NULISaseq Neuro 220 Panel for the detection of >220 biomarkers associated with neuroinflammation, synaptic pathology, and vascular dysfunction including brain-derived (BD) pTaus and eMTBR Tau. We analyzed 300 plasma samples (mean age = 75.42, 71.33% females) from cognitively unimpaired individuals (CU, n=93), mild cognitive impairment (MCI, n=163) and dementia cases (n=44) and used linear regression models to identify differentially expressed (DE) proteins and those associated with amyloid positron emission tomography (PET) positivity (centiloid > 20) and ATN PET staging.

		CU (N=93)	MCI (N=163)	Dementia (N=44)	Overall (N=300)
Age	Mean (SD)	73.5 (7.47)	76.4 (7.63)	75.7 (9.25)	75.4 (7.92)
	Median [Min, Max]	75.0 [50.0, 86.0]	78.0 [57.0, 90.0]	76.5 [55.0, 93.0]	77.0 [50.0, 93.0]
Gender	Female	73 (78.5%)	108 (66.3%)	33 (75.0%)	214 (71.3%)
	Male	20 (21.5%)	55 (33.7%)	11 (25.0%)	86 (28.7%)
CL < 20		63 (67.7%)	53 (32.3%)	3 (6.8%)	119 (39.7%)
	CL > 20	30 (32.3%)	109 (66.9%)	41 (93.2%)	180 (60.3%)
Centiloid Score	Not available	0 (0%)	1 (0.6%)	0 (0%)	1 (0.3%)
APOE4 Status	Negative	65 (69.9%)	103 (63.2%)	17 (38.6%)	185 (61.7%)
	Positive	28 (30.1%)	60 (36.8%)	27 (61.4%)	115 (38.3%)
MMSE Score	Mean (SD)	27.5 (1.84)	23.1 (4.01)	15.4 (5.39)	23.3 (5.34)
	Median [Min, Max]	28.0 [22.0, 30.0]	24.0 [10.0, 30.0]	16.0 [10.0, 23.0]	25.0 [1.00, 30.0]

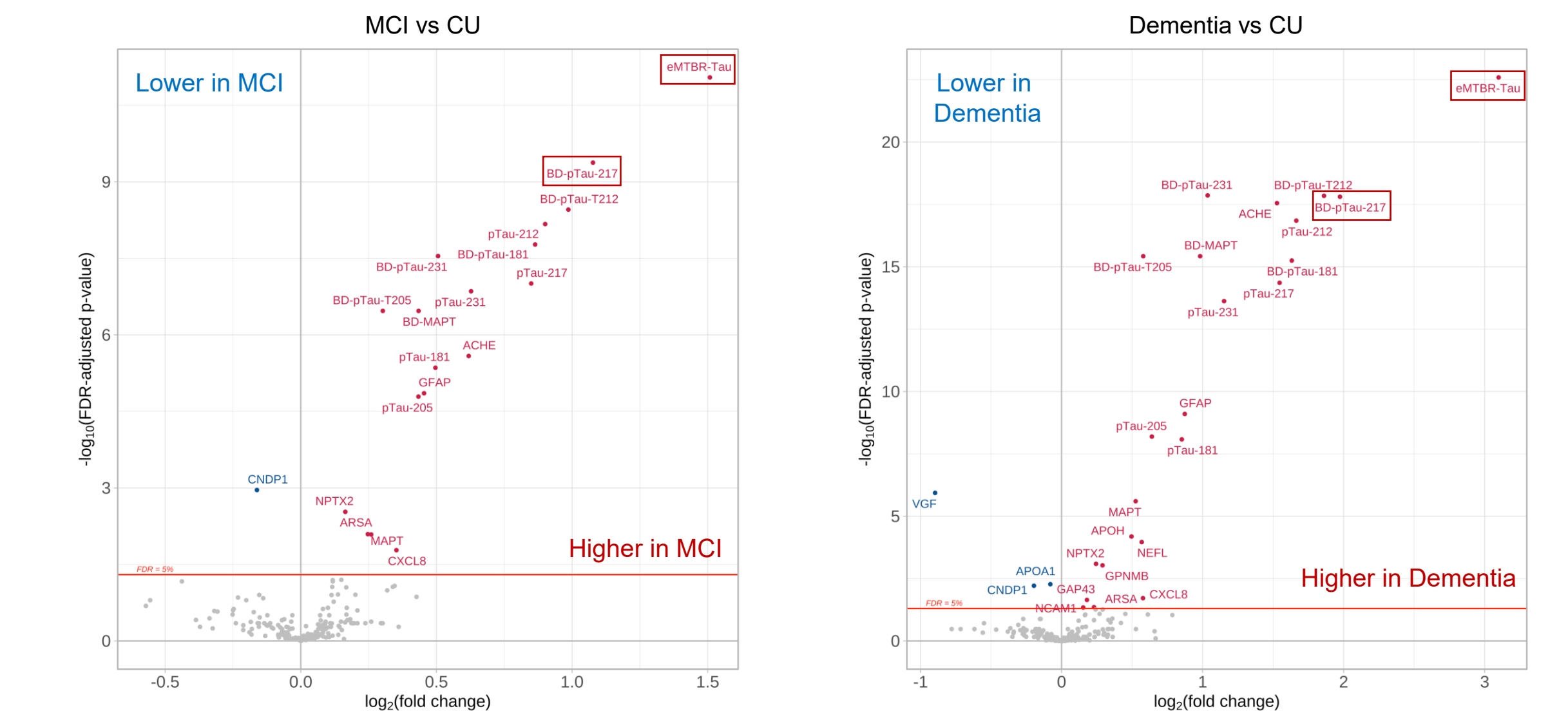
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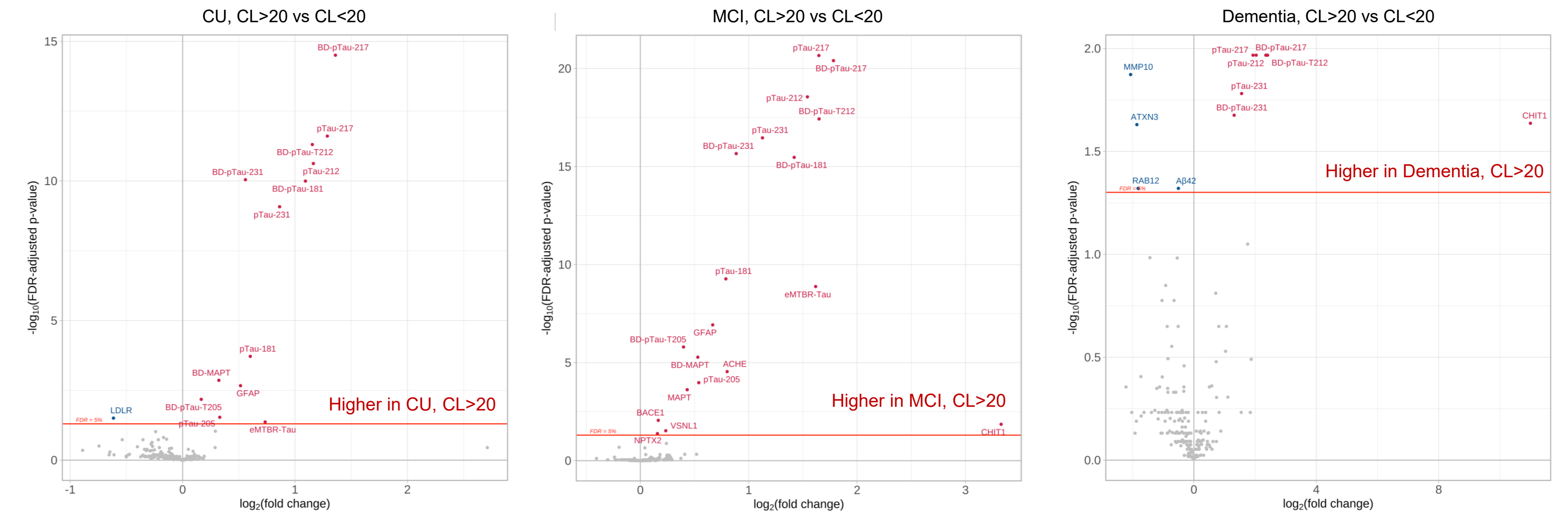
NULISaseq Neuro 220 Panel for Broad Profiling of Brain Health

Pathological Protein Aggregation	Synaptic/Neuronal Network Dysfunction	Aberrant Proteostasis	Inflammation
Abeta38 Abeta40 Abeta42 ATXN2 ATXN3 BACE1 BD-pTau-181 BD-pTau-T205 BD-pTau-T212 BD-pTau-217 BD-pTau-231 BD-tTau eMTBR-Tau HTT mHTT-exon1 Oligo-SNCA	pQ-ATXN3 pQ-HTT PSEN1 pSNCA-S129 pTARDBP-S409 pTau-181 pTau-205 pTau-212 pTau-217 pTau-231 SNCA SNCB SOD1 TARDBP tTau	ACHE BASP1 BCAN BDNF CALB2 CNTN2 CRH CST5 DDC DLG4 ENO2 GAP43 GDI1 GDNF L1CAM MAG MOG NCAM1	NELL1 NGF NPTX1 NPTX2 NPTXR NPY NRGN NTRK2 NTRK3 PDLIM5 PTPRS REST SNAP25 STX4 VGF VSNL1 YWHAG YWHAZ
Neuronal Cell Death	LRRK2/Rab Pathway	Cytoskeletal Abnormalities	Altered Energy Homeostasis
ANXA5 GSDME	LRRK2 pLRRK2-S1292 pRab10-T73 pRab12-S106	NEFH NEFL STMN2	ARS GOT1 PGK1
Growth Factor Signaling	Wnt/mTOR Signaling	Systemic/Comorbidity Markers	Lipid Metabolism/APOE
AXL EDA2R FGF2	CTNNB1 Dkk1	CGRP CST3 FAM3B MSLN	APOA1 APOA2
DNA/RNA Defects	EIF4EBP1 SFRP1	NT-ProBNP PPY PROS1	APOH LDLR

Differential Abundance Analysis Identified Key Neurodegenerative Markers in MCI and Dementia with eMTBR-Tau Demonstrating the Largest Fold Change

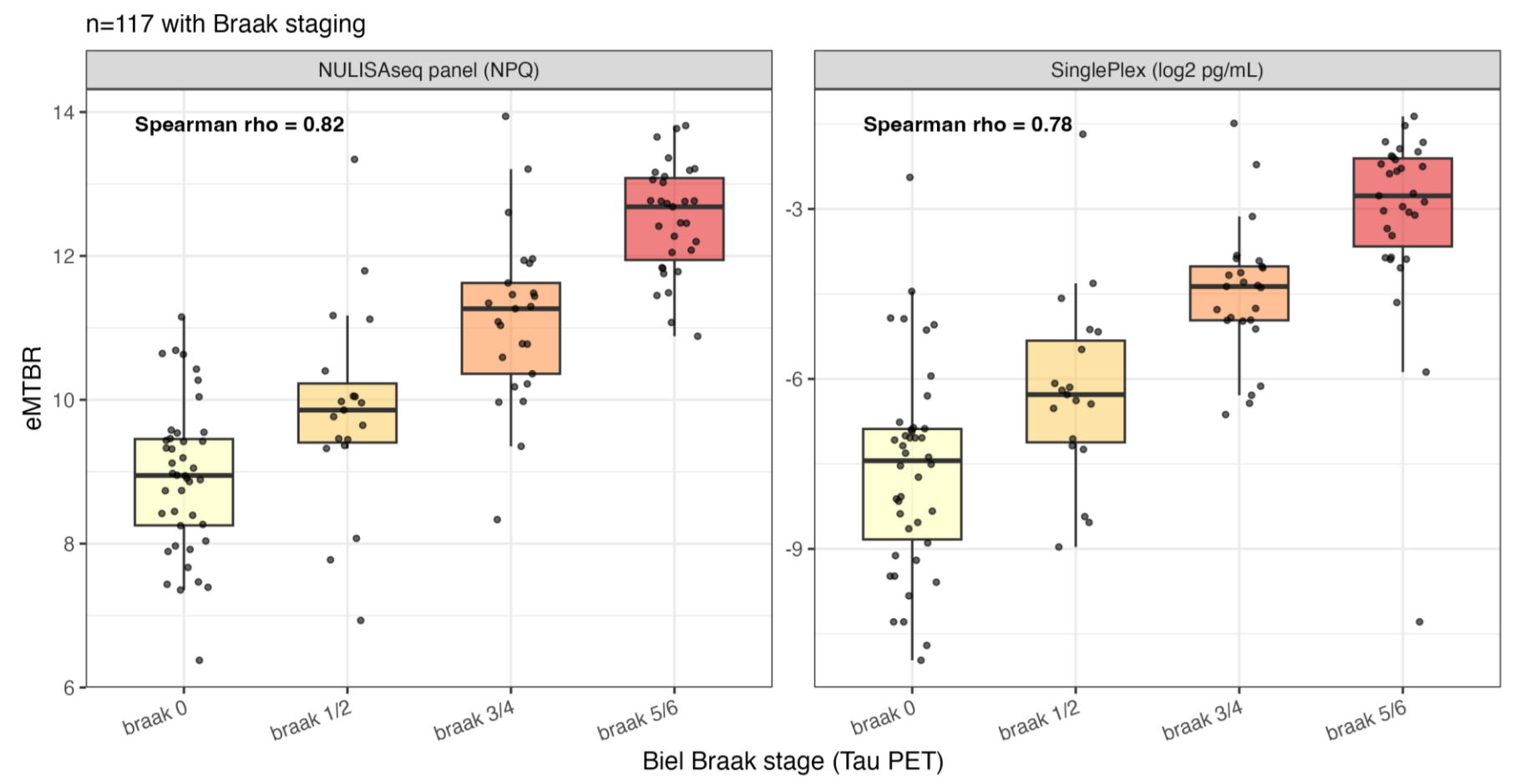


Analysis with the Neuro 220 Panel Identified BD-pTau Associated with Amyloid Burden (CL>20) in Plasma Samples Spanning the AD Continuum



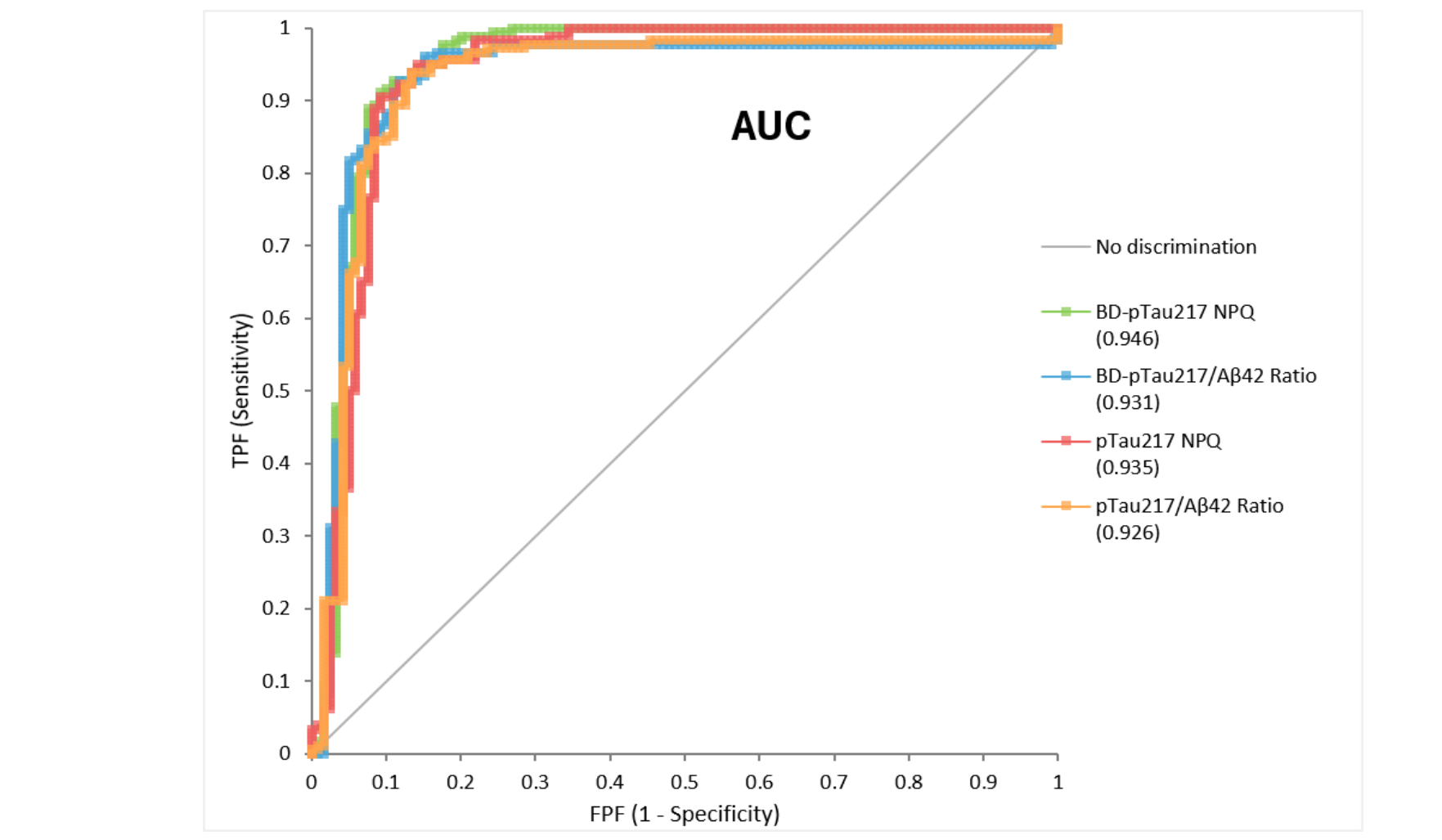
eMTBR-Tau Demonstrates Higher Correlation with Tau PET than BD-pTau217

Tau Stage	Correlation (eMTBR)	Correlation (BD-pTau217)
Braak stage (ordinal)	0.817	0.766
Tau PET global SUVR	0.806	0.751
Tau PET Braak I/II	0.643	0.621
Tau PET Braak III/IV	0.848	0.796
Tau PET Braak V/VI	0.756	0.701



BD-pTau217 outperforms pTau217 in detecting positive amyloid pathology

Analyte	AUC (p<0.0001)
BD-pTau217 NPQ	0.946
BD-pTau217/Aβ42 Ratio	0.931
pTau217 NPQ	0.935
pTau217/Aβ42 Ratio	0.926



Significant Findings

- Analysis of plasma samples spanning the AD continuum identified key biomarkers including brain-derived and total Tau proteoforms, eMTBR-Tau, NPTX2, GFAP, ARSA and CXCL8 in MCI and AD (FDR p<0.05)
- Brain-derived pTau217 is the best single biomarker for amyloid positivity across cognitively normal, MCI and AD clinical groups
- eMTBR is the best biomarker for Tau PET pathological staging with strongest correlations with mid/late tangle stages

The NULISaseq Neuro 220 Panel provides a comprehensive and ultrasensitive tool for biomarker discovery and validation across Alzheimer’s Disease and other neurodegenerative diseases.

References

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