Total Tau, p-Tau$_{181p}$ and A$\beta_{1\text{-}42}$ in CSF of ADNI subjects at BASELINE

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ADNI Biomarker Core report, April 14, 2008

Biomarker studies completed or planned

BASELINE CSF samples:

102 AD, 200 MCI & 114 NC

Analyses

- 416 CSF
  - Tau, $pTau_{181p}$, $A\beta_{1-42}$ (completed, data uploaded on ADNI & Loni websites)
  - Homocysteine (completed by MRL, will be uploaded soon)
  - Isoprostanes (will be completed summer 2008)

YEAR ONE CSF and plasma samples:

YEAR ONE CSF (303 as of April 1, 2008)

- **Tau, $pTau_{181p}$, $A\beta_{1-42}$, $A\beta$42/40 ratio** (analyses should be completed by Fall 2008 when all YEAR ONE SAMPLES collected); isoprostanes completion by Fall 2008

Baseline, 6 & 12 mos **2,400(+)** plasma samples

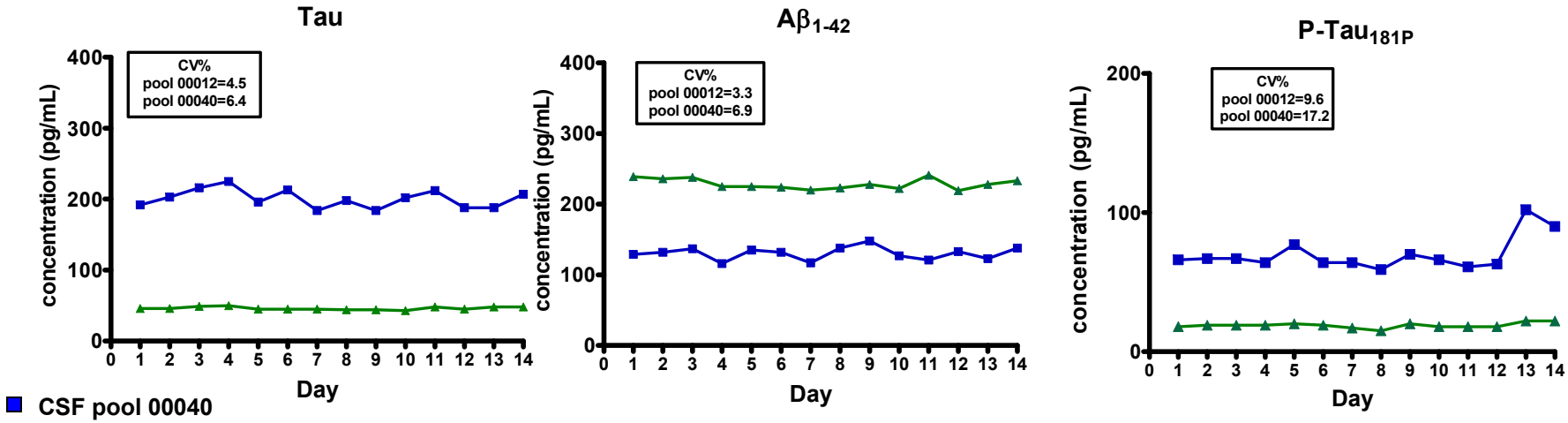
- **$A\beta$ species** (validation will be started first half of 2008, analyses start late summer, 2008)
  - Homocysteine (completed for BASELINE samples; 6 mos, 1 yr well underway)
  - Isoprostanes (analyses start on completion of collection of YR 1 plasma samples)

CSF Tau, $A\beta_{1-42}$, $pTau_{181p}$: measured using the Luminex multiplex platform and Innogenetics INNO-BIA AlzBio3 immunoassay reagents

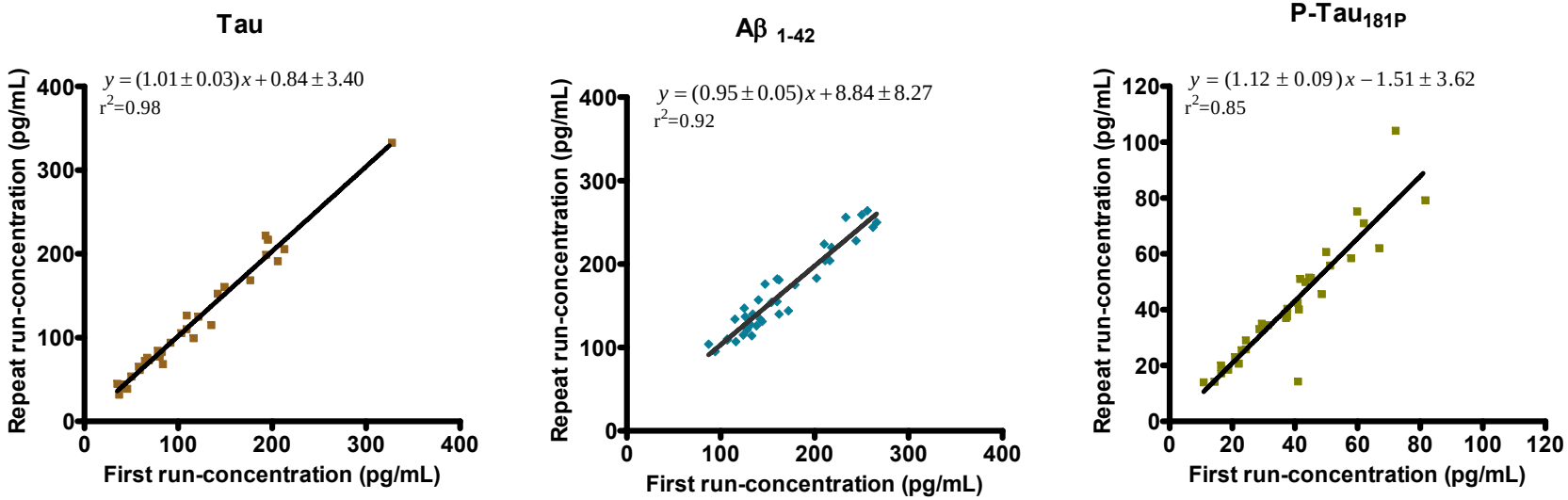
Key characteristics of the xMAP system compared to ELISA:

	xMAP	**ELISA**
ormat	Antibody covalently bound to beads	Antibody coats plate well
iomarker tests per run	3	1
olume	75 μL(x2)	125 μL(x2)
recision	3-10%;excellent test-re-test precision and better dynamic range for xMAP calibration curves.	
nalytical validation	Completed 7 lab interlab validation study	
iomarker concentrations	**Equivalent clinical correlation for xMAP vs ELISA**	
	ELISA Tau concentrations ~4x higher than xMAP; $A\beta_{1-42}$ ~2x higher than xMAP; $pTau_{181p}$ ~25% higher than xMAP	

Day to day variability of CSF pools



Test retest sample performance



ADNI BASELINE CSF biomarker concentrations show the expected average differences between AD and MCI and NC

AD (n=102)	Tau	$A\beta_{1-42}$	P-Tau_{181P}	Tau/$A\beta_{1-42}$	P-Tau_{181P}/$A\beta_{1-4}$
Mean±SD	122±58	143±41	42±20	0.9±0.5	0.3±0.2
MCI (n=200)					
Mean±SD	103±61	164±55	35±18	0.8±0.6	0.3±0.2
NC (n=114)					
Mean±SD	70±30	206±55	25±15	0.4±0.3	0.1±0.1

<0.0001, for each of the 5 biomarker tests for AD vs NC and for MCI vs NC.
or AD vs MCI:p<0.005, Tau; p<0.01, $A\beta_{1-42}$; p<0.01, P-Tau $_{181P}$; p<0.0005, Tau/$A\beta_{1-42}$; p<0.005, P-Tau $_{181P}$/$A\beta_{1-4}$
lann-Whitney test for statistical differences used for these non-normally distributed data sets.

Qualification of the multiplex immunoassay system for AD detection using C. Clark's independent set of **autopsy-based AD & FTD vs NC subjects' CSF samples**

AD (n=58)	Tau	$A\beta_{1-42}$	P-Tau $_{181P}$	Tau/$A\beta_{1-42}$	P-Tau$_{181P}$/$A\beta_{1-42}$
Mean±SD	135±95	131±33	39±29	1.1±1.0	0.3±0.2
NC (n=57)					
Mean±SD	57±30	233±64	18±16	0.3±0.2	0.1±0.1
FTD (n=16)					
Mean±SD	61±28	186±52	7±5	0.4±0.2	0.07±0.05

lark C, et al, 2008

8 autopsy-based AD cases and 57 NC subject CSF samples were included in this study.

Using the Innogenetics Inno-Bia AlzBio3 research immunoassay reagents and Luminex platform:

AD mean age±SD; median age(range): 71±10; 75(44-86);

NC mean age±SD; median age(range): 70±11; 69(41-94);

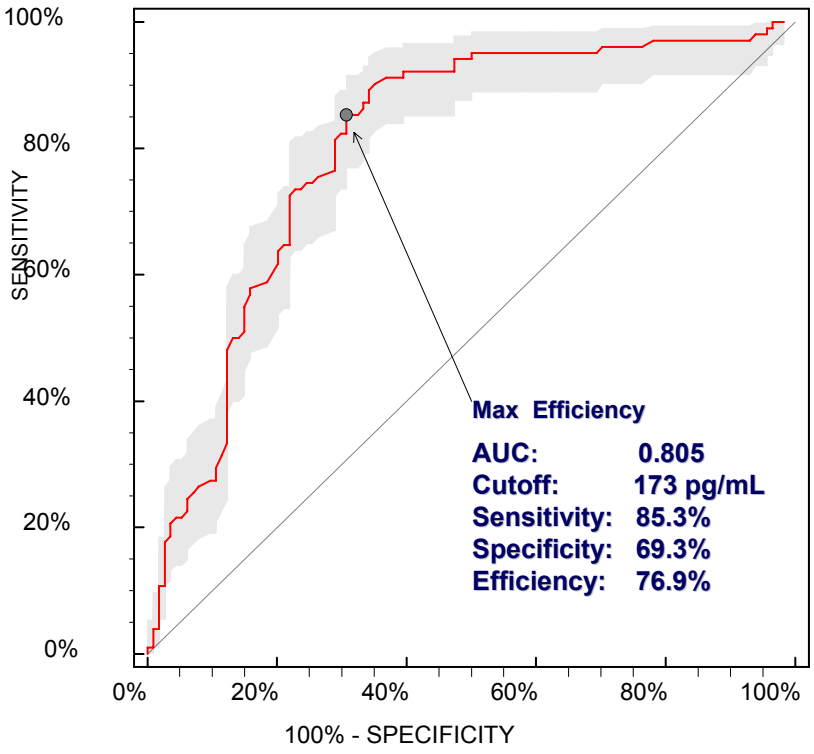
FTD mean age±SD; median age(range): 68±9; 68(51-84).

ROC curve characterization of diagnostic utility of multiplex immunoassay system for AD detection using C. Clark's independent set of **autopsy-based AD vs NC subjects' CSF samples**

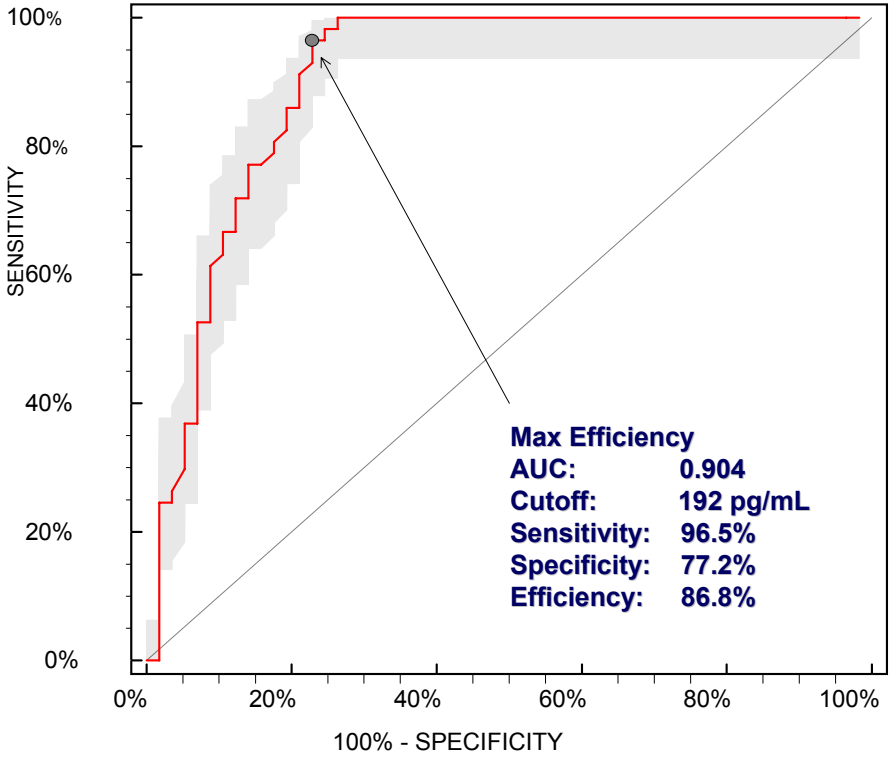
	Tau	$A\beta_{1-42}$	$p\text{-}Tau_{181p}$	$Tau/A\beta_{1-42}$	$p\text{-}tau_{181p}/A\beta_{1-42}$
ROC AUC	0.833	0.904	0.748	0.919	0.856
Threshold values	93 ng/mL	192 ng/mL	21 ng/mL	0.39	0.10
Sensitivity (%)	69.6	96.5	72.4	85.7	91.2
Specificity (%)	92.5	77.2	69.6	84.9	69.8
Test accuracy (%)	80.7	86.8	71.1	85.3	80.9

Receiver Operating Characteristic curves for AD vs NC, $A\beta_{1-42}$ concentration

ADNI BASELINE CSF



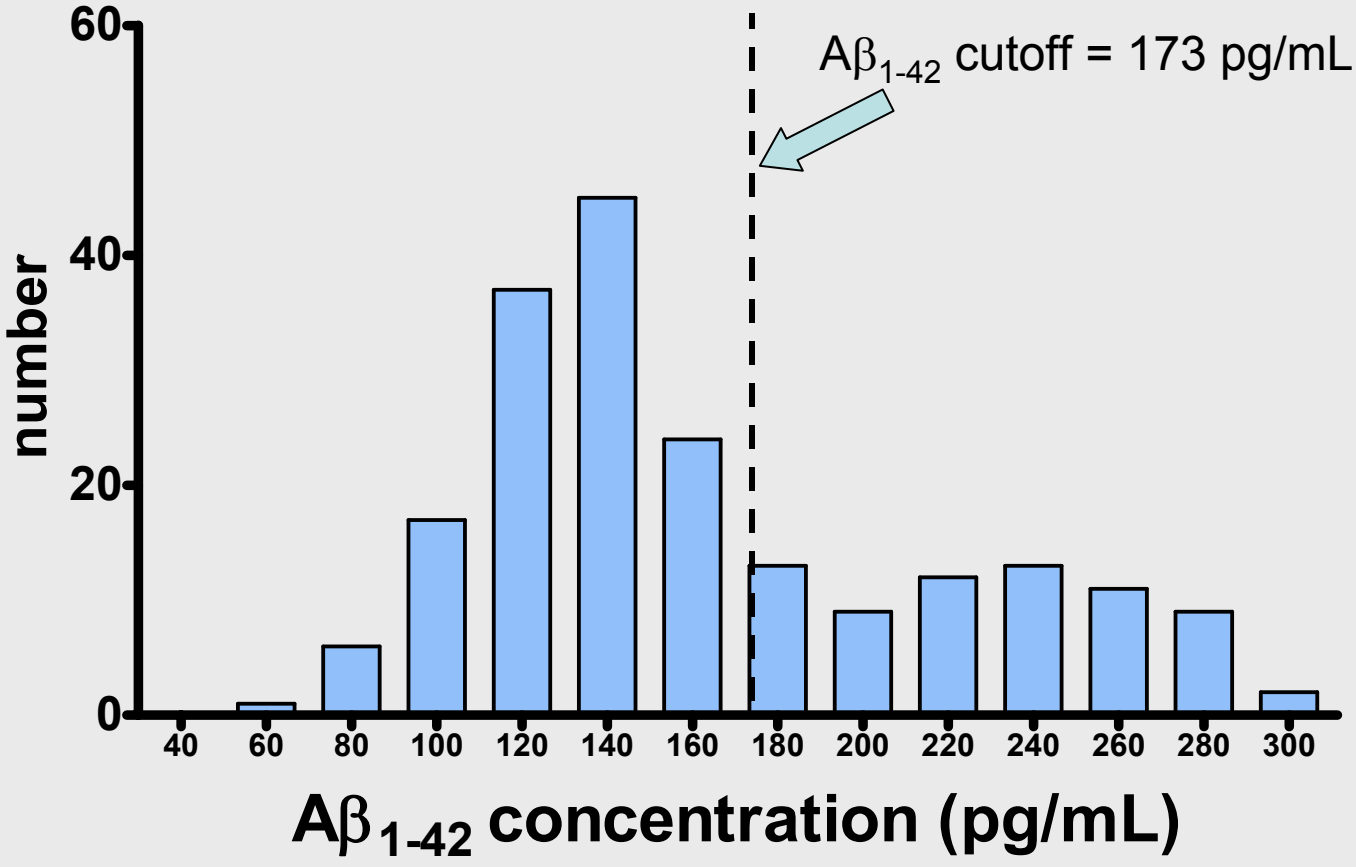
Autopsy-based CSF



ADNI BASELINE CSF biomarkers, stratified by APOE ε4 carrier status

	Tau	$A\beta_{1-42}$	$pTau_{181p}$	$Tau/A\beta_{1-42}$	$pTau_{181p}/A\beta_{1-42}$
	mean±SD, (pg/mL)			ratio	
AD ε4+ (n=71)	120±52	131±27	42±19	0.96±0.48	0.34±0.19
AD ε4- (n=31)	125±69	170±52	42±22	0.82±0.50	0.28±0.17
p value	0.99	*p*<0.0001	0.65	0.22	0.17
MCI ε4+(n=108)	118±67	144±41	40±18	0.93±0.71	0.31±0.18
MCI ε4- (n=92)	86±47	188±59	30±16	0.55±0.40	0.19±0.15
p value	*p*<0.0001	*p*<0.0001	*p*<0.0001	*p*<0.0001	*p*<0.0001
NC ε4+ (n=27)	80±40	157±49	32±21	0.57±0.37	0.24±0.19
NC ε4- (n=87)	66±26	221±48	23±11	0.33±0.19	0.11±0.09
p value	0.11	*p*<0.0001	0.03	*p*<0.0001	*p*<0.0001

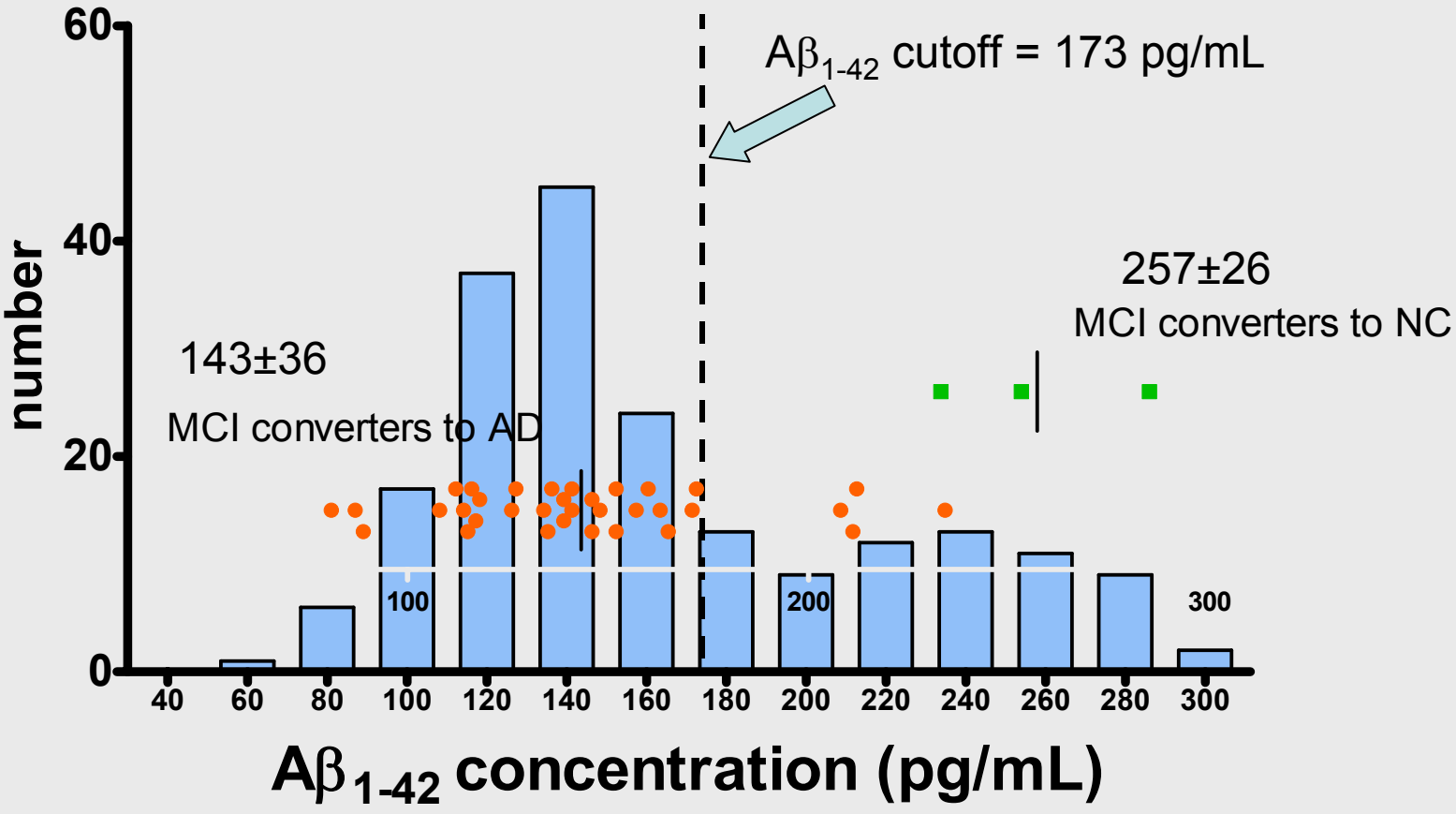
Frequency distribution of BASELINE CSF $A\beta_{1-42}$ in ADNI MCI cohort



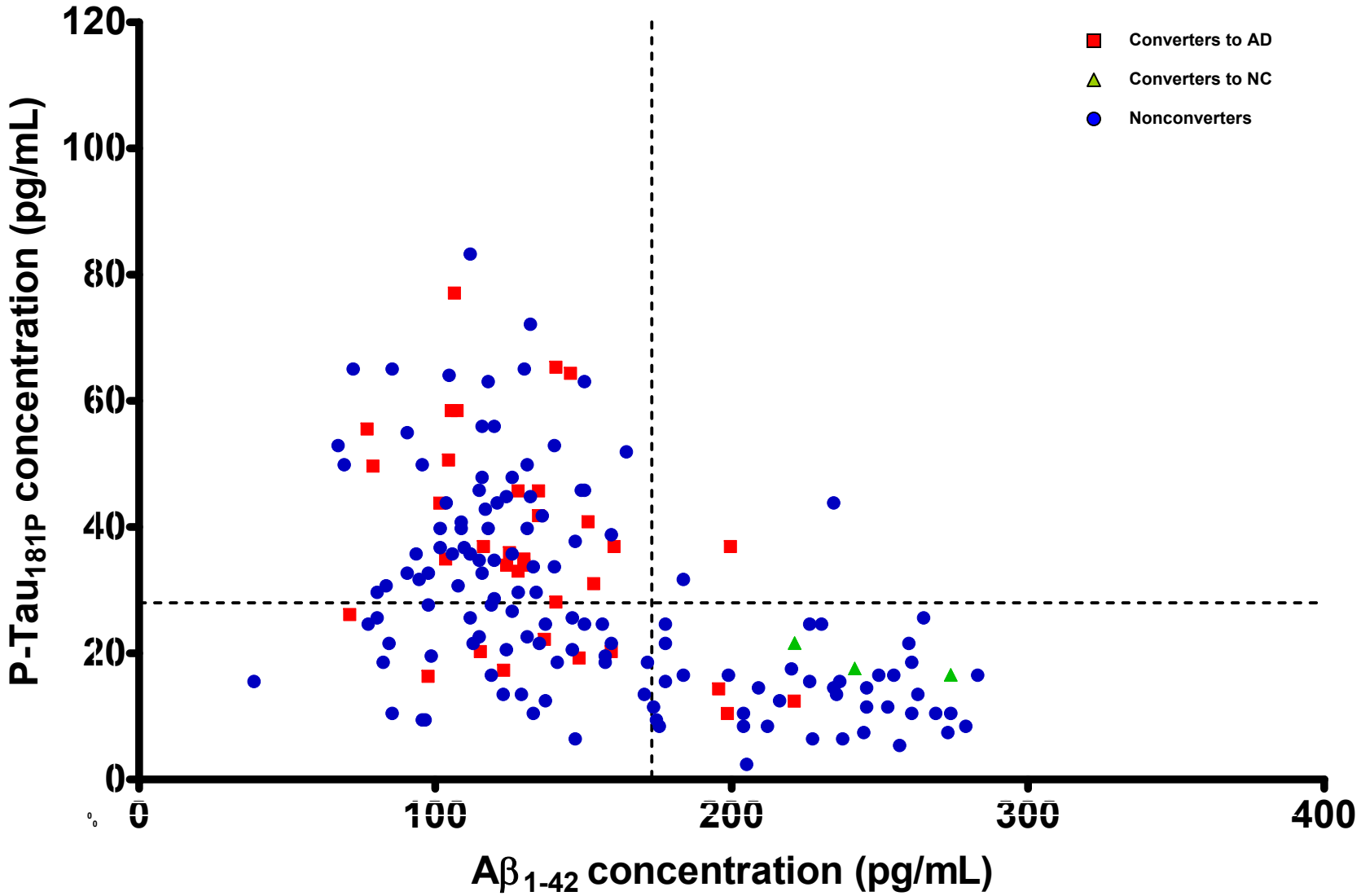
BASELINE CSF data for ADNI MCI subjects who converted to AD or to NC at YEAR 1

Status as of 4/1/2008	Tau	$A\beta_{1-42}$	$pTau_{181P}$	$Tau/A\beta_{1-42}$	$pTau_{181P}/A\beta_{1-4}$
ADNI MCI converters to AD (n=34)	104±50	143±36	41±17	0.78±0.43	0.31±0.17
ADNI AD (n=102)	122±58	143±41	42±20	0.9±0.5	0.3±0.2
ADNI MCI converters to NC (n=3)	75±7	257±26	22±3	0.29±0.02	0.09±0.02
ADNI NC (n=114)	70±30	206±55	25±15	0.4±0.3	0.1±0.1

MCI converters to AD at YEAR 1(n=34)



CSF P-Tau$_{181P}$ and Aβ $_{1-42}$ BASELINE concentrations for ADNI MCI converters to AD or NC and nonconverters



No differences between ADNI study cohorts for average plasma or CSF homocysteine

	Plasma Homocysteine (μmole/L)	CSF Homocysteine (μmole/L)
AD (n=102)		
Mean±SD	10.4±3.25	0.11±0.02
MCI (n=200)		
Mean±SD	10.4±2.82	0.11±0.06
NC (n=114)		
Mean±SD	10.0±2.73	0.11±0.03

P=0.66 for AD vs NC; p=0.81 for MCI vs NC; p=0.38 for AD vs MCI, Mann-Whitney

ADNI-2 Biomarker Core Aims

- Continue to collect, aliquot, store, curate, track all samples collected from subjects in ADNI-1 and ADNI-2
- Continue biomarker studies launched in ADNI-1:
  - APOE genotyping of all new study subjects
  - CSF Aβ and tau (partner with Innogenetics to assay all measurable species)
  - CSF and plasma isoprostanes (all measurable species)
  - CSF and plasma homocysteine
  - Plasma Aβ (partner with Innogenetics to assay all measurable species)

ADNI-2 Biomarker Core Aims (continued)

- Implement/validate promising new biomarkers such as BACE, and other species of tau and Aβ in CSF, but especially in plasma
- Partner with ISAB/other investigators in proteomic, metabalomic, lipidomic and targeted biomarker studies
- Partner with other investigators who pursue additional approved Add- On studies
- Collaborate with all ADNI Cores/Investigators in correlative analyses of biomarker, clinical, imaging and autopsy data
- Collaborate with World-Wide ADNI Sites in Europe, Japan and Australia in biomarker studies and comparative analyses of previously collected biomarker data

summary

1. Analytically validated multiplex immunoassay provided precise CSF biomarker data for Tau, $pTau_{181p}$ and $A\beta_{1-42}$
2. Statistical separation for ADNI BASELINE AD, MCI and NC groups achieved for each of the 3 biomarkers and ratios
3. Diagnostic classification of ADNI AD and NC based on CSF Tau, $pTau_{181p}$ and $A\beta_{1-42}$ concentrations was achieved consistent with autopsy-based pathology of AD and FTD in AD & FTD cohorts vs NC group (Chris Clark, et al)
4. APOE ε4+ subjects demonstrated greater abnormalities for Tau, and 181pTau concentrations in the MCI & NC cohorts compared to APOE ε4- subjects and for $A\beta_{1-42}$ in all three ADNI cohorts.
5. MCI subjects (n=34) who converted to AD at 12 months had a BASELINE CSF biomarker profile like that of ADNI AD subjects
6. MCI subjects (n=3) who converted to NC at 12 months had a BASELINE CSF biomarker profile like that of ADNI NC subjects
7. Plasma and CSF homocysteine concentrations at BASELINE did not differ among the ADNI study groups
8. Analyses of YEAR 1 CSF for Tau and Aβ will be completed by the end of 2008; analyses of BASELINE through YEAR 1 plasma samples for Aβ species will be initiated in FALL 2008 and should be completed by first quarter, 2009.

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