ADNI Biomarker Core Report

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ADNI Biomarker core 2013- July 2014

- Studies reported in the ADNI/LONI website & studies newly approved by RARC/NIA/ADNI using ADNI biofluids
- 2014 ADNI II batch analyses of CSF completed, uploaded on ADNI/LONI website June 2014
- mrm/tandem mass spectrometry reference method for Aβ1-42, progress report
- Planned analyses

ADNI Biomarker core 2013-July 2014:

Add-on studies reported on the ADNI/LONI website & add-on studies newly approved by RARC/NIA/ADNI using ADNI biofluids

Reported

- **mrm/tandem mass spectrometry of 567 tryptic peptides associated with 221 proteins**, Caprion/FNIH/ADNI/PPSB in ADNI I CSF

Approved/shipped or to be shipped

- **YKL40 & Vilip1 in longitudinal** ADNI CSF, WashU, Anne Fagan, 4th qtr 2013
- **Metabolic Pathways & Network**s in ADNI I BL serum, DukeU, Rima Kaddurah-Douk, 2nd qtr 2014
- **DDE*** in ADNI serum, EmoryU, Allan Levey, 2nd qtr 2014
- **Neurogranin** in BASELINE CSF of ADNI I subjects, UGothenberg, Sweden, Kaj Blennow, 2nd qtr 2014
- **Tau in plasma** of ADNI I BASELINE subjects, UGothenberg, Sweden, Kaj Blennow, 3rd qtr 2014
- **Phosphorylated α-synuclein** in ADNI I BL CSF, UWash, Jing Zhang, 2nd qtr 2014

*DDE-a major breakdown product of the insecticide DDT that is highly fat soluble, very long biological half-life, potential risk factor for neurodegeneration. JAMA Neurology 2014.

Aliquot counts by study subject

- Updated as of 4/14 2014 on the ADNI/LONI website
- Aliquot counts for plasma, serum, CSF, urine
- Total volume and # of pristine aliquots available
- Aliquots utilized for Biomarker Core measurements
- Aliquots sent to investigators who had RARC/NIA/ADNI-approved studies

2014 batch analyses of ADNI II CSFs

- N=428 ADNI II CSFs + 17 pristine randomly selected replicates assayed using the AlzBio3 RUO immunoassay
- 275 BASELINE samples; 153 have a paired BL(2013) + 24 month sample
- Results uploaded on ADNI/LONI website June 2014.
- QC data summary in next ppt.

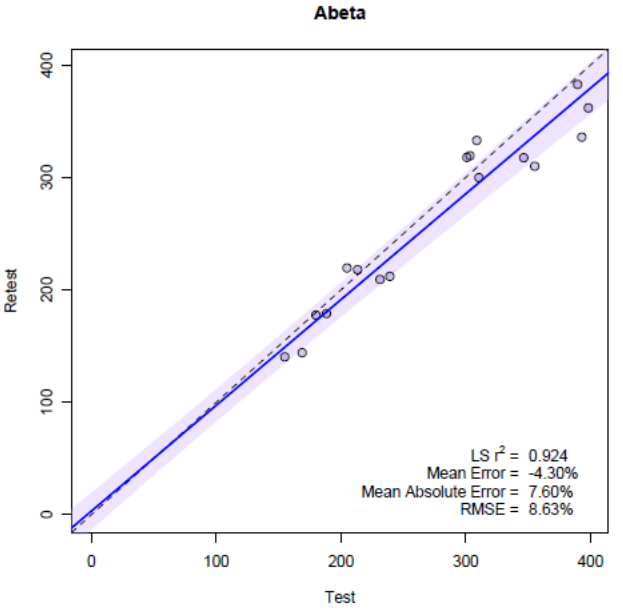
2014 batch analyses of ADNI II CSFs

2013	Sample	N	Mean ± SD	2014	N	Mean ± SD
t-tau	CSF **abnormal pool** #53	25	**128±10.4**	**t-tau**	14	**120±4.9**
	CSF **normal pool** #54	25	**65.9±6.0**		14	**59.8±4.7**
$A\beta_{1-42}$	CSF **abnormal pool** #53	25	**148±9.4**	**$A\beta_{1-42}$**	14	**148±8.4**
	CSF **normal pool** #54	25	**236±18**		14	**249±13.7**
p-tau_{181}	CSF **abnormal pool** #53	25	**26.5±1.4**	**p-tau_{181}**	14	**28.0±1.7**
	CSF **normal pool** #54	25	**19.1±1.2**		14	**20.4±1.3**

Test-retest performance

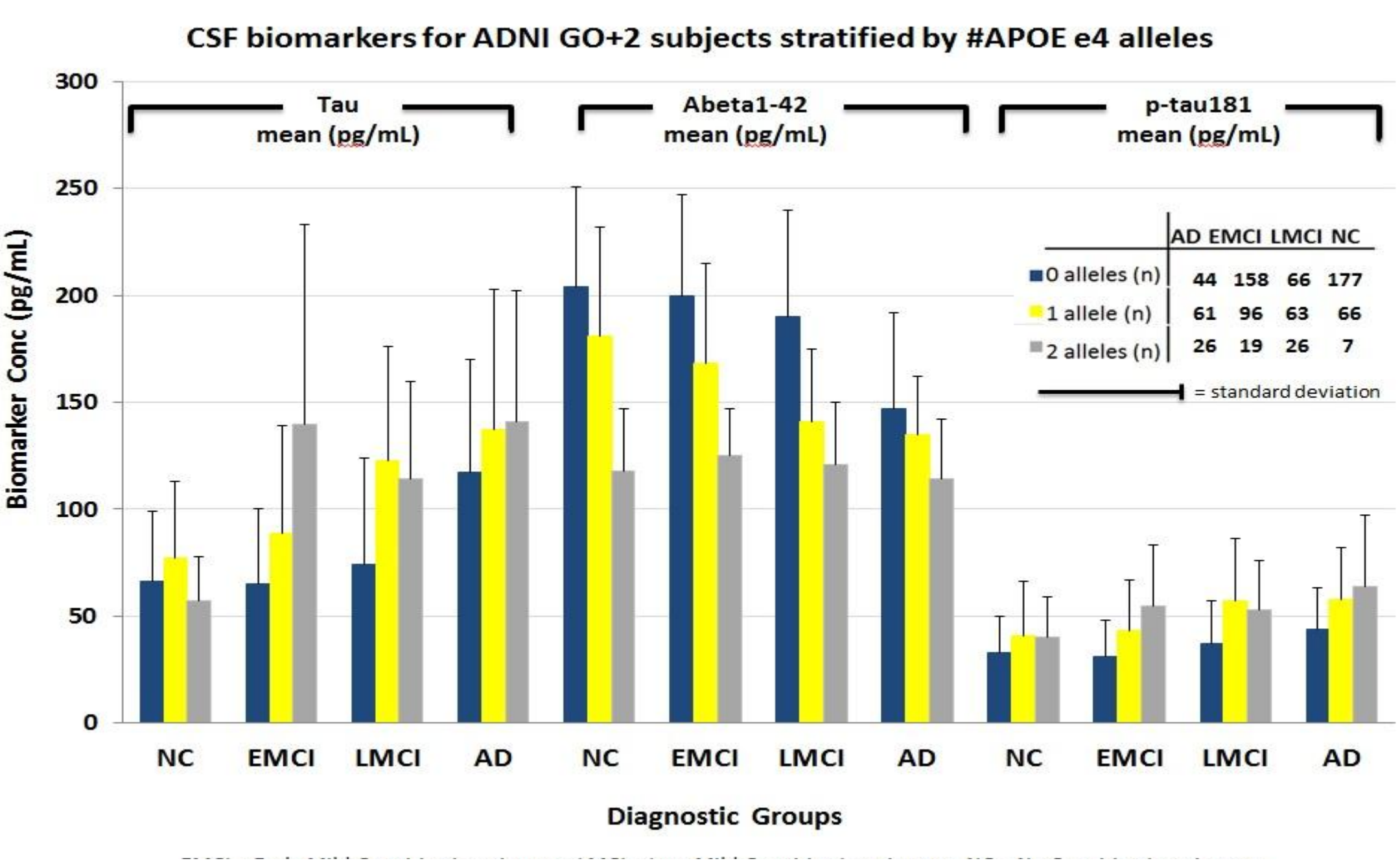
- Linear regression R^2 values
  - Tau, 0.986
  - $A\beta_{42}$, 0.924
  - $ptau_{181}$, 0.988

- Bland-Altman avg %CV
  - Tau, 7.2%
  - $A\beta_{42}$, 5.6%
  - $ptau_{181}$, 4.9%



ADNI I and GO+2 BASELINE results

	N	% Apoe ε4	t-tau (pg/mL)	$A\beta_{1-42}$ (pg/mL)	p-tau_{181} (pg/mL)	t-tau/$A\beta_{1-42}$	p-tau_{181}/$A\beta_{1-42}$	LRTAA2i
AD								
ADNI I	100	69.0	122±58	144±41	42±20	0.92±0.48	0.32±0.19	
ADNI II	131	66.4	133±62	132±33	56±26	1.1±0.61	0.46±0.28	0.79±0.29
LMCI								
ADNI I	196	54.1	103±61	164±55	36±18	0.75±0.62	0.26±0.18	
ADNI II	155	57.4	101±56	158±49	49±28	0.72±0.48	0.35±0.24	0.63±0.38
EMCI								
ADNI I	--	--	--	--	--	--	--	--
ADNI II	273	42.1	77±49	184±51	37±21	0.49±0.46	0.24±0.19	0.40±0.36
NC								
ADNI I	114	23.7	70±30	206±55	25±15	0.39±0.27	0.14±0.13	
ADNI II	157	26.7	68±34	196±51	35±19	0.39±0.27	0.20±0.16	0.32±0.34
SMC								
ADNI I	--	--	--	--	--	--	--	--
ADNI II	93	33.3	65±32	201±49	38±21	0.36±0.24	0.21±0.17	0.31±0.32

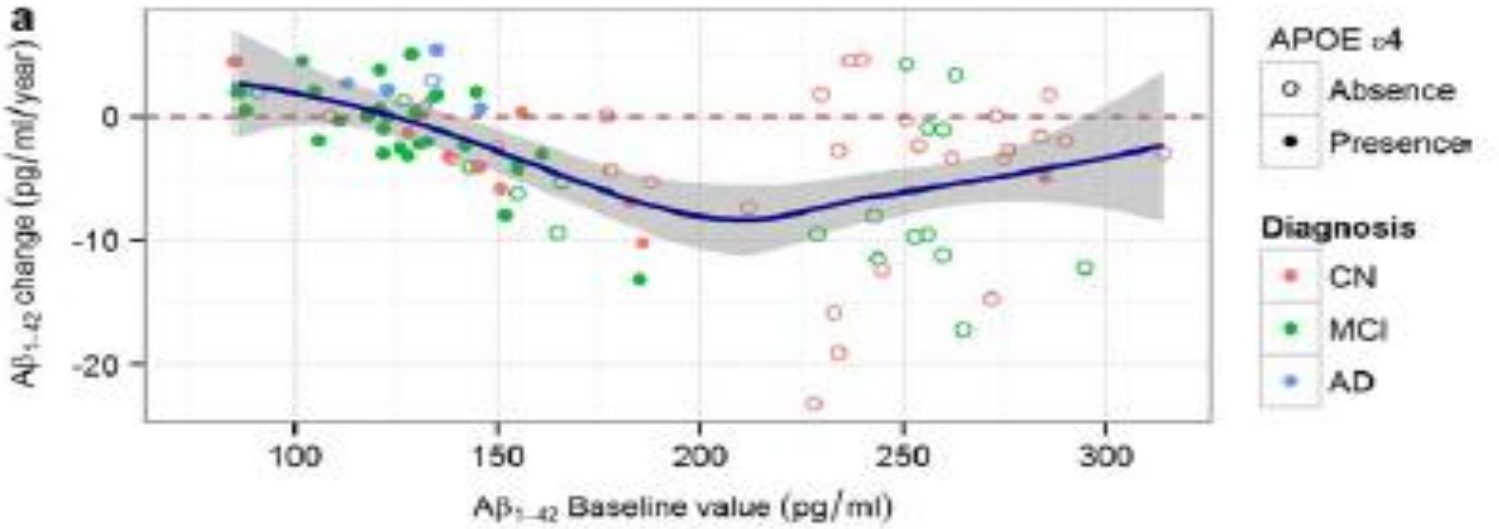


see text below for stats

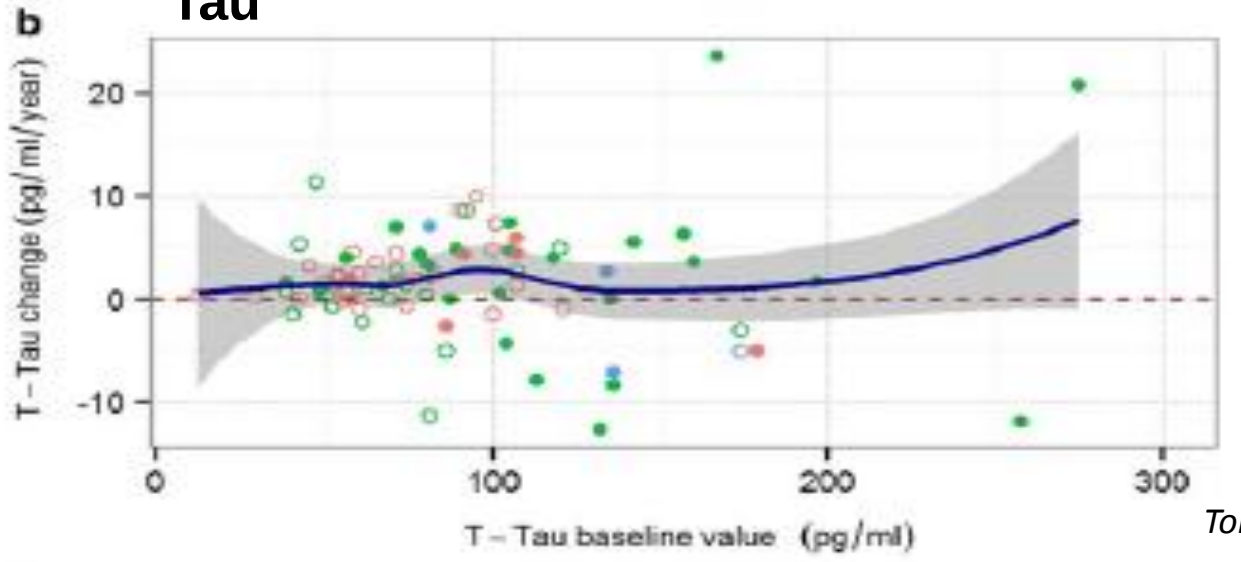
ADNI Longitudinal Biomarkers Changes

ADNI 1

Aβ42



Tau



Toledo et al, Acta Neuropath, 2013

ADNI 2: Biomarker Core

mrm LC/MSMS method for Aβ peptides in CSF

Eppendorf LoBind Tubes

Oasis MCX µElution Plate

ACQUITY UPLC

Trapping column

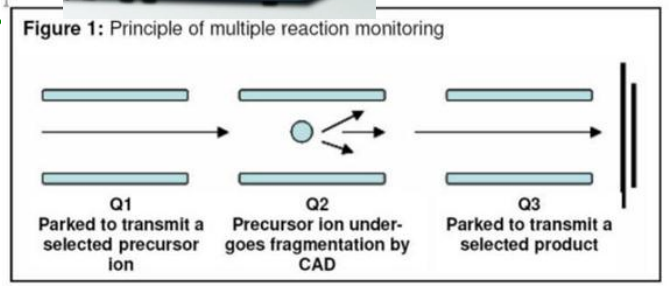
Analytical column

•UPLC BEH-300

•C18 2.1x150mm, 1.7 µm

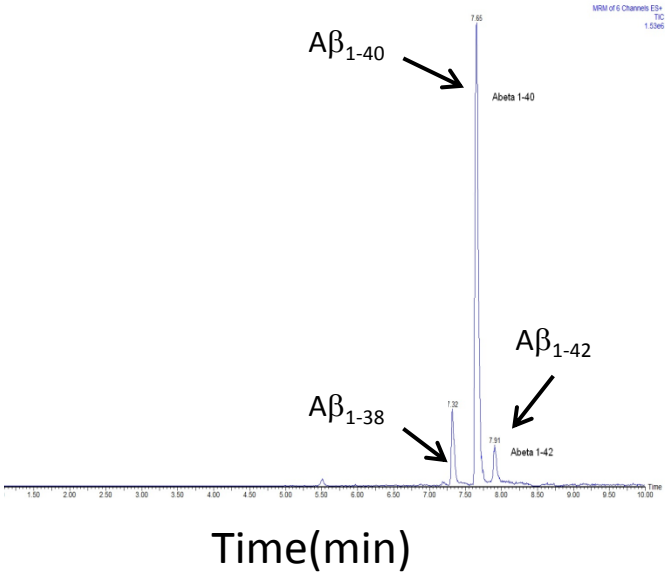
Injection position of switching valve - 2D chromatography

Xevo TQ-S tandem mass spectrometer



m/z 1129.0 → *m/z* 1078.8

($A\beta_{1-42}$ precursor [4+] ion) (product [4+] ion)



- Further improved using a Xevo TQ-S tandem mass spectrometer; CSF aliquot size 100 µL
- Accuracy-based measurement of $A\beta_{1-42}$, $A\beta_{1-40}$ & $A\beta_{1-38}$ for all ADNI CSF samples
- Round Robin study completed(4 centers) in collaboration with Kaj Blennow, manuscript submitted
- Pilot assessment of IRMM-prepared $A\beta_{1-42}$ is underway
- Will help answer questions about potential contribution of other metabolites, eg, $A\beta_{1-40}$, $A\beta_{1-38}$ to utility of $A\beta_{1-42}$ and other APP species, tau fragments.

Candidate reference methods for CSF Aβ42 published

Clinical Chemistry 60:7
987–994 (2014)

Proteomics and Protein Markers

Mass Spectrometry–Based Candidate Reference Measurement Procedure for Quantification of Amyloid-β in Cerebrospinal Fluid

Andreas Leinenbach,[1†] Josef Pannee,[2†] Thomas Dülffer,[1] Andreas Huber,[1] Tobias Bittner,[1] Ulf Andreasson,[2] Johan Gobom,[2] Henrik Zetterberg,[2,3] Uwe Kobold,[1] Erik Portelius,[2] and Kaj Blennow[2*] on behalf of the IFCC Scientific Division Working Group on CSF proteins

Journal of Alzheimer's Disease 41 (2014) 441–451
DOI 10.3233/JAD-132489
IOS Press

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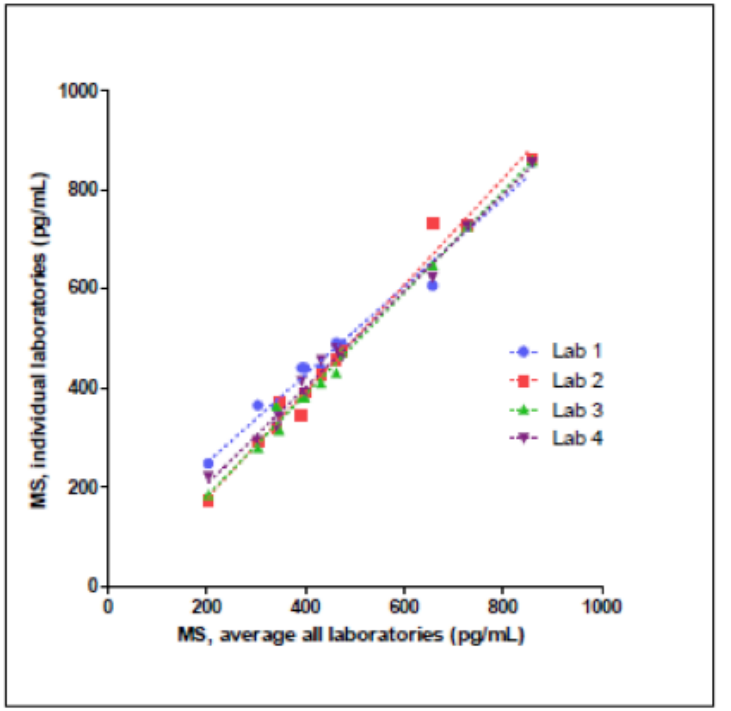
Qualification of a Surrogate Matrix-Based Absolute Quantification Method for Amyloid-β_{42} in Human Cerebrospinal Fluid Using 2D UPLC-Tandem Mass Spectrometry

Magdalena Korecka[a], Teresa Waligorska[a], Michal Figurski[a], Jon B. Toledo[a,d], Steven E. Arnold[b,c], Murray Grossman[c], John Q. Trojanowski[a,d] and Leslie M. Shaw[a,d,*]

Four laboratory Round Robin study on SRM Aβ42 methods

- **12 CSF samples**
- **On sample = Candidate Reference Material**

➔ SRM mass spec suitable as a Reference Measurement Procedure (RMP) for CSF A β 42



Support of standardization efforts

- ADNI-longterm commitment to standardization of all methods
- Alz Assn Global Biomarker Standardization Consortium
  - Analytical methods standardization--strong support for improved performance of existing and new immunoassays for CSF biomarkers
  - Support for mrm/tandem mass spectrometry for direct measurement of absolute $A\beta_{1\text{-}42}$ concentration
  - IFCC/IRMM project to develop reference $A\beta_{1\text{-}42}$ peptide material and using mrm/msms and large pools of CSF with accurately measured $A\beta_{1\text{-}42}$
  - Need same for t-tau
- CAMD(Coalition Against Major Diseases) has made a substantial commitment to support use of HV and CSF AD biomarkers in treatment trials
  - Hippocampal volume
  - CSF AD biomarkers
- Close collaboration with Japan ADNI on a joint effort to standardize lab-to-lab method performance of AlzBio3 immunoassay
  - Completed development and testing of a unified test procedure
  - A follow up study now underway for a larger scale assessment in AD and normal CSF samples

Planned Analyses of ADNI CSF Biomarker data
Leslie M. Shaw and John Q. Trojanowski

- Continue systematic documentation of the analytical performance of the AlzBio3 immunoassay and the validated mrm mass spectrometry assay for Aβ42/40/38
- Document the CSF biomarker characteristics in ADNI II subjects to test for replication of these findings in ADNI I
  - Bimodal distribution for Aβ1-42 and mixture modeling for cutpoint determination
  - Incidence of CSF biomarker based pathology across the ADNI subject groups
  - Predictive performance of BASELINE CSF biomarkers for decline in memory, cognition and daily function at 2 years
- Establish the clinical utilities of the qualified mrm/mass spectrometry method for $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-30}$ and ratios of the latter two to $A\beta_{1-42}$
- Assess the potential for new biomarkers to add sensitivity and specificity to CSF $A\beta_{1-42}$, tau and p-tau_{181} for detection of AD neuropathology and add for prediction of progression from MCI to AD dementia, decline of cognition, memory and functions of daily living. **This is an area we expect to expand on and build on for the ADNI III competitive renewal.**

Planned Analyses of ADNI CSF Biomarker data

Longitudinal CSF biomarker data

Characterize the 2 yr trajectories in ADNI II BASELINE + 24 months for AD, LMCI, EMCI, SMC and NC. For those subject trajectories that are “normal” at BASELINE but move significantly toward “pathologic” and those that remain stable normal-test for progression of cog performance over time. Does the progression to “pathologic” CSF biomarker(s) predict or correlate with progression of cog perf over time; does the “stable normal” trajectory predict lack of cog/mem/functional decline?

A. New biomarkers**{natural lead-in to planning analyses for ADNI III}**.

We expect that by the end of 2014 there will have been uploaded on the ADNI website sets of new biomarker data including CSF biomarkers and serum or plasma biomarkers, mostly in ADNI I study subjects. This affords us the opportunity to collaborate with others on the analyses of these data sets including:

1. CSF
    a. VILIP-1 & YKL40
    b. mrm/mass spectrometry (Caprion/FNIH/PPSB/ADNI) study protein/peptides profiles
    c. neurogranin
    d. $A\beta_{1-42}$ oligomers(in collaboration between UPENN ADRC and Mary Savage) using (non-ADNI) UPENN CSF samples in a study that will be planned during summer, 2014.
2. serum or plasma
    a. DDE-a major breakdown product of the insecticide DDT that is highly fat soluble, very long biological half-life, potential risk factor for neurodegeneration. JAMA Neurology 2014
    b. t-tau in plasma

We are very interested to study the relationships of BASELINE values of these new CSF biomarkers to prediction of progression from MCI to AD dementia, and to decline of cognition, memory and functions of daily living and to CSF levels of $A\beta_{1-42}$, t-tau and p-tau_{181}.

It takes a great team effort!

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Uwe Christians
Kaj Blennow
Henrik Zetterberg

Holly Soares
Adam Simon
Robert Dean
Eric Siemers
Piotr Lewczuk
William Potter
Rand Jenkins
Erin Chambers

Supported by the NIH/NIA and families of our patients

*Deceased

ADNI investigators include: (complete listing available at www.loni.ucla.edu\ADNI\Collaboration\ADNI_Manuscript_Citations.pdf).