World Wide Alzheimer's Disease Neuroimaging Initiative
Teleconference Minutes

May 4, 2017
3 pm Australia / 2 pm Japan & South Korea / 1 pm China / 7 am Europe
2 am Argentina / 1:00 am Eastern / 12:00 am Central

May 3, 2017
10:00 pm Pacific

I. **Roll Call and Welcome** Jim Hendrix welcomed the group to the meeting and reviewed the agenda.

II. Progress Updates

a) **NA-ADNI** – Les Shaw
- Mike Weiner was unable to make the call. Instead, Les Shaw, leader of the NA ADNI Biomarker Core, provided an update.
- Les discussed the value of automation in CSF analysis. Automation reduces the number of manual steps while providing the best possible precision and accuracy. It also reduces uncertainty as much as possible within lab and between labs using common samples (i.e. Alzheimer's Association QC program) and improves lot-to-lot performance.
- Between lab performance data was shared from labs participating in the Alzheimer's Association QC program where replicate CSF samples from common pools were shared. The newer assay formats (Elecsys® and Lumipulse®) have shown very good lab-to-lab performance (4-7% variability).
- The second aim for the ADNI3 Biomarker Core is to provide highly standardized $A\beta_{1-42}$, t-tau and p-tau_{181} measurements on all ADNI subject CSF samples using the Roche automated immunoassay platform (Cobas e601) and immunoassay reagents. CSF samples from ADNI1, 2 and GO have been run. Results for $A\beta_{1-42}$ using the three methods (LC-MS/MS, Elecsys®, AlzBio3) were compared and show a linear relationship between LC-MS/MS vs Elecsys®. Clinical performance of the three methods with $A\beta_{1-42}$ shows equivalence. A description of the method and performance for $A\beta_{1-42}$ for the Roche Elecsys® has been published. The technical range is 200 to 1700 pg/mL. In the case of $A\beta_{1-42}$, some were greater than 1700 pg/mL and Roche has provided an extrapolation methodology. In looking at the relationship between Elecsys® and AlzBio3, the p-tau_{181} measurements are very noisy, as expected based on earlier experience with the AlzBio3 test system. Summaries of the CSF concentrations of the three analytes were provided across the study phases (ADNI1, and 2 plus GO) and across disease diagnosis (NL, SMC, eMCI, lMCI and AD). Good agreement is seen across ADNI1 and ADNI2. Cutpoint assessments were made with three different methods, ROC analysis with flurobetapir PET as the endpoint, disease-independent mixture modeling and prediction from BioFINDER. The group then used the cutpoint analyses to predict cognitive decline as reflected by CDR-SB. The t-tau/Ab1-42 and p-tau181/Ab1-42 ratios outperformed Ab1-42 alone for

clinical utilities, a finding also made in the Swedish BioFINDER study using the Roche immunoassay reagents and platform.

- The data that shows the area under the curve for pTau may be consistent with other literature where there seems to be about 20% of people with a clinical presentation of AD and who are amyloid PET positive but who appear to have negative Tau PET scans. Is this a limitation of the biomarkers for Tau or a form of dementia where people have high levels of amyloid but apparently normal levels of Tau? The 20% may be the result of other pathologies such as vascular disease, Lewy Bodies, etc. Les cited a recent summary provided by John Trojanowski where, based on autopsy data, only about 35% of clinically diagnosed AD cases were pure AD (i.e. just amyloid plaques and Tau tangles).

b) AIBL – Chris Rowe

- AIBL was started in 2006 with 2135 subjects with MRI and amyloid PET in 75% of participants. The recruitment of healthy controls has increased in recent years in order to support preclinical treatment trials such as A4. An additional 220 participants with MCI/Mild AD (MMSE >20) were included for clinical trials screening for AIBL. Subjects in AIBL undergo Amyloid PET and MRI at 0, 18, 38 months then every 3 years.
- Tau PET has recently been added and 250 AIBL subjects have been scanned. However, it is unclear which Tau tracer to focus on for use in AIBL. THK-5351 has a great deal of off-target MAO-B binding. The Merck tracer, MK-6240, has also been evaluated but currently the Avid tracer appears to be the best compound. Tau tracer development is still an emerging field and it is still unclear how to get quantitative measure from Tau PET. Avid has recently changed the reference region for their tracer from cerebellum to white matter and AIBL is also experimenting with different reference regions.
- There has been an increasing emphasis on CSF studies with samples from 250 subjects collected. 85 of the 250 have come back for repeat LP's and the numbers of subjects providing CSF samples is expected to increase.
- AIBL is releasing data on LONI/ADNI/AIBL website this month from 6 year time point scans. They are adding amyloid scan classification (positive or negative results) to AIBL data on GAAIN and the florbetaben conversion to centiloids this month. Conversion factors need to be added for each amyloid PET tracers and have been published or will be soon. There is an on-going effort to convert all amyloid PET results to centiloid units. A variety of amyloid PETtracers have been used in AIBL so this effort will help to standardize the way that the data gets expressed.
- Quest for a blood biomarker continues internally and via the supply of AIBL samples to many academic and commercial groups.
- AILB is supporting clinical drug trials in preclinical and prodromal AD and aiming to move this to a wider national platform (A-PAD similar to E-PAD).
- Genetic and lifestyle analysis continues in AIBL.
- AIBL is supporting research on retinal scans (multispectral) with curcumin. Curcumin appears to bind to amyloid in the retina where it can be visualized.

- AIBL is facing the challenge of losing many amyloid positive participants to drug trials, particularly the prevention trials.
- AIBL is increasingly reliant on commercial and philanthropic support with the lowering of government funding.
- Researchers interested in collaborations with AIBL or for more in-depth data access, go to: Christopher Fowler - AIBL Co-ordinator, christopher.fowler@florey.edu.au.

c) Japanese ADNI - Takeshi Iwatsubo

- J-ADNI ran from 2008 to 2014 and the whole database has been made public via the Japanese government. Researchers world-wide can gain access to the data through the homepage of the National Bioscience Database Center (NBDC) with approval of the ethics committee.
- The database includes data from 537 cases in total including imaging and CSF data.
- A network of members to perform co-analysis of the J-ADNI data has been established and includes Laurel Beckett of NA-ADNI. The goal of this group is to write a paper describing the basic characteristics of the J-ADNI population with comparisons to the North American population. The results will be presented in the WW-ADNI meeting in London or at CTAD in November.
- Dr. Ryoko Ihara is the liaison for J-ADNI data and is working to connect the J-ADNI data to GAAIN.
- J-ADNI-2 started in 2013 but was delayed and then was renamed AMED when the study resumed in 2015 with Hiroshi Mori of Osaka City U. as the PI. The study is enrolling cognitively normal individuals including preclinical AD subjects as well as early and late MCI volunteers. Enrollment is just getting started with 3 individuals enrolled so far.
- An Add-On Study is being launched on Tau PET imaging in a pre-clinical population. The Add-On Study is being funded from a gift from an anonymous foundation and the Alzheimer's Association. The study will be conducted in five selected clinical sites using AV1451 in two sites and THK-5351 in three sites on amyloid positive pre-clinical or on MCI individuals.
- The A4 study is starting in one site in Japan. So far one individual has been screen in A4 in Japan.

d) E-ADNI / EPAD / AMY PAD – Giovanni Frisoni

- Giovanni provided and update of EUROPEAN ADNI/PharmaCOG. The project has studied about 150 MCI patients with imaging and CSF collection every 6 months.
- The group has developed an imaging composite measure that can detect disease progression using multiple MR modalities. The composite was compared to the best single outcome measure from MR, the right lateral ventricle. The composite is much more sensitive and one can decrease the sample size in clinical trial up to 70% vs the best single outcome measure. Therefore, a

composite measure would be beneficial for use in clinical trials of disease modifying drug candidates.

- An update on recent publications was provided.
- EPAD (European Prevention of Alzheimer's Dementia) is a multi-center research initiative that aims to create a platform for faster and better assessment of drugs for the prevention of Alzheimer's disease (AD), in people with very early or no symptoms.
- EPAD is establishing a registry of 24,000 subjects from multiple existing cohorts with individuals at risk for AD.
- From the registry, a longitudinal cohort study (LCS) of 6,000 participants who will have cognitive and biomarker assessments. The LCS will be run in an ADNI-like way. In addition, the participants in the LCS will also be a trial-ready cohort where participants can move into therapeutic trials. When the trial is complete, they can move back into the LCS where they could again be eligible for another clinical drug trial if they meet the clinical criteria.
- The LCS will collect biosamples (blood, urine, saliva, CSF), neuroimaging (structural MRI, fMRI), lifestyle and clinical data. A prerequisite for entering the LCS is to consent to LP to collect CSF. Genetic analysis will not be done in EPAD.
- EPAD centers opened for recruitment in July 2016 in 4 sites. So far, about 100 patients per month have been recruited. Five additional sites are about to start recruitment.
- AMYPAD is the amyloid PET sub-study of EPAD so some of the 6,000 participants in the LCS will participate in AMYPAD. AMYPAD is an independent diagnostic and patient management study which is similar to the IDEAS-Study.
- There will be three arms to the study.
    - In arm 1, patients that come to a memory clinic and require a diagnostic work-up will be given an amyloid PET scan early in the process.
    - In arm 2, amyloid PET will come one year after the diagnostic work-up.
    - In aim 3, the physician can chose the appropriate time to utilize amyloid PET or never use it.
- The main aim of the study is to determine the usefulness of amyloid PET if used early or late in the diagnostic work-up.
- The cost of doing amyloid PET early vs late in the diagnostic work-up will also be assessed.
- The first patients are expected to be screened in October 2017.

e) Argentina ADNI - Patricio Chrem

- Patricio provided an update on Arg-ADNI which started in 2012.
- He reported that a cohort of 45 of the 56 subjects with baseline data (CSF Aβ-tau, FDG and PiB PET) have been followed for 30 months. The 30 month visit was completed earlier this year but there has been a high drop-out rate in the study and they are reaching a critical number of participants for statistical analysis.
- The group is considered recruiting more patients but decided to keep the same cohort but to add a 60 month visit.

- They would like to add Tau PET to the 60 month visit but are still negotiating with Avid for access to AV1451. They have the materials to synthesize the tracer but they don't yet have approval to use it in humans.
- So for now, the 60 month visit will have only the clinical assessment (NPS), MRI, and an Alzheimer's cost survey (a socio-economic survey to estimate the cost of AD). So far, five participants have completed the 60 month follow-up visit.
- An update on publications from 2016, 2017 and in progress was provided.

III. Next Meeting – The next meeting is a Face-to-Face meeting and is scheduled for Friday, July 14, 2017 at 1 pm in London, UK prior to the start of AAIC.