WW-ADNI Meeting Attendees

Susan Abushakra
Paul Aisen
Hiroyuki Arai
Takeshi Asada
Lisa Bain
Andrea Baruchin
Martin Bednar
Joanne Bell
Sandra Black
Neil Buckholtz
Leah Burns
Nigel Cairns
Maria Carrillo
Jesse Cedarbaum
Marcia Chaves
Howard Chertkow
Pat Cole
Rod Corriveau
Susan DeSanti
Michael Donohue
Paul Edison
Kathryn Ellis
Nick Fox
Niles Frantz
Giovanni Frisoni
Laura Gault
Serge Gauthier
Robert Green
Barry Greenberg
Salvador Guinjoan
Deb Gustafson
Dean Hartley
David Henley
Carole Ho
Richard Hodes
Takeshi Ikeuchi
Kenji Ishii
Atsushi Iwata
Takeshi Iwatsubo
Cliff Jack
William Jagust
June Kaplow
Florence Keime-Guibert
Zaven Khachaturian
Ara Khachaturian
Ryozo Kuwano
John Lawson
Per Johan Luthman
Lance Macaulay
Ken Marek
Richard Margolin
Colin Masters
Dawn Matthews
Meredith McNeil
Annette Merdes
Mark Mintun
Yi Mo
Shigeo Murayama
Brad Navia
Francois Nicolas
Susanne Ostrowitzki
Robert Paul
Suzana Petanceska
Ron Petersen
Creighton Phelphs
Holly Posner
Harry Ramos
Chris Rowe
Laurie Ryan
Ikuhisa Sawada
Andrew Saykin
Rachel Schindler
Adam Schwarz
Jeff Sevigny
Gustavo Sevlever
Daniel Skovronsky
Heather Snyder
Holly Soares
Diane Stephenson
Morihiro Sugishita
Erika Tarver
Bill Thies
Art Toga
Yukiko Tomoyoshi
Gary Tong
Marni Uger
Jim Vandergriff
Michael Weiner
Meg Yoder
Chantal Bazenet
Andy Simmons
Leslie Shaw
Kuncheng Li
Pachai Chahin
Holly Posner
Rachel Nosheny
Dave Dornsife
Dana Dornsife
Annelys Farrell

Introductions and Welcome

Dr. Maria Carrillo opened the 2012 WW-ADNI meeting at AAIC.

Overview of GO and ANDI2

Dr. Michael Weiner opened the meeting by commenting on successes of ADNI and the open access policy. This is quite unique and has contributed to the success with over 500 manuscripts and 350 published articles. In addition, the pharmaceutical industry has indicated the ADNI data is helpful to simulate trials and design future trials.

The Alzheimer's Association is funding the Global Alzheimer's Association Interactive Network (PIs: Arthur Toga and Giovanni Frisoni) to promote open access, moving to more rapid acceleration for therapies, new ideas, etc. In addition, the Alzheimer's Association along with the Brin Wojicki Foundation funded whole genome sequence of DNA from 800+ subjects enrolled in US ADNI. This is the largest project funded for whole genome sequencing in AD and the raw data will be available for use by the scientific community.

Clinical CORE Update GO and ADNI2

Dr. Ron Petersen provided update on the clinical CORE. For ADNI 2, there are 57 sites operating; 826 people have been screened; 226 screen failures; 297 ADNI 1 continuations. Recruitment for ADNI GO + ADNI 2 includes: 165 individuals for cognitively normal (target = 150); 225 individuals for early MCI (eMCI) (target =300); 116 individuals for late MCI (lMCI) (target= 150); and 50 individuals for AD (target= 150). Target recruitment for each month is approximately 30 individuals.

Of those enrolled, 15 cognitively normal individuals have progressed to MCI; 163 MCI individuals have progressed to AD. There is a 16-20% progression rate from lMCI to AD. In addition, they have expanded the cognitively normal subject group to include individuals that test cognitively normal (CDR 0) and have subjective cognitive concern.

Dr. Paul Aisen discussed the process of revealing cognitive, biomarker, and other information in the context of the spectrum of AD to inform clinical trials and support design of clinical trials.

Three areas of focus – challenges:

(1) How to capture the information in the over 1,000 individuals in ADNI that are artificially stratified in cohorts to design biomarker and clinical trajectories of AD.
(2) Moving from short term follow up to the much longer follow up – most of us believe AD is a 15 year process. When ADNI started, the plan was to follow 2-3 years. As we moved from ADNI 1 to ADNI GO to ADNI 2, we realized we want to follow subjects as long as possible. Now, ADNI 2 is focused on long term follow up. Biggest challenge on analysis front – how to take short term data to create long term disease trajectories. There is the need to collect more longitudinal data.
(3) Missing piece of the puzzle. Mean ages in ADNI across all cohorts is over age 70. However, the brain changes approximately 15 years prior and we need data on individuals in their 50s and 60s. There is a need to test ideas of what risk factors may enrich this population to transition to early biomarker stages of AD to design primary prevention studies in general population.

MRI Update

Dr. Cliff Jack reviewed the MRI protocol. There are three different MRI sequences and vendor specific sequences. The major goal of ADNI 1, ADNI GO and ADNI 2 is to evaluate tenor and structural based MRI accelerated and non-accelerated. Accelerated and non-accelerated are largely equivalent when evaluated eMCI at 6 and 12 months. There is some evidence that accelerated equivalent to non-accelerated, but evidence is not uniform. If these are equivalent techniques, then we could move to

accelerated as these scans take significantly less time. There is reasonable atrophy signal presented at 3 months in all the clinical groups in cognitively normal, eMCI, lMCI and AD groups. The sample sizes for eMCI group at 3 and 6 months ~400 ppl and ~150/200 ppl at 12 months.

The Mayo group looked at grading of ARIA using long TE 2D gradient echo. Each micro-hemorrhage is tracked as individual entity over time. Prevalence of one or more micro-hemorrhage is approximately 25%, increasing with age and AB load. Another study at Mayo, the Mayo Clinical Study of Aging (n=892) analyzed data to determine relationship between fMRI metrics and disease severity. This relationship seems non-linear and non-monotonic. There is more work needed to identify optimal ways to analyze this data in a clinical trial context.

PET Update

Dr. William Jagust shared an update from the PET CORE. There have been 931 baseline scans of FDG-PET in ADNI GO/ ADNI 2. The set threshold is 1.21 which provides an 82% sensitiviey and a 70% specificity for AD verses controls (published: Landau et al, Neurology 2010). They have also done some work comparing tracers by using both tracers in one individual (PIB and Florbetapir; PIB and Flutemetamol). Do not see significant differences, although there are different techniques and slightly different processing methods used. There are robust correlations no matter how the data is processed. Although numerical values can be compared, there are still the possibility of threshold errors (false + and false -). Tracer performance characteristics differ in ways we still do not fully understand. Using Florbetapir and a 1.11 threshold for the ADNI data, 602 scans have been analyzed (another 150 in process) and show 29% cognitively normal are +; 42% eMCI are +; 63% lMCI are +; and 80% AD are +.

Of note, the FDG-PET and AB tracer PET imaging agents do not always agree in their + or – assessment. This requires further study to understand what may be happening in these cases as well as what role ApoE4 may be playing.

Biomarker CORE Update

Dr. Leslie Shaw provided an update. The Biomarker CORE receives and aliquots bio-fluids for ADNI. The batch analysis of ADNI GO and ADNI 2 CSF (n=467; 390 baseline and 77 follow up) in addition to 28 randomly selected replicated samples. There are many eMCI subject CSF samples, smaller numbers of lMCI and early AD. They are using the AlzBio3 immunoassay. In a comparison of 2007 data versus 2012 data, they assessed CSF across concentration range for lot to lot performance. They are continuing this type of assessment to help assess any potential lot to lot variation of reagents. Data from ADNI GO and ADNI 2 CSF are cross sectional data (107 cognitively normal; 192 eMCI; 66 lMCI; 25 AD). The eMCI CSF biomarker values are closer to the cognitively normal group than the lMCI group, consistent with other imaging biomarker findings. apoE4 enrichment (22% normal; 39% eMCI; 53% lMCI; and 58% AD). Qualitatively we see a bimodal distribution in ADNI GO/ ADNI 2 that we saw in ADNI 1. Still more work needs to be done to relate AV45 AB imaging and CSF measures because while they may have differences, they are clearly related and overall very good concordance between the two is shown. The concordance between AV45 as an index of plaque burden and CSF A□1-42 is assessed further using ROC analyses in which the AUC, sensitivity, specificity, PPV, NPV, accuracy and cut point of the each biomarker is determined. AUC values were 0.93, 0.89 and 0.93, respectively for ADNI normal, eMCI and lMCI.

Dr. Shaw also discussed the Alzheimer's Association Global Biomarkers Standardization Consortium's work on developing a candidate reference method for AB1-42. Currently, there is no reference material or method for AB42; however, the worldwide community of investigators have reach consensus that we want reference methods and materials so that when we do the next batch of sample, they are able to be compared to this/ these standard(s).

Publications Update

Dr. Robert Green provided an update from the data and publications committee. This group manages the access to data, approve each and every user, maintains the table of user and their goals; obtain annual renewal for each user; troubleshoot data access for users; manage publication process for ADNI users; reviews for compliance; and track publications. ADNI is a unique experience in open data access. There is consent for sharing for each site and this Committee has gone to each RORR statement to make sure network of information is protected. ADNI averages about 600 applications a year; those we reject are seemingly strange e-mail address and those that do not respond to queries. Data is available in real time (no embargo) and no advantage specific to ADNI investigators. More than 900,000 imaging files downloaded in academic year 2011/2011; 515 publications reviewed; 300 publications published.

Dr. Green also shared more information regarding the whole genome sequencing project (funded by the Alzheimer's Association and the Brin Wojicki Foundation). This will be the largest number of individuals to be sequenced in any single disease related study. There are challenges around analyzing and managing the data and the team is currently assessing.

Genetics CORE Update

Dr. Andrew Saykin provided update on the Genetics CORE of NA-ADNI. The use of ADNI genetic data changes the methodological capability. For instance, FRMD6 – FERM domain-containing protein 6 – was detected in 3 imaging genetic studies (2 ADNI; 1ADNI/ANM) and validated by case-control GWAS. Many of the identified genes play a role in endocytosis, clearance of AB, pathways underlying memory performance, LTP, cell adhesion, neuronal differentiation and outgrowth pathways, inflammation. Other factors that may play a role are gene doses (i.e. copy number variation).

Neuropath CORE Update

Dr. Nigel Cairns provided information on the Neuropath CORE. This CORE provides information, consent in autopsy, collects brain tissue from ADNI participants to correlate autopsy information with biomarker, imaging and genetic studies. The CORE was established in 2007 and has a total of 20 autopsies from the 33 deaths of ADNI participants. In 2011/12, there was a 100% agreement from volunteers to participate. They are seeing concomitant pathology, including TDP43. Of the 20 participants, approximately a third had pure AD and the remainder had mixed pathology. Future studies will be able to assess the contribution of the co-morbid pathologies to variance in biomarker and neuroimaging data.

Biostatistics CORE Update

Dr. Michael Donohue shared an update on this CORE. They are approaching 1,400 baseline. There is a mean change from baseline on several markers; for instance, eMCI is falling in-between cognitively normal and lMCI.

WW-ADNI CORE Presentations

Dr. Maria Carrillo opened the WW-ADNI section of this meeting.

E-ADNI Update

Dr. Giovanni Frisoni updated the efforts of E-ADNI. There are now 8 centers in Europe. For these centers, the MRI reproducibility is in line with literature, including estimation of thickness of cortex in a number of brain areas. The first 20 volunteers for E-ADNI are similar in profile to the pilot E-ADNI and the US-ADNI. Recruitment for E-ADNI began in January and they are seeing an increase in the rate of enrollment in the past few months.

Japan-ADNI

Dr. Takeshi Iwatsubo shared the activities of Japan ADNI. There are 38 sites in Japan, and enrollment is at 150 early AD, 300 MCI, 150 cognitively normal. There seems to be a slightly higher conversion rate

compared with the NA/US ADNI. At 12 months, there is a 29.6% conversion rate (similar to the AIBL group). They are analyzing why there is this difference. In addition, they are analyzing rates of atrophy, PIB amyloid positive imaging (89% AD are +; 71% MCI are + and 21% cognitively normal are +). ApoE4 has a high rate of positivity in the MCI and normal.

There is a correlation between US and J-ADNI data for CSF. In addition, low CSF AB level is a good predictor of conversion from MCI to AD. The initial autopsy was performed; there was a mixed pathology. J-ADNI 1 completed in 2014. They are working on J-ADNI 2 proposal to be submitted this August with a focus on eMCI and lMCI as well as preclinical AD population. The data from J-ADNI will gradually be made available.

AIBL

Dr. Kathryn Ellis, on behalf of the AIBL management team, described updates from AIBL. There are 1,000 volunteers that have been followed through AIBL since 2006. They are using a number of methodologies to collect data at baseline, 18 months and 36 months. This analysis included cognitively normal; subjective memory complainers (smc); mild cognitive impairment (MCI) and Alzheimer's disease (AD). At baseline, there were 372 cognitively normal; 296 smc; 133 MCI and 211 AD. At 18 months, there were 317 cognitively normal; 375 smc; 82 MCI; 197 AD. At 36 months, there were 301 cognitively normal; 309 smc; 55 MCI; 154 AD.

The rate of conversion from cognitively normal to MCI was 2.5% at 18 months and 5.7% at 36 months. In addition, the rate of conversion was 30.5% from MCI to AD at 18 months and 80% at 36 months. The higher conversion rate may be due to the recruitment strategy used. There is also a higher percentage of ApoEe4 in the transition group than in the non-converters and PIB+ (high) group shows a greater rate of decline over 18 months (memory domain – short, long and working memory).

Other ongoing projects including:

- AIBL Active: RCT of physical activity to determine if it is able to delay the progression of white matter hyper intensities in older adults at risk of cognitive decline.
- AIBL WARP: Prospective data from midlife, 3 cognitive time points over 20 years prior. 100 participants seen so far 80% retention from 2002 cognitive test.
- AIBL ROCS: Characterize the cognitive performance of a group of 205 healthy older adults, and adults with MCI, and AD over short test-retest intervals (10 times over 18-months).

Dr. Christopher Rowe gave an overview of the AIBL Imaging components. At baseline, 299 individuals were imaging; 230 at 18 months; and 192 at 36 months. They are targeting all volunteers to be imaged at the 54 month time point. In addition, they are adding new volunteers with MCI and subjective memory complaints. They have done some preliminary data to detect level of PIB positivity: 4% in 50-59 years of age; 12% in 60-69 years of age; 32% in 70-79 years of age; 54% in 80-89 years of age. Dr. Rowe also shared an example of PIB+ individual that did not convert and remained stable six years out. In addition, the atrophy rate over one year in a health control PIB- verses PIB+ is 20% to MCI/AD from cognitively normal and 66% to AD and 14% to non-AD dementia from MCI.

The group used their data to rank various predictors of conversion from cognitively normal to MCI, including hippocampal atrophy, PIB+, composite memory less than 1SD, and combinations of these factors. This preliminary analysis shows that the combination of biomarkers provides the best prediction.

Canada ADNI

Dr. Sandra Black gave an overview of Canada ADNI, a component of North America (NA) ADNI. The CIHR funded the Canadian part of NA-ADNI. Part of the CIHR roadmap is the International Collaborative Research Strategy for Alzheimer's Disease, as well as many other international initiatives

with the UK, France, China. For Canada ADNI, CIHR funded five sites that joined ADNI 2. There were regulatory issues that delayed the enrollment; competitive enrollment has now started. In addition, there is a Canadian trail being planned using ADNI protocols to assess stroke patients and small vessel disease.

China-ADNI

Dr. Li provided an overview of China ADNI. They plan to enroll 800-1000 individuals including cognitively normal, eMCI, lMCI and AD (approx. 200-250 each group). The PIs of the group are Drs Kuncheng Li, Jun Wang and Hongzheng Wang. They have organized seven cores – clinical, MRI, PET, pathology, Biomarker and Genetics, Biostatistics and Informatics, Data Post process. They are in recruitment of phase I (50 per group). They have completed the training and qualification of researchers in the clinical core, as well as the validation of tests in Chinese language. They have tested the phantom of PET and MRI and the ADNI PET data flow has been established.

Dr. Li also updated the status of the funding for China ADNI. The following funds have been committed including: research funds from Beijing Municipal Science and Technology Committee, 500,000RMB, and funds from National Science and Technology Support Program, 3 million. Additional funds include: Neuroimaging studies – Ministry of Science and Technology – 5 million RMB and funds to establish evaluation study of preclinical stage and early AD – Ministry of Health – 3.6 million

Argentina-ADNI

Dr. Gustavo Sevlever updated the progress of Argentina ADNI. In February, the Argentine ministry agreed for the Argentina ADNI to proceed. They will recruit adults age 55-70. The IRB has been approved and recruitment has started. In addition, the neurocognitive and clinical MCI/AD evaluation are in place; lumbar puncture protocols and CSF evaluation are in place; and the phantom is in place. There have been some issues in access to Florbetapir being worked through. Logistics set up is complete. There was quite a bit of media in the national press regarding Argentina ADNI establishment.

Recruitment is at 25% of planned target (n=15). ApoEe4 distribution in the Argentine population is approximately 5.7% ApoEe4 positive.

AddNeuroMed

Drs Chantal Bazenet & Andy Simmons presented on the AddNeuroMed initiatives. Dr. Bazenet updates the plasma biomarker study. There are 6 European sites, compatible with the US ADNI study. There are 716 subjects (259 AD; 225 MCI; 232 cognitively normal). In addition, 385 subjects are undergoing imaging (133 AD; 134 MCI; and 118 cognitively normal). The goal is combine blood biomarker data with imaging to derive multimodal biomarker signature. Two studies are on-going (candidate based and discovery based). Candidate based investigating cytokines and complement proteins. Discovery based includes 45 protein candidates for over 1,000 ppl in a classification study. Future studies will look at PIB-PET measures and CSF Abeta/tau ratios using various proteomic measures.

AddNeuroMed initiatives are tapping into the power of large diverse datasets within the European Medical Information Framework on over 40 million patients; AD research on 10 times more subjects than ADNI; linking clinical and omics data. The EMIF-platform is developing a platform for evaluating and enhancing access to human health data across Europe and support for specific topics of research (i.e. identify predictors of AD).

Dr. Simmons provided an update on the imaging studies. They are pooling together imaging datasets including ADNI 1 and ADNI 2; AIBL; London cohort (200 ppl); memory clinics (500 ppl); some studies have 2000 young controls = for a total of 4,000 individuals in the larger dataset. There is a small amount of funding to make this information publically available. They are currently using multivariate analysis to

look to distinguish between various groups – OPLS, regional cortical thickness measures, regional MRI volumes, etc.

Industry Perspective of WW-ADNI

The ADNI PPSB chair, Dr. Johan Luthman from Merck, gave an update on the industry perspective of WW-ADNI. The ADNI PPSB participates in an independent, pre-competitive forum for study-related scientific exchange among partners. They hold two face-to-face meetings (November and April, during AAN). In addition, there are ADNI Core discussions and working groups of topics that group decides need further discussion. The ADNI PPSB forum has enabled collaborations with each other, with Alzheimer's Association, CAMD, etc. To date, the private partnerships have contributed $45M to NA-ADNI as well as to J-ADNI, Pharm-Cog, etc. However, there are challenges for industry to participate across WW-ADNI initiatives – such as consortium fatigue with engagement both $$ and people cost with efforts around the world. There is a redefinition of disease stages and at least one company has moved to prodromal/ pre-dementia clinical trials. There are technical challenges, however, it can be done and many want to move ultimately to preclinical AD for primary or secondary prevention.

In addition, there is a need for the early development of determinants that a drug is doing its job and support of label claims. The PPSB has developed several work groups (i.e. Biofluid/biomarker working group – supplementary effort ot the AA GBSC, CAMD, etc.; Plasma Proteomics project; AB as a Biomarker working group; CSF targeted proteomic; Informatics working group (formerly database working group); PET Imaging endpoints; NPS and ADAS Cog PLUS working group; and Clinical End Points working group).

The PPSB is incredibly valuable because although originally formed because of ADNI, they are now addressing issues beyond the ADNI project with companies working together in pre-competitive space.

Korean ADNI

On behalf of the Korean ADNI team (Dr. Seol Hee Han and Dr. Duk Na), Dr. Seong Yoon Kim presented an update of the Korean ADNI efforts. Korean ADNI is planning to recruit 500 volunteers (100 normals; 100 MCI; 100 mild to moderate dementia; 100 severe dementia volunteers; and also inclusion of subcortical ischemic vascular dementia and its pre-dementia state). There are several infrastructures pieces including national dementia working group and two of the larger dementia groups CRCD (clinical research centers for dementia) – 31 centers – and KLoSCAD (Korean Longitudinal Study on Cognitive Aging and Dementia) – 18 centers. The timeline is to develop infrastructure of year 1; recruit volunteers for year 2 and 3; and follow up in year 3+. The research funding is an annual budget of $1.8M/year. Government is supporting 50-75% of year 1 for setup.

Taiwan ADNI

A representative was unable to join the meeting however, it is important to note that the Taiwan ADNI is also under development.

PPMI

Dr. Ken Marek shared and update on the PPMI (Parkinson's Progression Markers Initiative) regarding the focus on biomarker discovery and validation in PD. Like ADNI, LONI supports the PPMI data. The predominant funder of the PPMI is MJ Fox Foundation; however, there are also many industry representatives. The PPMI set-up is similar to ADNI. They restricted the number of sites to standardized acquisition to 25 sites; 19 in the US; 5 sites in Europe; and 1 in Australia. To volunteer, an individual must have an abnormal imaging scan. CSF is acquired at baseline and 6 months, 1 year, and yearly. The

data is publically available. To date, there are 430 ppl enrolled (target is 600). Enrollment breakout is 239 PD; 154 HS; 35 SW. They are working to incorporate pre-motor PD.

Global Alzheimer's Association Interactive Network (GAAIN)

Dr. Arthur Toga described GAAIN, emphasizing the role that centralized projects can play in global, collaborative projects. GAAIN will create method to federate data – mechanism to honor philosophy of open access, honors stipulation of network of data availability around the world. Because of the disease complexity, AD clearly requires expertise across the entire spectrum of disease. In addition, GAAIN is a federated network; the user experience allows individuals to come to a single portal to come together in different ways and have fundamental ways of sharing data. This will allow anybody anywhere to access any data anywhere - - however, there are still rules and we need to develop technology to achieve those rules. GAAIN will utilize a cloud enabled infrastructure to take advantage of computers and storage that may live in other places. There is a Scientific Advisory Board (SAB) that includes representatives from Google, Intel, GE Healthcare.

Dr. Toga also recognized the challenges of a federated network including: subject privacy across international borders; complexity from cross-disciplinary data collection and analysis; and need to create robust and compelling tools to search, visualize and share federated data. Language and common terms (semantics and ontologies) will be utilized.

Close Out

Chief Medical and Scientific Officer, Dr. Bill Thies officially closed the meeting by thanking the Alzheimer's field for their commitment to getting ADNI effort underway, as well as the committed donors of the Alzheimer's Association who help make these types of efforts possible.