July 15, 2011

# Minutes from World-Wide ADNI Meeting; Paris, France

## Attendees:

Hiroyuki Arai
TakashiAsada
AndreaBaruchin
LaurelBeckett
Martin Bednar
LuisellaBocchio
RobertBrashear
David Brooks
LenaBrynne
SamanthaBudd
Nigel Cairns
ScottCampbell
Maria Carrillo
SophiaClaudel
PatCole
SusanDeSanti
PeggyDiab
MichaelDonohue
Alison Drone
PaulEdison
MichaelEgan
Nick Fox
Karl Friedl
Giovani Frisoni
Kim Gallagher
Devon Gessert
Ana Graf
RobertGreen
XioTing Guan
SalvadorGuinjoan
DebGustafson
Arne Hengerer
RichardHodes
KengoIto
Hirotaki Ito
Takeshiiwastsubo
Dani Jachino
Clifford Jack
William Jagust
GusJimenez
Yves,Joanette
FlorenceKeime-Guibert
GunnarKrueger
RyozoKuwano
JessicaLangbaum
John Lawson
Chi-Ming Lee
KungchengLi
JiHui Li
Leslie Liedtke
CK Liu
Enchi Liu
CristinaLopez
Ken Marek
Colin Masters
Yoshifumi Maya
MeredithMcNeil
AnnetteMerdes
AndrewMilner
Mark Mintun

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| Mikhail Ugrumov | Michael Weiner |
| Hugo Vanderstichele | Mark Weinstein |
| Laura Vernoux | Dirk Wouters |
| Jack Watters | Yan Zhang |

# ADNI Updates

Scott Campbell , President and CEO of the FNIH, welcomed all attendees and thank you to those who contribute to the ADNI endeavor. ADNI is one of the premier activities of FNIH.

**ADNI, ADNI Go, ADNI 2 Overview (Michael Weiner)**

Mike gave overview of the ADNI, ADNI Go and ADNI 2 activities:

- Susanne Mueller from USCF received AA Funding to perform hippocampal sub field analysis in ADNI 2. Will be incorporated into 26 sites.
- WMH – reasonable longitudinal consistency
- DTI – reasonable correlation with age, longitudinal consistency
- ASL – reasonable initial results; made changes to the ASL sequence in January 2010 to adjust timing parameters and add a product phase map.
- Resting state fMRI
    - Became aware of an issue regarding fat aliasing does not appear to be significant – working in conjunction with Phillips. Made changes to increase SI coverage to 159 mm (now 7 minutes). Distributed in April 2011.
    - Reasonable initial results

**PET Core (Bill Jagust)**

Major accomplishments – F18 florbetapir add on

For PET, there are two mechanisms to look at processing free surfer processing (automatic, in native space) and SPM processing (template for region of interest).

- Review of data for the comparison between these methods – not significant differences, conversion possible
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and AlzBio3) are similar – both comparative in predicting amyloid plaque buildup in brain).

- Incorporated automatic processing (up to 17 steps) – contributed to reproducibility
- Evidence in plasma about what is in brain and modest correlation between CSF Aβ42 and Aβ1-40. There are other sources of AB in the circulation, so still pending whether this is useful biomarker.
- Summer-fall, 2011:
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- Maintain table of users and their goals (allows identification of users, collaborators, etc)
- Annual renewal for each user
- Trouble shoot data access for users
- Require minimalistic review of publications for ADNI data – ADNI investigators acknowledgement in authorship (one issues is the NLM adds all ADNI investigators to the authorship in PubMed)
- Track all publications
    - 2,463 investigators; 1,802 requests for data; 154 denied
    - On-going growth in image downloads – other data, over 90,000 downloads
    - 352 manuscripts utilized ADNI data (199 published)
    - In independent search, found 50 not submitted through Committee – 13 compliant; 37 non-compliant
- What if anything should researchers be sharing with their subjects/ patients/ individuals regarding the on-going findings
    - Return of incidental findings from research is a hot topic – forming a workgroup in ADNI to look at this issue.

**Neuropathology Core Update (Nigel Cairns):**

To date, 131 deaths of ADNI subjects (9/1/2005 through 2/1/2011); 113 autopsies – the core was not in establishment at beginning, reflecting discrepancy

- Diagnostic accuracy of cases that have come to autopsy is 100% accurate – AD pathology at autopsy;
- In addition to amyloid and tau, other pathologies are present: most commonly alpha synuclein and Lewy Body Dementia. Two other pathologies – Hippocampal Sclerosis present; Argyrophilic Grain Disease (4R Tauopathy)
- 40% of cases have co-existing LB pathology

**Biostatistics Core Update (Michael Donohue):**

Overview of the Biostatics core activities since April ADNI meeting:

- Many biomarkers predict rate of decline, when looked at individually. When you take into account baseline cognitivie and functional performance, individual biomarkers add somewhat less:
    - In MCI, hippocampal volume, Tau and Tau/Abeta
    - In AD, hippocampal volume, FDG PET ROI, Abeta, Tau/Abeta
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Informatics Core: neuGRID – unprecedented data management. At this year's AAIC 2011, t
first study where three datasets have been used together will be presented. In the coming years,
we will have significant increase in the number of images and data available. Vision of a cloud
network to allow for integration and migration of data from neuGrid, Canarie, LONI will be
known as OutGrid. This is not going to be enough.

- In silico identification for potential markers for AD – looks through literature to identify published descriptions of proteins or factors that may be linked to potential AD - candidate biomarker = not associated with MMSE but highly significantly correlated to baseline of AD.
- Next steps – RNA analysis studies, continuing collaborations with ADNI, proteomic studies, vitamin E forms, combined imaging-omics MCI conversion

**C-ADNI Update (Kuncheng Li)**
Update on progress on the C-ADNI set up. The Advisory Committee is established. Clinical core includes neurologists, psychologists and geriatricians from five hospitals in Beijing area constitute the clinical core. Currently, working on the training of standard operating procedure and workflow, especially the battery of Neuropsychological examinations.
Recruitment will included four types of new subjects – cognitively normal, eMCI, late MCI, AD Groups will be recruited accordingly:

- Cognitive normal and eMCI recruited from community investigation of epidemiological research
- Late MCI and AD recruited from memory clinical at the Dept of Neurology, Psychiatry and Geriatrics

MRI and PET core are in process of being established. PET scan will be completed in one site.
Funds – funds from the Sciences and Technology Committee of Beijing to initiate the project in Dec2010. The group is preparing to apply for more funding from the Chinese government.

**K-ADNI (Duk NA)**
Korea was unable to participate.

**Arg-ADNI (Silvia Vazquez)**
FLENI organization – on 2/7/11, the Argentine Ministry of Science agreed to the support of Argentina ADNI and create and support future national initiatives. They are proposing to establish initiative in Buenos Aires. Goal is to recruit 60 Argentine adults age 55-90 (inclusive) over 3 year period – 15 MCI, 15 normal, 20 AD

**T-ADNI (CK Liu)**
Start from north Taiwan with 6 medical centers. Starting work for three-year longitudinal study – neuropsychological tests, biomarkers (blood, apoe, amyloid, tau, csf) imaging. MRI/ Neuroimaging Core – DTI, RSFC, MRS, SWI and 3D 1.5T and 3T imaging – will not only include current measures, but additional measures for imaging techniques. Will have on-going training workshops to standardize neuropsychological tests (may and august, 2011) procedures, as well as standardized procedure manual.

**Industry Perspective of WW-ADNI (Enchi Liu)**
Enchi Liu is this year's PPSB Chair and is representing this group.

Who is the PPSB: Collaborate with ADNI2 Steering and Executive Committees and core leader. Identify areas of gaps: database working group; PET imaging endpoints; and AB as a Biomarker working groups.

Major hurdles facing AD Drug development:

- Is it the target? Is it the mechanism? Is it the clinical trial design? Other
- Clinical trial design for disease modifying therapeutics is difficult – importance of standardization.

Examples of collaborations – PPSB collaborations with ADNI cores in discussion or ongoing; Biomarkers Consortium ADNI Plasma Proteomics Project, etc.

ADNI has some "unexpected" benefits – the ability to understand shifts in AD disease progression and placebo response over time; more regularly attention to Alzheimer's disease (FDA and EMA); engagement of the global community; and a sense of shared responsibility in understanding AD etiology, improving clinical trial methodology and helping patients (unprecedented level of cooperation and engagement between industry, academic, and federal sectors in the US as well as other countries).

Future directions:

- ADNI Go and ADNI 2– inclusion of more patients in the eMCI and late MCI to help us understand this disease in the earlier sections of the continuum.
- Treatment earlier in disease continuum: parallel thinking of the field and the industry (i.e. two companies in early trials – BMS and Roche)
- Individual patient vs group prognosis – utility in clinical practice as well as for drug development in the pre-symptomatic phases

Remaining Gaps:

- Drug development tools
  - Need to be able to monitor disease in the earlier stages
  - Clinical scales
- Biomarkers
  - Need to align with regulatory agencies regarding use of biomarkers for clinical use
  - Lack of F18 amyloid imaging acceptance to use in patient sectors
- Other
  - Address emerging safety issues
  - Need for common data base

**PPMI (Ken Marek)**

Parkinson's Progression Marker Initiative (PPMI) – another example of an initiative spawned by ADNI. Asks audience to think about ways PPMI may help to inform ADNI and vice versa, based on patient population.

- Study was developed by the Scientific Advisory Board of the MJ Fox Foundation (primary sponsor) – collaboration of academic, industry and government advisees
- Identify cohort of individuals and focus on standardization of data collection/ analysis, and ensure data available and open to the community.
- Project design is similar to ADNI format – LONI houses the database (similar to ADNI)
- Commitment to making data and biospecimens available
- 400 subjects with PD and 200 age matched controls to be evaluated over 4 years (Cognition, behavioral, autonomic – i.e. constipation, bladder, sexual, cardiac, olfaction,

sleep, Motor analysis, imaging, biologicals, RNA profiling, and genetics – alpha synuclein, LRRK2, tau, DJ1

- Validating biochemical markers (tau, alpha synuclein, LRRK2, tau, DJ1, and amyloid beta).
- Enrollment ongoing. 21 sites (16 in US and 5 in Europe) and will be developing 3 sites in Australia. Unlike ADNI, all recruit under same protocol and send info to the same repositories.

**Discussion**

Success of all we have heard has led to a persistence movement forward despite the economy,