ALZHEIMER’S DISEASE NEUROIMAGING INITIATIVE

November, 2011
Neil Buckholtz, Ph.D.
National Institute on Aging/NIH
NEED FOR VALIDATED BIOMARKERS FOR AD TRIALS

• Biomarkers useful in Phase 2 to make decisions about Phase 3 (e.g. doses)

• Biomarkers useful in Phase 3
  – Provide additional evidence to support primary outcome findings
  – Provide evidence for “disease modification” and not simply symptomatic improvement
GOALS OF THE ADNI: LONGITUDINAL MULTI-SITE OBSERVATIONAL STUDY

• Major goal is collection of data and samples to establish a brain imaging, biomarker, and clinical database in order to identify the best markers for following disease progression and monitoring treatment response
• Determine the optimum methods for acquiring, processing, and distributing images and biomarkers in conjunction with clinical and neuropsychological data in a multi-site context
• “Validate” imaging and biomarker data by correlating with neuropsychological and clinical data.
• Rapid public access of all data and access to samples
Mild Cognitive Impairment

Normal  MCI  AD

ADNI 2  ADNI 1
(EMCI)  (LMCI)

0  0.5  1

CDR
New Diagnostic Criteria

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on workgroups on diagnostic guidelines for Alzheimer's disease.


• MCI (n= 400): 0, 6, 12, 18, 24, 36 months
• AD (n= 200): 0, 6, 12, 24 months
• Controls (n= 200): 0, 6, 12, 24, 36 months
• Clinical/neuropsychological evaluations, MRI (1.5 T) at all time points
• FDG PET at all time points in 50%
• 3 T MRI at all time points in 25%
• PIB sub-study on 120 subjects
• Blood and urine at all time points from all subjects; CSF from 50% of subjects 0, 1 yr, 2 yr (subset); DNA and immortalized cell lines from all subjects
• GWAS study
ADNI 2 Private Partner Scientific Board
23 companies, 1 government entity and 2 non-profit organizations
Data and Sample Sharing

• Goal is rapid public access of *all raw and processed data*
• Central repository for all QA’d MRI and PET [Laboratory of Neuroimaging, UCLA (LONI)]
• Clinical data base at UCSD is linked to LONI
• Databases- in the public domain, available to all qualified investigators
• Sample sharing-Resource Allocation Review Committee
• No special access
• Data Sharing & Publication Committee (DPC)
  -ADNI Data Use Agreement
## ADNI Demographics

<table>
<thead>
<tr>
<th></th>
<th>Normal controls (n=229)</th>
<th>MCI (n=398)</th>
<th>AD (n=192)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>76.4 (5.0)</td>
<td>75.3 (7.5)</td>
<td>75.8 (7.4)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>48.0</td>
<td>35.4</td>
<td>47.4</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Years of education, mean (SD)</strong></td>
<td>15.6 (3.1)</td>
<td>16.0 (2.9)</td>
<td>14.7 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Apolipoprotein E e4: Positive (%)</strong></td>
<td>26.6</td>
<td>53.5</td>
<td>65.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Subject Evaluation

- Baseline/screening eval and q 6 mo.
  - Labs, Apo E
  - Hamilton(S)
  - Beck
  - MMSE
  - ANART
  - ADAS-cog
  - NPI
  - CDR
  - ADL

- Neuropsyc(B and q 6 mo)
  - Logical Memory(S)
  - AVLT
  - BNT
  - Trails A &B
  - Symbol digit
  - Clock drawing
  - Category fluency
ADAS Cog 11
MMSE

AD
NL
MCI

Mean MMSCORE (95% CI)

0 5 10 15 20 25
Month

0 5 10 15 20 25
Months

0 5 10 15 20 25

MMSCORE

0 5 10 15 20 25

Mean MMSCORE (95% CI)
## ADNI Progression Rates

<table>
<thead>
<tr>
<th>Year</th>
<th>Normal $\rightarrow$ MCI</th>
<th>MCI $\rightarrow$ AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1.4% (0.0-3.2)</td>
<td>16.0% (11.3-20.4)</td>
</tr>
<tr>
<td>1-2</td>
<td>2.4% (0.0-4.7)</td>
<td>23.9% (19.0-29.5)</td>
</tr>
<tr>
<td>2-3</td>
<td>0.0% (0.0-3.4)</td>
<td>9.1% (5.8-13.5)</td>
</tr>
</tbody>
</table>
Mean Cortical Thickness Change (over 12 months)

Diagnosed as AD

Diagnosed as NC

Lateral View

Medial View
Statistical ROI’s of 12-Month CMRgl Decline
ADNI 1 Baseline PIB data (N=101)

Mean Cortical SUVR

Cutoff > 1.46
PIB+
(Berkeley Data)

Normals 9/19 (47%)  MCI 47/63 (68%)  AD 17/19 (89%)
PIB+  PIB+  PIB+
Follow-Up of PIB-Positive ADNI MCI’s

ADNI PiB MCI’s
N = 65, 12 mo. follow-up

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PiB(-)</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Converters to AD</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>PiB(+)</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Converters to AD</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>
ADNI BASELINE CSF biomarker concentrations show the expected average differences between AD and MCI and NC

<table>
<thead>
<tr>
<th></th>
<th>Tau</th>
<th>Aβ&lt;sub&gt;1-42&lt;/sub&gt;</th>
<th>P-Tau&lt;sub&gt;181P&lt;/sub&gt;</th>
<th>Tau/Aβ&lt;sub&gt;1-42&lt;/sub&gt;</th>
<th>P-Tau&lt;sub&gt;181P&lt;/sub&gt;/Aβ&lt;sub&gt;1-42&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD (n=102)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>122±58</td>
<td>143±41</td>
<td>42±20</td>
<td>0.9±0.5</td>
<td>0.3±0.2</td>
</tr>
<tr>
<td><strong>MCI (n=200)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>103±61</td>
<td>164±55</td>
<td>35±18</td>
<td>0.8±0.6</td>
<td>0.3±0.2</td>
</tr>
<tr>
<td><strong>NC (n=114)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>70±30</td>
<td>206±55</td>
<td>25±15</td>
<td>0.4±0.3</td>
<td>0.1±0.1</td>
</tr>
</tbody>
</table>

p<0.0001, for each of the 5 biomarker tests for AD vs NC and for MCI vs NC. For AD vs MCI:p<0.005, Tau; p<0.01, Aβ<sub>1-42</sub>; p<0.01, P-Tau<sub>181P</sub>; p<0.0005, Tau/Aβ<sub>1-42</sub>; p<0.005, P-Tau<sub>181P</sub>/Aβ<sub>1-42</sub>. Mann-Whitney test for statistical differences used for these non-normally distributed data sets.
Ab$_{1-42}$ concentrations in CSF, collected at the baseline visit, of 37 ADNI MCI subjects who at their one year visit converted to a diagnosis of probable AD. The data points for the MCI→AD converters are presented as a horizontal dot plot with the x axis scale identical to that of the Ab$_{1-42}$ frequency plot for the entire ADNI MCI group. The vertical line indicates the Ab$_{1-42}$ cutoff concentration obtained from ROC analysis of an ADNI-independent cohort of autopsy-based AD subjects’ CSF.
**GOAL:** Leverage ADNI Plasma and CSF samples to assess the utility of existing AD biomarker panels studies.

**PLASMA STUDY:**
- Baseline and 1 year ADNI plasma samples analyzed using RBM190 analyte multiplex immunoassay platform (Luminex xMAP) containing proteins previously reported in the literature to be altered as a result of cancer, cardiovascular disease, metabolic disorders, inflammation, Alzheimer’s disease
- All data posted to ADNI website and available as of Nov, 2010
- Project Team - completed statistical analyses; finalizing manuscript

**CSF STUDY:**
- ADNI CSF samples to be sent to RBM for analysis (July, 2011)
- Additional studies planned to to qualify a Multiple Reaction Monitoring (MRM) Mass Spectrometry panel and to examine Beta-Site APP Cleaving Enzyme (BACE-1) levels and enzymatic activity in CSF.
Hippocampal atrophy rates (L+R) – free surfer data – in ADNI subjects with CSF $A\beta_{1-42} > 192$ pg/mL or <192 pg/mL

These data show that in ADNI AD, MCI and NC subjects the rate of hippocampal atrophy increases at a significantly higher rate in subjects with $A\beta_{1-42} < 192$ pg/mL cutoff concentration compared to those >192 pg/mL.
<table>
<thead>
<tr>
<th>Test</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>803</td>
</tr>
<tr>
<td>RAVLT</td>
<td>607</td>
</tr>
<tr>
<td>ADAS</td>
<td>592</td>
</tr>
<tr>
<td>CDR SOB</td>
<td>449</td>
</tr>
</tbody>
</table>
### 1.5T MRI Comparisons - AD (n=69)

<table>
<thead>
<tr>
<th>Lab</th>
<th>Variable</th>
<th>SS/arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander</td>
<td>L. Hippo. Formation</td>
<td>334</td>
</tr>
<tr>
<td>Dale</td>
<td>Whole Brain</td>
<td>207</td>
</tr>
<tr>
<td>Schuff - FS</td>
<td>Hippocampus</td>
<td>201</td>
</tr>
<tr>
<td>Dale</td>
<td>Ventricles</td>
<td>132</td>
</tr>
<tr>
<td>Dale</td>
<td>Hippocampus</td>
<td>126</td>
</tr>
<tr>
<td>Studholme</td>
<td>Temporal lobe % change</td>
<td>123</td>
</tr>
<tr>
<td>Schuff - FS</td>
<td>Ventricles</td>
<td>119</td>
</tr>
<tr>
<td>Studhome</td>
<td>CV - % change</td>
<td>106</td>
</tr>
<tr>
<td>Fox</td>
<td>VBSI % change</td>
<td>105</td>
</tr>
<tr>
<td>Fox</td>
<td>BSI % change</td>
<td>71</td>
</tr>
<tr>
<td>Thompson</td>
<td>CV - % change</td>
<td>54</td>
</tr>
</tbody>
</table>
ADNI Genotyping

• Initial goal: high density genome wide scan
  – Identified major microarray platforms for GWAS
    • Compared marker selection strategies, HapMap coverage of genome, performance & reliability, as well as cost/sample
      – Illumina platform was selected by consensus of the Genetics Committee & ISAB for this project
      – TGen (Phoenix, AZ) was selected to perform the assays
      – Illumina Human 610-Quad
Shen et al 2010: Overview

Baseline MRI Scans
- FreeSurfer: 56 volume or cortical thickness measures
- VBM: 86 GM density measures

QC’ed genotyping data
- 530,992 SNPs
- 142 QTs

GWAS of Imaging Phenotypes
- Strong associations represented by heat maps

GWAS of candidate QT

VBM of candidate SNP

Refined modeling of candidate association
Conclusion: Imaging Gene Discovery

Gene Identification with Imaging “Deep Phenotypes”: GWAS

Structural MRI + 600k SNPs = GRIN2b as Novel Risk Factor for MTL deficits in Alzheimers

Stein et al 2010; ADNI
Survival Plot for MCI to AD Conversion by APOE Genotype (comparing ε4 negative to ε4 positive)

- **APOE4 Genotype**
  - e4- (blue line)
  - e4+ (red line)

- **n = 363**
  - (163 MCI-C, 200 MCI-S)

- **Overall: p < 0.001***
  - *Using Cox Regression (covaried for baseline age)

- **163 MCI-C** (50 ε4 negative, 113 ε4 positive)
- **200 MCI-S** (112 ε4 negative, 88 ε4 positive)

*Updated as of 3/29/11, S. Risacher*
ADNI Genetics: Next Steps

- ADNI-GO/2
  - Ongoing DNA, RNA, cell line sample collection
  - Planning for genotyping of new samples
- ADNI-1 data analysis
  - Baseline and rate of change
  - Copy number variation
  - Candidate genes & pathways, GWAS approaches
  - Associations with PET & CSF/plasma biomarkers
  - Collaborative projects, replication, other cohorts
- Future:
  - Targeted DNA and RNA resequencing – identify key regions for intensive scrutiny
  - Epistasis, Transcriptomics/expression, microRNA
  - Epigenomics (DNA methylation, etc)
AD Progression

- CSF Aβ42
- Amyloid imaging
- CSF tau
- Cog
- FDG-PET
- MRI hipp
- Fxn

Time:
- Pre-Symptomatic
- eMCI
- lMCI
- Dementia

Abnormal vs. Normal

Legend:
- CSF abeta42
- FDG PET
- MRI Hippocampal Volume
- CSF Tau
- Cognitive Performance
- Function (ADL)
Continue to follow all EMCI, LMCI and NC from ADNI 1 and ADNI GO for 5 more years

Enroll:
- 100 additional EMCI (supplements 200 from GO)
- 150 new controls, LMCI, and AD

3T MRI at 3, 6, months and annually

F18 amyloid (AV-45)/FDG every other year

LP on 100% of subjects at enrollment

Genetics
Summary: ADNI

- **Standardization**: imaging, biomarkers
- **Neuroscience**: relationships among biomarker trajectories elucidate neurobiology
- **Trials**: new understanding of biomarkers has facilitated interventional studies in very early AD
- **Data sharing**: ADNI has demonstrated the power of real-time public data sharing
- **Collaboration**: academia, industry, non-profits, regulatory agencies world-wide
ADNI Data and Publications Committee: Key Charges

- Creation and revisions as needed or data application and publication policy
- Approval of data applications
- Review and standardization of manuscripts - administrative review
## ADNI Data Applications

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Applications</td>
<td>1,590</td>
</tr>
<tr>
<td>Initially Approved</td>
<td>1,463</td>
</tr>
<tr>
<td>Challenged</td>
<td>127</td>
</tr>
</tbody>
</table>
ADNI Data Applications

Challenged Applications (127)

- 113 Asked to clarify
- 14 Nonsense users
ADNI Data Applications by Sector (cumulative)
Countries with ADNI Data Applicants

- Countries with ADNI data use applicants
- New countries since last meeting
ADNI Manuscripts

305 manuscripts utilized ADNI data

<table>
<thead>
<tr>
<th>Status</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Published</td>
<td>175</td>
</tr>
<tr>
<td>Epub ahead of print</td>
<td>26</td>
</tr>
<tr>
<td>In Press</td>
<td>3</td>
</tr>
<tr>
<td>Under revision</td>
<td>10</td>
</tr>
<tr>
<td>In submission</td>
<td>86</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>2</td>
</tr>
<tr>
<td>Under review by ADNI</td>
<td>3</td>
</tr>
</tbody>
</table>
Data Archived and Downloaded

- 140,000 images archived (raw and processed)
- 1.2 million image downloads
- 90,000 downloads of non-image data (clinical, genetic, proteomic, summary) from 36 countries
Websites Maintained by LONI with Input from DPC

REVISED DATA USE AGREEMENT:

PUBLICATION POLICY:

ACTIVE ADNI INVESTIGATORS WITH KEYWORDS:
http://adni.loni.ucla.edu/research/active-investigators/

PUBLICATIONS:
http://adni.loni.ucla.edu/publications/
ADNI as a model for other diseases

- Parkinson’s disease
- FTD
Manuscript Submission Procedure

1. Manuscript submitted to DPC
2. Administrative review conducted
3. Compliant papers sent to individual DPC members for quality review
4. Revised paper re-submitted to DPC
5. DPC emails author with review results
6. Non-Compliant returned to author for revisions