Alzheimer’s Disease Research Update

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Disclosures

- **Financial Support**
  - Research
    - NIMH: Improving Antipsychotic Appropriateness in Dementia Patients
      ARRA: PI - Carnahan R18 HS019355-01
    - NIMH: Combined Illness Management: PI - Turvey 1R01MH086482
    - NIA: Alzheimer’s Disease Neuroimaging Initiative-2 National Institute of Health/NIA, 3U01 AG024904 PI: Weiner
    - NIA: The Alzheimer’s Disease Cooperative Study; Baxter Healthcare; Placebo Controlled Study of intravenous 10% IGIV for AD.
    - Nellie Ball Trust Fund- PIB imaging in Schizophrenia
  - Other
    - Iowa Geriatric Education Center HRSA
    - CCOM UI Center on Aging
    - American Psychiatric Association
      - DSM-5
      - American Journal of Psychiatry
Unraveling the Mystery

- What is Alzheimer’s disease (AD)?
  - Dementia or Alzheimer’s?
  - Alzheimer’s Disease and Alzheimer’s Dementia?
- AD and the Brain: New Biomarkers
- AD Research
  - Alzheimer’s Disease Neuroimaging Initiative
A cooperative agreement between the National Institute on Aging (NIA) and UCSD

To advance the development of drugs for Alzheimer's disease (AD), particularly drugs that might not be developed by industry

- Conducted over 30 clinical studies with the majority carried out at 20 or more AD research centers and other academic sites

Studies at Iowa
- Valproate to Attenuate the Progression of Alzheimer's Disease
- Intravenous Immune Globulin (IVIg) for Alzheimer’s Disease
- ALZHEIMER’S DISEASE NEUROIMAGING STUDY (ADNI-2)
Alzheimer’s disease neurons

dead cells full of tangles

sparse, damaged cells

amyloid plaques

withered branches

Alzheimer’s disease neurons
- Blood vessel health matters for memory!
- Exercise!
- Healthy diet
Take Home Message

• Research in last 5 years: AD need not be a postmortem diagnosis
• Amyloid and tau proteins
  – Can now be measured in life
  – In healthy adults!
Fig. 3. Hypothetical model of dynamic biomarkers of the AD expanded to explicate the preclinical phase: Aβ as identified by cerebrospinal fluid Aβ42 assay or PET amyloid imaging. Synaptic dysfunction evidenced by fluorodeoxyglucose (F18) positron emission tomography (FDG-PET) or functional magnetic resonance imaging (fMRI), with a dashed line to indicate that synaptic dysfunction may be detectable in carriers of the e4 allele of the apolipoprotein E gene before detectable Aβ deposition. Neuronal injury is evidenced by cerebrospinal fluid tau or phospho-tau, brain structure is evidenced by structural magnetic resonance imaging. Biomarkers change from normal to maximally abnormal (y-axis) as a function of disease stage (x-axis). The temporal trajectory of two key indicators used to stage the disease clinically, cognitive and behavioral measures, and clinical function are also illustrated. Figure adapted with permission from Jack et al [22].
Mild Cognitive Impairment?

**Normal Aging**
- Occasional loss of memory for words and names.
- Slowed processing speed.
- Difficulty sustaining attention when faced with competing environmental stimuli.
- No functional impairment.

**MCI**
- Memory impairment beyond that expected for age, increasing over last six to 12 months.
- Other cognitive functions generally unimpaired.
- Daily function not significantly impaired.
- No dementia diagnosis.

*Source: Dr. Pierre Tariot, University of Rochester Medical Center. “What is on the Horizon for Alzheimer’s Disease Research?”*
Mild Cognitive Impairment

- Changes can be first be detected as changing on repeated MRI scans over time.
  - Detected in MRI scans done for research.
  - FDG PET scanning may be used in the future.

- Memory loss, the first visible sign, is the main feature of mild cognitive impairment (MCI).

- MCI is considered to be a transition phase between normal aging and AD.
M. Weiner, PI (UCSF) http://www.adni-info.org/  
Site PIs, Core Directors, Study Coordinators  
822 subjects enrolled since 2004  

- Public-private research partnership coordinated by the ADCS tasked with identifying biomarkers to detect Alzheimer’s disease (AD).  
- The study has gathered and analyzed thousands of brain scans, genetic profiles and biomarkers in blood and cerebrospinal fluid (CSF).  
  - Shared data access (like all ADCS studies)
ADNI Cores

• PROTOCOL PRINCIPAL INVESTIGATOR
CLINICAL CORE LEADER
Ron Petersen, Ph.D., M.D.
Mayo

• ADCS PRINCIPAL INVESTIGATOR
CLINICAL CORE
Paul Aisen, M.D.
UCSD

• MRI CORE DIRECTOR
Clifford Jack, M.D.
Mayo

• PET CORE DIRECTOR
William Jagust, M.D.
Berkeley

• BIOMARKER CORE DIRECTORS
Leslie M. Shaw, Ph.D.
John Trojanowski, Ph.D.
Penn

• BIOSTATISTICS CORE LEADER
Laurel Beckett, Ph.D.
UC Davis

• LONI PRINCIPLE INVESTIGATOR
Art Toga, Ph.D.
UCLA

• GENETICS CORE
Andrew Saykin, Psy.D.
U Indiana

• NEUROPATHOLOGY CORE
John C. Morris, M.D.
Wash U

• RESOURCE ALLOCATION REVIEW COMMITTEE
Tom Montine, Ph.D.
Wash U

• ADNI DATA AND PUBLICATIONS COMMITTEE
Robert Green, M.D., MPH. BU
Mission: To find more sensitive methods to detect AD pathology at earlier stages

- Mild Cognitive Impairment (MCI) samples presently too heterogeneous to be optimal intervention points.

Measures

- Cerebrospinal fluid amyloid and tau
- Amyloid Imaging (PIB in ADNI-1, AV-45 in ADNI-2)
- FDG PET Imaging
- Structural Imaging
- Genetic Biomarkers, Post-mortem data
Iowa ADNI Collaboration

- **Recruitment/Clinical Assessment**
  - Geriatric Psychiatry / PI: Susan K. Schultz MD
    - Karen Ekstam-Smith BSN, Laura Scheetz MS, CRU Staff

- **Magnetic Resonance Imaging**
  - Radiology
    - Vincent Magnotta PhD, Marla Kleingartner BS, Joe Ekdahl BA,

- **Positron Emission Tomography (FDG, AV-45)**
  - Radiology / Nuclear Medicine
    - Laura Boles Ponto PhD, Yusuf Menda MD, John Sunderland PhD, Julie Koeppel BS; John Richmond BS

- **Cerebrospinal Fluid/LP**
  - Neurology
    - Deema Fattal MD, Neurology Clinic staff

- **Decedent Care Service**
  - Pathology
    - Marcus Nalshelsky MD, Heidi Nobiling, Pathology Admin.
Neuroimaging in AD at Iowa

• UI Magnetic Resonance and PET Centers
  - FDG PET, Amyloid (florbetapir) PET, CSF sampling (Neurology)
• ADNI Collaborators: Laura Boles Ponto PhD, Yusuf Menda MD, Vince Magnotta PhD, Deema Fattal MD, John Sunderland PhD, Michael Graham MD, PhD, Hyungsub Shim MD
• C-11 PIB Amyloid Imaging
  - IND for C-11 PIB – Michael Graham, MD, PhD - sponsor
  - Laura Boles Ponto PhD and Yusuf Menda MD
  - Long-standing use of O-15 water for rCBF mapping of cognitive function
Samples to Date

• **ADNI-1** 2004-9
  – N= 200 Healthy Controls
  – N=200 Mild Cognitive Impairment
  – N=400 Alzheimer’s dementia

• **ADNI-GO** 2009-11
  – N=300 E-MCI (Early-Mild Cognitive Impairment)

• **ADNI-2** underway
  – N=150 Healthy Controls
  – N=150 Early-Mild Cognitive Impairment *
  – N=150 MCI (or Late MCI)*
  – N=150 Alzheimer’s dementia

* Based on edu-adjusted scores on Logical Memory II subscale from Wechsler Memory Scale-Revised
• **225+ Publications**

Amyloid Imaging

RED = maximum uptake

VIOLET = minimum uptake

University of Pittsburgh
PET Amyloid Imaging Group
Amyloid Imaging

- General pattern is one of significant retention of tracer in areas with post-mortem documented amyloid deposits
  - Pike, et al, 2007, found that 97% of AD, 61% of MCI and 22% of healthy aging subjects had increased [11C]PIB retention.

florbetapir Amyloid Imaging

Florbetapir PET scans

A  Participant age at death, 82 y
Mean cortical SUVr = 0.87, PET score = 0

B  Participant age at death, 78 y
Mean cortical SUVr = 1.17, PET score = 2

C  Participant age at death, 70 y
Mean cortical SUVr = 1.68, PET score = 4

β-Amyloid antibody 4G8 immunohistochemistry

β-Amyloid burden = 0.15%
Low likelihood of Alzheimer disease

β-Amyloid burden = 1.63%
High likelihood of Alzheimer disease

β-Amyloid burden = 7.92%
High likelihood of Alzheimer disease

Clark, C. M. et al. JAMA 2011;305:275-283
Amyloid Imaging

- 30% of entirely normal individuals may have elevated amyloid
- Longitudinal follow-up over YEARS is essential to understand why some amyloid+ people go on to have memory loss and others do not.
Imaging Brain Metabolism

- FDG PET Scan of a Normal Brain
- FDG PET Scan of a Brain with AD
BIOMARKERS for AD

• PET: Positive Amyloid imaging
• Spinal Fluid
  – Low CSF amyloid
  – High CSF total tau and p-tau
• FDG PET Reduced cerebral metabolism
• MRI: Reduced medial temporal volumes
Hypothetical model of AD pathophysiological cascade

- **Age Genetics**
  - Cerebrovascular risk factors
  - Other age-related brain diseases

- **Amyloid-β Accumulation**

- **Synaptic Dysfunction**
  - Glial Activation
  - Tangle Formation
  - Neuronal Death

- **Cognitive Decline**

- **Brain and cognitive reserve**
  - ? Environmental factors
<table>
<thead>
<tr>
<th>DX</th>
<th>PIB status</th>
<th>N</th>
<th>Age</th>
<th>Sex F/M</th>
<th>MMSE</th>
<th>ApoE (-/+)</th>
<th>Edu</th>
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<tr>
<td>HC</td>
<td>-</td>
<td>73</td>
<td>75.6</td>
<td>38/35</td>
<td>29.0</td>
<td>69/4**</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>51</td>
<td>76.4</td>
<td>21/30</td>
<td>29.2</td>
<td>27/24</td>
<td>16.0</td>
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<tr>
<td>MCI</td>
<td>-</td>
<td>63</td>
<td>74.8</td>
<td>15/48</td>
<td>27.3</td>
<td>25/11</td>
<td>15.7</td>
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<tr>
<td></td>
<td>+</td>
<td>166</td>
<td>74.4</td>
<td>63/103</td>
<td>26.8</td>
<td>55/111</td>
<td>15.9</td>
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<tr>
<td>AD</td>
<td>+</td>
<td>122</td>
<td>74.9</td>
<td>47/65</td>
<td>23.6</td>
<td>36/76</td>
<td>15.1</td>
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<tr>
<td></td>
<td>CSF Ab1--42, pg/ml</td>
<td>CSF total tau, pg/ml</td>
<td>CSF p-tau, pg/ml</td>
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<tr>
<td><strong>HC-</strong></td>
<td>244.7 (27.6)**</td>
<td>62.0 (23.0)*</td>
<td>20.5 (8.0)*</td>
<td></td>
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<tr>
<td><strong>HC  PIB+</strong></td>
<td>152.0 (27.6)</td>
<td>79.5 (37.6)</td>
<td>31.0 (19.1)</td>
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<tr>
<td><strong>MCI-</strong></td>
<td>244.1 (26.9)**</td>
<td>62.6 (23)**</td>
<td>20.0 (7.6)**</td>
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<tr>
<td><strong>MCI  PIB+</strong></td>
<td>136.4 (26.0)</td>
<td>116.5 (62.8)</td>
<td>40.5 (17.5)</td>
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<tr>
<td><strong>AD</strong></td>
<td>142.5 (39.6)</td>
<td>121.5 (57.5)</td>
<td>102.4 (19.8)</td>
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</tbody>
</table>

- **ADNI thresholds:**  $\text{A}\beta_{42} < 192$  
  $\text{t-tau} > 93$  
  $\text{p-tau} > 23$

- **Ratios:**  $\text{t-tau}/\text{A}\beta_{42} > 0.39$  and  $\text{p-tau} / \text{A}\beta_{42} > 0.10$

Survival plot for conversion from MCI to AD for PIB-PET(+) shown in red and PIB-PET(−) shown in black.

- MCI individual who convert to AD, Amyloid positive vs negative

Ewers M et al. Cereb. Cortex 2011; cercor.bhr271

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Revised Criteria

<table>
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<th>Normal</th>
<th>Pre-clinical</th>
<th>MCI</th>
<th>Alz dementia</th>
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<tbody>
<tr>
<td>Research setting</td>
<td>Research setting</td>
<td>Clinical setting</td>
<td></td>
</tr>
<tr>
<td>Early stages – no symptoms</td>
<td>Early stages – mild symptoms</td>
<td>Similar to criteria used today AD-C</td>
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<tr>
<td>Biological markers</td>
<td>Biological markers</td>
<td>Use of biological markers to improve diagnostic confidence:</td>
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<tr>
<td>Need validation</td>
<td>Need validation</td>
<td>AD-P</td>
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</table>

Normal Pre-clinical MCI Alz dementia
The Iowa ADNI2 Study

- Tests include Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) florbetapir and FDG scans, CSF (spinal fluid) sampling conducted at regular intervals over 5 yrs.
- Participants will be between 55-90 (inclusive) years of age.
- Subjects will include:
  - Cognitively normal participants
  - Early Mild Cognitive Impairment (MCI)
  - Late Mild Cognitive Impairment (MCI)
  - Early Alzheimer’s Disease (AD)
Thank you!

This study is being conducted by the Alzheimer’s Disease Cooperative Study (ADCS) and supported by the National Institutes of Health (NIH) through the American Recovery and Reinvestment Act of 2009 funds.

- The Federal government’s lead agency for AD research is the National Institute on Aging (NIA), part of the National Institute of Health (NIH). NIH is part of the U.S. Department of Health and Human Sciences.
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- Karen Ekstam-Smith BSN
- Research Nurse; 319 353-5158