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Disclosure of Interest

Research Support

1. NIA-ADNI
2. NIA-DIAN
3. Alz Assoc-DIAN Clinical Trials
4. Fain Family Foundation, Champlin Foundation, White Family Foundation
5. Avid Radiopharmaceuticals

Speakers Bureau
Athena

Clinical Trials
Elan, Janssen Al, Baxter, BMS, Pfizer, Medivation, Genentech, Bayer, GE, Avid, Roche

Consultant
Elan, Janssen Al, Astra-Zeneca, Avid-Lilly, Baxter, Pfizer, Athena, BMS, Merck, and Sanofi

I own no stocks or equity in any pharmaceutical company
Alarming Alzheimer’s Statistics and Call to Action

- Every 67 seconds someone develops AD in the US!
- The rate of AD doubles every 5 years after age 65 reaching 30-50% in those 85 and over
- 10,000 baby boomers will be turning 65 every day for the next 15 years (77 million)
- Delaying onset by 1-2 years can significantly reduce the number of cases, disease burden, and cost

* Alz Dementia 2007;3:186-191
Predicted Percent Increase in Alzheimer's by 2050

Note: Based on estimated data for 2006 and 2050.
Source: Alzheimers Dement. 2007;3:S168-9
Dramatic Decrease in Cardiac Deaths 1980-2000
Alzheimer’s Disease Trajectory

Normal Aging

Amyloid accumulation

MCI

AD
Reconceptualizing Alzheimer’s Disease

McKhann et al, Albert et al, & Sperling et al, Alzheimers Dement 2011
Amyloid-β accumulation (CSF/PET)
Synaptic dysfunction (FDG-PET/fMRI)
Tau-mediated neuronal injury (CSF)
Brain structure (volumetric MRI)
Cognition
Clinical function

Hypothetical Model of Biomarkers in AD

Clinical Disease Stage

No pathology Preclinical MCI Dementia

Amyloid-β accumulation (CSF/PET)
Synaptic dysfunction (FDG-PET/fMRI)
Tau-mediated neuronal injury (CSF)
Brain structure (volumetric MRI)
Cognition
Clinical function

Sperling, Jack, Aisen Science Translational Medicine (in press)
Figure adapted from Jack et al. 2010; Sperling et al. 2011
Mixed dementia is the most common form of dementia

Cerebrovascular Disease and the Expression of Dementia in AD

• Among the AD-path cases
  – without infarcts: 57% demented
  – with infarcts: 93% demented
    • large infarct: OR 6.7 (0.9-48.3)
    • small infarct: OR 20.7 (1.5-288.0)

• The new criteria do not do a good job of integrating important comorbid conditions

Snowdon et al. The Nun Study. JAMA 1997; 277: 813-817, Schneider Ann Neurol 2009
Modulators of Biomarker Temporal Relationships

C⁻ = cognition in the presence of co-morbid pathologies (eg, Lewy bodies or vascular disease) or risk amplification genes
C⁺ = cognition in subjects with enhanced cognitive reserve or protective genes
C₀ = cognition in subjects without co-morbidity or enhanced cognitive reserve

DIAN amyloid PET
Assessment of Cognitive Impairment

- Clinical history from patient and informant and review of medical records
- Neurological examination
- Cognitive testing
- Screening laboratories
- Brain imaging-MRI or CT
- Additional testing may include-ApoE genotype, dominant mutation, FDG PET, CSF amyloid and tau, amyloid PET
Clinical History

• Onset and course
  ▪ Gradual, abrupt

• Were there “events”?

• How have they changed from baseline cognitive and functional ability

• What are the primary and secondary symptoms
Identifying the Pattern of Symptoms

- Cognition
- Motor
- Bladder
- Medications, other medical or neurological
- Family history of dementia

- Behavior
- Substance use
- Sleep
- Living situation, stressors, family awareness, resources, burden
Clock Drawing

MMSE=26  MMSE=21  MMSE=26

MCI  AD  DLB
MONTREAL COGNITIVE ASSESSMENT (MOCA)

- 30 point assessment tool

www.mocatest.org
Determining the Level of Impairment

Cognitive Continuum

- Normal
- Mild Cognitive Impairment
- Dementia

Functional Continuum

- Mild-Moderate, Moderate-Severe
Change in Hippocampal Volume from Normal Aging through AD

<table>
<thead>
<tr>
<th>Normal</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Normal Image" /></td>
<td><img src="image2.png" alt="MCI Image" /></td>
<td><img src="image3.png" alt="AD Image" /></td>
</tr>
</tbody>
</table>

% of nl
- >50% of nl
- 1-50%
- 1st %

conversion rate
- 9%
- 26%
- 50%

Jack Neurology 1999;52:1397-1403
Imaging Brain Vascular Changes
Evaluating for NPH

- Ventricular enlargement disproportionate to the amount of atrophy
- Bowing of the corpus callosum
- Smooth rimming of high signal around the ventricles due to transependymal flow of CSF
Three Levels of Amyloid PET Binding (Florbetapir) with Post-Mortem Correlation

Unlikely AD

Intermediate likelihood of AD

Likely AD
CSF Biomarkers of AD

**CSF \(\beta\)-Amyloid_{1-42}**

- **Controls** (n=72)
- **Alzheimer Disease** (n=131)

**CSF Tau**

- **Controls** (n=72)
- **Alzheimer Disease** (n=131)

*Published \(A\beta_{42}\): sensitivity, 70-100%
specificity, 40-90%

*Published Tau: sensitivity, 40-85%
specificity, 65-85%

Based on clinical criteria*

## Presence of ApoE 4 allele in general population

<table>
<thead>
<tr>
<th>Number of E4 alleles</th>
<th>Percent of population</th>
<th>Risk of developing AD</th>
<th>Average age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>73%</td>
<td>20%</td>
<td>84</td>
</tr>
<tr>
<td>1</td>
<td>24%</td>
<td>47%</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>3%</td>
<td>91%</td>
<td>68</td>
</tr>
</tbody>
</table>

Clinical Development of Tau PET
Case 1: Early AD or Depression?

- 66-year-old woman with 7 years of education and mild cognitive symptoms and depression
- Trouble recalling names and recognizing people, mildly repetitive, and mild misplacing
- Cognitive problems began soon after breakup with boyfriend who promised to marry her. She has been tearful and upset
- She is working full-time cleaning in an office complex, driving, and paying her bills without difficulty
- Fam Hx—mother with late-onset dementia and brother with onset of dementia in his 70s
Case 1: Continued

- Exam nl except for tearfulness when discussing the breakup from her boyfriend
- MMSE 28, 2/3 recall and 3rd with prompting, MOCA 23, 2/5 on delayed recall
- Neuropsych-impaired verbal learning, recognition and recall
Additional Testing

- MRI WNL
- ApoE 3,4
- Aβ42-203, Total tau 92, Phospho tau 84, Total tau/Aβ42 0.45
- Amyloid PET
- Diagnosis-Amnestic mild cognitive impairment, due to AD
- Treatment options-cholinesterase inhibitor, participation in clinical trial to slow disease progression
CSF Predictors of Progression from Amnestic MCI to Dementia

A \((\beta 42)/\text{P-tau} < 6.16\)

Buchave Arch Gen Psych 2012
Case 2- Mild Memory Complaints

- 69 yo retired social worker with trouble recalling names and mildly repetitive. Mild difficulty finding her way while driving
- Thinking a little more slowly, more distractible, and mild difficulty multi-tasking
- H/o depression well-controlled on fluoxetine
- Mother with dementia beginning at 80, sister, 72, with mild cognitive symptoms
- Concerned she may have early symptoms of AD
• MMSE 30, MOCA 25
• Very talkative, normal mood
• MRI-mild cortical atrophy
• Cognitive testing-borderline difficulty learning verbal information, otherwise WNL
• Diagnosis-Age Associated Memory Impairment
• Consider Anti-Amyloid Treatment in Asymptomatic AD Trial (A4)
Frequency of abnormal PIB uptake in diagnostic groups

<table>
<thead>
<tr>
<th>Group</th>
<th>PiB(-)</th>
<th>PiB(+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl</td>
<td>n = 10</td>
<td>9 (47%)</td>
</tr>
<tr>
<td>MCI</td>
<td>n = 18</td>
<td>47 (72%)</td>
</tr>
<tr>
<td>AD</td>
<td>n = 2</td>
<td>17 (89%)</td>
</tr>
</tbody>
</table>

ADNI 1
Treatment and Prevention of Alzheimer’s Disease
Reconceptualizing Alzheimer’s Disease

McKhann et al, Albert et al, & Sperling et al, Alzheimers Dement 2011
Benefits of Cholinesterase Inhibitors for AD

- Stabilize functioning during the first year and may make subsequent decline more gradual
- May delay time to nursing home placement
- May decrease behavioral symptoms
- Show some benefit in moderate-to-severe stages of AD
- Cholinergic loss increases as the disease progresses and higher doses (donepezil) may provide additional benefit

Farlow, Salloway et al. 2010
Memantine Plus Donepezil for Mod-Severe AD

Figure 2. SIB and ADCS-ADL, by Visit (Observed Case) and at End Point (LOCF)

![Graph showing the comparison of Severe Impairment Battery and Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory between Memantine and Placebo groups.]

- **Severe Impairment Battery**
  - **Mean Change from Baseline**
  - **Worsening** vs. **Improvement**
  - **Study Week**:
    - Baseline
    - End Point (LOCF)
  - **No. of Patients**:
    - Memantine: 198, 197, 190, 185, 181, 171, 198
    - Placebo: 197, 194, 180, 169, 164, 153, 196
  - **LS Mean Difference**: 
    - Memantine: -1.2, -1.5, -3.1, -2.7, -3.4, -3.4
    - Placebo: -0.8, -1.1, -1.3, -1.4, -1.6, -1.4
  - **P Value**: 
    - Memantine: .06, .03, <.001, .006, <.001, <.001
    - Placebo: .03, .01, .02, .03, .02, .03

Tariot, JAMA 2004
Helping Caregivers Cope

• Facing the situation directly
• Common sense problem solving
• Getting educated and developing a support network
• Familiar, calm environment with a predictable routine
• Keeping it simple, limit choices and matching activities to capacities and preferences
• Avoid arguing and overwhelming situations
• Driving and home safety
Findings from Disease-Modifying Treatments in Development
Anti-amyloid Immunotherapy: Amyloid “Vaccine” Reduced Plaque Burden and Memory Loss in Transgenic Mouse Model of AD

Amyloid Stain (Mouse Brain)

Unvaccinated

Vaccinated

Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse


Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA

Change in C11 PIB with Bapineuzumab

Rinne Lancet Neurology 2010
Distribution of PIB PET Global Cortical Average SUVr

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Carrier GCA SUVr</th>
<th>Non-Carrier GCA SUVr</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All PiB PET analysis population</td>
<td>2.07</td>
<td>1.72</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>PiB PET analysis population</td>
<td>2.14</td>
<td>2.05</td>
<td>p=0.18</td>
</tr>
</tbody>
</table>

8/123 (6.5%) Below threshold for inclusion
22/61 (36.1%)

APOE ε4 carriers
302 Study N=123

Non-carriers
301 Study N=61
Examples of vMRI Outcomes in AD Clinical Trials
Will the rate of atrophy decrease or increase?

• MRI
  – AN1792-antibody responders had greater loss of brain volume and larger ventricles but no difference in Hc and no correlation with cognitive decline (Fox, 2005)
  – Bapineuzumab phase 2-no difference in brain volume for all Rx groups combined. Less volume loss in ApoE 4 non-carriers and increased ventricular size in ApoE4 carriers (Salloway, 2009)
  – Scyllo-inositol-No difference in cortical volume but increase in ventricular volume in the 250 mg group (Salloway, 2011)
  – Semagastat phase 3-n=229, 4.3% decrease in hc volume and 1% decrease in WBV with treatment (Siemers, AAIC 2011)
  – Bapineuzumab phase 3-no difference in ApoE4 carriers and non-carriers on annual cortical rate of change but increase in rate of ventricular enlargement (Salloway, Sperling, and Fox CTAD 2012)
Amyloid-Related Imaging Abnormalities

Leptomeningeal involvement with bapineuzumab

Parenchymal effusion with gantenerumab

First seen on routine MRI at week 6 (2 weeks after the 2nd dose) in ApoE4,4 subject and resolved by week 17

Ostrowitzki 2011, Salloway 2009
Change in Amyloid Burden as assessed by $[^{11}\text{C}]$ PiB-PET at Week 71 APOE ε4 Carriers (PiB PET analysis population)

APOE ε4 Carriers

Reduction

PiB PET

Global Cortical Average SUVr Mean (+/-SE)

Bap 0.5 mg/kg p=0.004

Salloway and Sperling, in press
Change in CSF Phospho-tau by Treatment Group at Week 71
APOE ε4 Carriers (CSF analysis population)

APOE ε4 Carriers

- Reduction
- CSF P-tau 181P
- Mean (+/-SE) Change From Baseline (pg/mL)

Placebo (n=85)
Bap 0.5 mg/kg (n=127)

Bap 0.5 mg/kg p=0.005

Salloway and Sperling, in press
Change in ADAS-Cog 11 by Treatment Group Over 78 Weeks (mITT population)

.csrf

Study 302 (Carriers)

- Placebo (n=432)
- Bap 0.5 mg/kg (n=658)

Study 301 (Non-Carriers)

- Placebo (n=493)
- Bap 0.5 mg/kg (n=314)
- Bap 1.0 mg/kg (n=307)

Mean (+/-SE) Change From Baseline

- Placebo vs Bap 0.5 mg/kg \( p=0.798 \)
- Placebo vs Bap 0.5 mg/kg \( p=0.642 \)
- Placebo vs Bap 1.0 mg/kg \( p=0.620 \)

MMRM (mixed model for repeated measures) analysis. Error bars represent 1 SE. Salloway and Sperling, in press.
Recent AD Trials: promising targets, mostly negative trials

- Negative Phase III:
  - Xaliproden (neuroprotection)
  - Tramiprosate (amyloid anti-aggregation)
  - Tarenflurbil (gamma secretase modulator)
  - Rosiglitazone (metabolic, anti-inflammatory)
  - Leuprolide (endocrine)
  - Dimebon (mitochondrial?)
  - Semagacestat (gamma secretase inhibitor)
  - Bapineuzumab, solanezumab (monoclonal anti-amyloid Abs)
  - IGIV
Solanezumab Efficacy Results Summary

*p values for solanezumab-placebo difference at 80 weeks*

<table>
<thead>
<tr>
<th></th>
<th>EXP1 overall</th>
<th>EXP1 mild</th>
<th>EXP2 overall</th>
<th>EXP2 mild</th>
<th>Pooled overall</th>
<th>Pooled mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ADASCog_{11}</td>
<td>.312</td>
<td>.008</td>
<td>.060</td>
<td>.097</td>
<td>.042</td>
<td>.001</td>
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<tr>
<td>ADASCog_{14}</td>
<td>.155</td>
<td>.006</td>
<td>.075</td>
<td>.120</td>
<td>.025</td>
<td>.001</td>
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<tr>
<td>MMSE</td>
<td>.067</td>
<td>.002</td>
<td>.004</td>
<td>.099</td>
<td>.002</td>
<td>.001</td>
</tr>
<tr>
<td>Functional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>.931</td>
<td>.302</td>
<td>.062</td>
<td>.076</td>
<td>.217</td>
<td>.057</td>
</tr>
<tr>
<td>ADCS-iADL</td>
<td>.919</td>
<td>.319</td>
<td>.080</td>
<td>.029</td>
<td>.250</td>
<td>.045</td>
</tr>
</tbody>
</table>

**BOLD = primary outcome(s)**
**RED = statistical significance**
Implications for These Results

• Too little, too late
  – Find ways to safely maximize dose to optimize biological effects
  – Intervene earlier in the disease course using combination therapies

• Use cut-offs to only enroll amyloid + subjects
  – Study the causes of cognitive decline in amyloid – subjects

• Develop and test new targets
Other Targets

- Tau Hyperphosphorylation
  - TAU-related agents

- Oxidation
  - Antioxidants

- Excitotoxicity
  - NMDA receptor antagonists

- Inflammation
  - Anti-inflammatory agents

- Apoptosis
  - Anti-apoptotic agents (Caspase inhibitors)

CELL DEATH
Thinking Out of the Box: Deep Brain Stimulation Works for Parkinson’s Disease, Will it Work for AD?

A  Entorhinal Region

B  Hippocampus

**Primary Prevention**
Delay onset of AD pathology
- Decrease Aβ$_{42}$ production
- Prevent tangle formation

**Secondary Prevention**
Delay onset of cognitive impairment in individuals with evidence of pathology
- Decrease accumulated Aβ burden and neurotoxic forms of Aβ
- Decrease neurodegeneration with anti-tau or neuroprotective agents

**Tertiary Prevention and Treatment**
Delay onset or progression of dementia
- Neuroprotection - prevent neuronal loss
- Enhance function of remaining neurons
- Neurotransmitter repletion

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Sperling, Jack, Aisen *Science Translational Medicine (in press)*
Figure adapted from Jack *et al.* 2010; Sperling *et al.* 2011
Promoting Healthy (Brain) Aging

- Determine and promote the factors that promote longevity and healthy brain aging
- Staying mentally and physically active
- Staying socially engaged
- Controlling CV risk factors-weight, BP, chol, blood sugar, stop smoking
- Eating a balanced diet, vitamins, nutrients, anti-oxidants, red wine-resveratrol
Mean Cortical PIB Binding in Nondemented Controls (N=41)

Morris J

Red bars-AD dementia
Green bars-Nondemented controls
Preventing or Delaying AD in People at Risk

- DIAN-TU-2 year trial testing two anti-amyloid monoclonal antibodies in individuals with an autosomal dominant mutation
- API-5 year trial testing an anti-amyloid monoclonal antibody in patients with a PS1 mutation in Colombia
- A4-3 year trial testing an anti-amyloid monoclonal antibody in individuals 65-85 with normal cognition and a positive amyloid PET scan, will also study the impact of disclosure of amyloid PET results
- API-Under development, trial treating ApoE4 carriers (homozygotes) before expected age of onset
Urgent Need to Move Forward

- Growing wave of people at risk for AD
- Right drug(s), right time
- Combination treatments
- Forge public-private partnerships akin to a long-term Manhattan project to meet these goals
- Be persistent, innovative, and creative to identify novel targets and approaches
Back-up Slides
AD Phenotypes

- Limbic and Cortical AD-78%
- Limbic predominant-11%
- Frontal variant
- Hippocampal sparing-11%
  - Progressive aphasia
  - Corticobasal syndrome
  - Posterior cortical atrophy

Murray, Lancet Neurology, 2011