Biomarkers, Schmiomarkers…
Will they ever help us find a
disease modifying treatment for
neurodegenerative disease?

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Fundamental challenges in developing drugs for neurodegenerative disease

• Disease begins in the brain years (perhaps even decades) prior to clinically obvious symptoms
• Best opportunity to intervene may be prior to symptoms, but the earlier we go in the disease process the slower the rate of clinical change
• Animal models do not fully recapitulate the pathology or the phenotype
• Complex diseases – stage dependent treatment effects, may need to attack multiple mechanisms
Is Amyloid the Right Target for AD?

- Compelling genetic data supporting role of amyloid
- Converging data that Aβ positivity increases risk of cognitive decline in prodromal and preclinical AD
- Amyloid in isolation not sufficient - ? Critical factor
- Disappointing results from multiple anti-Aβ clinical trials at stage of mild-moderate dementia
- Unclear which “toxic species” of Aβ (APP) to target
- Unknown how much amyloid lowering is required
- How to measure therapeutic change on biomarkers?
- When to intervene with anti-Aβ therapy?
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

Sperling et al *Alzheimer & Dementia* 2011
NIA-AA Preclinical Workgroup
Amyloid is likely NOT sufficient to result in dementia in isolation – but is it a critical factor?

Molecular biology – Maybe (No cognitive readout)

Transgenic mice – Partial (No neuronal loss)

Clinical trials – Not so much… (At least at stage of dementia)
Issues with Animal Models (and iPS)

- Incomplete model of human pathology – even “Frankenmouse” triple transgenics – no neuron loss
- Anatomic differences – amyloid deposits early in hippocampus in mice, relatively late in humans
- Need interaction with age – takes many months
- AD (and several other CNS disorders) affects brain functions that may be uniquely human
- How to build brain networks from neurons – model emergent properties that subserve complex cognition
Biomarkers – Schmiomarkers
What good are they?

• Utility in selecting participants who have the target pathology for clinical trials - particularly important as we move towards earlier intervention
• Potential utility in demonstrating target engagement
• Unclear whether any biomarkers (or which ones) have theragnostic utility – ability to track and predict clinical therapeutic response
  – We need better synaptic function markers!
• How do we understand what the biomarkers are telling us in current AD trials?
PiB-PET Amyloid Imaging

Normal Aging

Alzheimer’s Disease

DVR = 1.0       2.0
Distribution of PIB PET Global Cortical Average SUVr

**Graph:**
- **X-axis:** Baseline PiB PET GCA SUVr
- **Y-axis:** Carrier GCA SUVr
- **Legend:**
  - Heterozygotes
  - Homozygotes
  - Noncarrier

**Table:**

<table>
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<th>Carrier GCA SUVr</th>
<th>Non-Carrier GCA SUVr</th>
<th>P-value</th>
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<td>All PiB PET analysis population</td>
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<td>1.72</td>
<td>p&lt;0.0001</td>
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<tr>
<td>PiB PET analysis population</td>
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<td>2.05</td>
<td>p=0.18</td>
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**Notes:**
- APOE ε4 carriers: 302 Study N=123
- Non-carriers: 301 Study N=61
- 8/123 (6.5%) Below threshold for inclusion
- 22/61 (36.1%) Below threshold for inclusion
Phase II Immunotherapy related decreases in fibrillar Aβ burden on PiB-PET imaging

Bapineuzumab

Gantenerumab

Rinne *Lancet Neurology* 2010

Ostrowitzki *Arch Neurol* 2011
Dissociation of biomarker and clinical outcomes in Phase 3 AD trials
(Double Dissociation? Too little, Too late?)

• Bapineuzumab with modest evidence of target engagement and effects on some CSF markers of neurodegeneration—No evidence of clinical benefit

• Solanezumab with modest evidence of clinical effect—slowing of cognitive decline only in pooled mild subgroup - ? evidence of target engagement on CSF Aβ markers but no evidence of effect on CSF markers of neurodegeneration
β-Secretase Inhibitors
Synaptic markers

- AD (and most neurodegenerative diseases) are fundamentally a disease of synaptic failure
- Need biomarkers that more closely reflect synaptic dysfunction (If you suck all of the amyloid out of the brain – do you make it work better?)
- Electrophysiological (EEG/ERP/MEG)
- FDG-PET, Perfusion MRI
- Task-fMRI
- Resting state (task-free) functional connectivity (fc-MRI)
Aβ burden in normal elderly associated with default network dysfunction in task and task-free fMRI

Sperling et al. *Neuron* 2009
(Also see Vannini *Neurobio of Aging* 2011; Vannini *Cerebral Cortex* 2012; Kennedy *NeuroImage* 2012)

Hedden et al. *J Neurosci* 2009
(Also see Sheline *Bio Psych* 2010; Mormino *Cerebral Cortex* 2011; Drzezga *Brain* 2011)
Evidence of Amyloid-Related Alterations in Network Function and Structure

PiB-PET  fMRI  FDG-PET  vMRI

Molecular  Electrophysiological  Microscopic

Beyond amyloid - multi-modality imaging

Amyloid Metabolism

PiB FDG PEB fMRI

Amyloid Metabolism mGluR5 BOLD/activity

Tau

Keith Johnson MGH
Need for earlier intervention

• Ten Phase III trial failures at stage of AD dementia over the past decade!
• Intervention prior to dementia (and stage of irreversible brain cell loss) may have better chance of changing clinical course of the disease
• Stage dependent effects - Cholesterol analogy
• Think about what happens in cancer, stroke, diabetes, osteoporosis, HIV…. if we wait to treat until after symptoms are clearly manifest?
Testing the Right Target and the Right Drug at the Right Stage of Alzheimer’s Disease

Primary Prevention
Delay onset of AD pathology
• Decrease Aβ production
• Prevent tangle formation

Secondary prevention
Delay onset of cognitive impairment in individuals with evidence of pathology
• Decrease accumulated Aβ burden
• 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

Clinical disease stage

Multi-center Task-free Functional Connectivity: DIAN

Chhatwal et al. AAIC 2012 (under review)
Potential Solutions

• Improve forward and back translation with animals
• Run Phase 1 in humans with the target pathology
• Imbed multiple biomarkers in Phase 1/2a – need to develop pharmacodynamic profiles quickly
• Develop synaptic (and other markers) that can give a functional readout in short time frame in humans
• Test drugs aimed at upstream processes before irreversible downstream damage
• Need more potent drugs-w/o dose-limiting toxicity
• Start combination therapies early
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