The Critical Scientific Challenges to Prevent Slow and Treat Alzheimer’s Disease

Dr. Howard Feldman
Professor, Division of Neurology
Director, Clinic for Alzheimer’s Disease and Related Disorders
Executive Associate Dean Research,
UBC Faculty of Medicine
Disclosure

- 2012 to present, service agreements, clinical trials and/or travel/meeting/lecture support
  - Eli Lilly, Kyowa Kirin, GE Healthcare, Biogen, Arena, Roche/Genentech, Eisai, Baxter

- 2009-2011, on leave from UBC and employed at Bristol-Myers Squibb Company in CT, USA
  - VP and Therapeutic Area Head, Neuroscience Global Clinical Research
Therapy for AD: Licensed Pharmacologic Therapies

The cholinergic hypothesis

Acetylcholinesterase inhibitors (AchEi),

Memantine
NMDA
Uncompetitive Receptor Antagonist


Galantamine

Donepezil
Mangialasche et al modified 2013 from *Lancet Neurol* 2010
Experimental Approaches to Amyloid Lowering

APP gene

Production

APP

Antisense Si RNA

Aβ Monomer

Beta and Gamma Secretase inhibitors & modulators

Aggregation

Aβ Oligomer

Fibrillogenesis modulators

Scyloinositol Tramiprosate

Immunotherapy

Fe, Cu²⁺ Chelator

PBT2

AN 1792

Bapineuzumab

Solanezumab 2018-2020

IVIG

Crenezumab

Aducanumab 2020-2022

Aβ Fibril

Deposition

Diffuse Plaque

Senile Plaque

Fibrillogenesis modulators
# Scorecard for Amyloid Immunotherapy for AD 2014

<table>
<thead>
<tr>
<th><strong>Bapineuzumab</strong> ¹</th>
<th>Status of Completed Trials</th>
<th>Results</th>
<th>Positive Findings on Subanalyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-terminus</td>
<td>Phase 3 studies (x2)</td>
<td><strong>Negative</strong> trials</td>
<td>E4 carriers + Effects PIB PET + Effects p-tau</td>
</tr>
<tr>
<td>Soluble/Fibrillar</td>
<td>Mild to Mod AD</td>
<td>Terminated program</td>
<td></td>
</tr>
<tr>
<td><strong>Solanezumab</strong> ²</td>
<td>Phase 3 studies (x2)</td>
<td><strong>Negative</strong> trials</td>
<td>mild AD on 2ndary outcomes Delayed start</td>
</tr>
<tr>
<td>Mid domaine</td>
<td>Mild to Mod AD</td>
<td>Currently mild AD and prevention of AD in DIAN</td>
<td></td>
</tr>
<tr>
<td>Soluble/Sink</td>
<td></td>
<td><strong>Negative</strong> trials</td>
<td></td>
</tr>
<tr>
<td><strong>Gammagard IVIG</strong>³</td>
<td>Phase 2-3 (x1)</td>
<td><strong>Negative</strong> trial</td>
<td>E4 carriers + cognitive effects ↓ Aβ 42 Mod AD benefit</td>
</tr>
<tr>
<td>Polyclonal</td>
<td>Mild to Mod AD</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td><strong>Crenezumab</strong></td>
<td>Phase 1</td>
<td><strong>Negative</strong> trials</td>
<td>Mild AD slower decline</td>
</tr>
<tr>
<td>Oligomers</td>
<td>Phase 2 trials (x2)</td>
<td>Current Ph 2 API trial in PS 1 FAD</td>
<td></td>
</tr>
<tr>
<td><strong>AN 1792</strong></td>
<td>Phase 1-2</td>
<td>Terminated</td>
<td>Effective removal of aggregated amyloid No correlative clinical benefit</td>
</tr>
<tr>
<td>Active vaccination</td>
<td></td>
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</tbody>
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Treatments Directed at Tau

- Epothilone D
- Paclitaxol
- Davunetide, NAP
- Tideglusib GSK 3 Inhibitor
- Lithium, Valproate
- Davunetide, NAP

HDAC Inhibitors:
- Methylene Blue

Autophagy enhancers

Immunotherapy directed at tau:
- AAD Vac 1, C2N8E12, BMS 986168

Tau Mutations:
- HDAC Inhibitors
- Microtubule stabilizers

Adapted from Brunden et al Nat Rev Drug Dis 2009; Boutajangout et al J Neurosci 2010;
Pathogenesis of AD
Web of Causation of AD

Anand R et al
Neuropharm 2014
Summary

- No new therapies approved in 12 years.....unmet needs in
  - Treating symptoms, cognitive and behavioral
  - Prevention of disease
  - Rx that can sustain benefits over the disease course

- Deep investment made by industry and academe in amyloid rx
  - Expected readouts in 2018-2022, negative trials to date
  - No well formed “plan B”

- Unique opportunity for academic networks to innovate and lead
  - Broaden targets and compound selections
  - Focus on achieving
    - POC including clinical evidence
    - advancing novel design and methods (GAP, CPAD)
    - biomarkers and outcomes
Priority Efforts for Consideration
Focus for our Meeting

- Public health interventions directed at prevention
- Advancing systems of care; workforce, delivery, societal change
  - Dementia friendly communities
  - National plan
- Mobilizing technologies
- Setting a broad agenda
- Consideration of a CAHS formal assessment
What Opportunities and Challenges Stand Out in the Canadian Environment?

Opportunities
- Recognition of the national significance of AD and dementia
  - Dementia Friends
  - National research strategies CCNA, CLSA, C5R
- Single payer system
- Systems of care
- Some provincial plans

Challenges
- Health as a provincial jurisdiction
- Speed of mobilization and adoption of research to practice