A Cure for Alzheimer’s Disease by 2025?

The case against ..........

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Professor of Neurology
Faculty of Medicine
University of British Columbia
Vancouver
Consulting, lectures and sponsored meetings in 2012-13
- Eli Lilly, Kyowa Kirin, Nutricia, GE Healthcare
- NIH, ASC, AS Man, Columbia U, Latin America Cognitive Impairment, NYAS, Fidelity Biosciences, ICER

2009-2011, on leave from UBC and employed at Bristol-Myers Squibb Company in CT, USA
- Directed Global Clinical Research in Neuroscience with a major focus on developing AD treatments
Summary of the Case Against a Cure by 2025...

- **Rate of progress to date** vs distance and time to go
  - No new approved treatments since 2003
  - Success only for symptomatic treatments
  - Multiple unsuccessful approaches methods/molecules
  - Timeline of disease modifying rx development = 15 years

- **Need to better understand biology, targets, and timing**
  - Single vs multiple interactive pathologies
  - Differences between genetic and sporadic diseases
  - Selecting the right targets and buying down risk
  - Intervening at the right time in the disease
Summary of the Case Against a Cure by 2025...

- **Current limitations**
  - Preclinical models of the disease
  - Biomarkers including surrogates
  - Clinical trials methodologies

- **Call/Need for an all out unprecedented global effort**
  - Committed resources public, private, industry
  - Unprecedented sharing of data/platforms
  - NAPA, UK, France, and others needed
  - Large initiatives
    - One Mind for Research
    - New York Academy of Science AD
    - US Alz Association
Therapy for AD: The first hundred years and a cure by 2025………

The cholinergic hypothesis

Acetylcholinesterase inhibitors (AchEI),

Memantine
NMDA
Uncompetitive Receptor Antagonist


A cure!

Results of Disease Modifying Rx

- IVIG
- Solenuzumab, Bapineuzumab
- readout of multibillion dollar investment
Donepezil and Cognition
Mild to Moderate AD (MMSE 12-24)

MMSE 5-13

- No significant advantage of combination
- Donepezil better monotherapy profile
- Memantine better behavioral profile

Total n=295
Current Therapies for AD

- Effect sizes with AchEIs are small but consistent
  - Cognitive benefits translate into overall functional benefit
  - Determining efficacy is challenging in the longer term
  - Evidence of sustained benefit through MSAD

- Effect sizes with memantine are smaller
  - Less robust particularly in milder stages of disease

- Unmet needs
  - Treatment with larger effect sizes
  - Longer term effects (disease modifying or not)
  - Better options for neuropsychiatric symptoms
Curing Alzheimer’s Disease

What do we know about the disease path?
Progress to date........
Signature AD Neuropathology:

August D pt of Dr. Alois Alzheimer

Key Neuropathological Findings:
- Damage to and ↓ numbers neurons
- Brain atrophy
- Abnormal material in brain/blood vessels
  - amyloid plaques (amyloid core)
  - neurofibrillary tangles (p-tau)
- amyloid angiopathy

Assumption since 1980s:
- Removing the pathology would cure the disease
- Tombstones or active pathology?

Title “On the peculiar disease process of the cerebral cortex” Über eine eigenartige Erkrankung der Hirnrinde: Alzheimer 1906) Allgemeine Zeitschrift fur Psychiatrie 1907:64
Progression of Signature AD Neuropathology

Neurofibrillary Tangles (NFTs)
Braak Staging

Senile Neuritic Plaques (SNPs)
CERAD Dx

Brain Amyloid:  
Processing to Neuritic Plaques and Blood Vessel Walls

- Amyloid Precursor Protein (APP)
- Membrane
- Amyloid β (Aβ) Species 1-40, 1-42
- β-secretase
- γ-secretase
- Protofibrils
- Oligomers
- EC amyloid
- Blood vessel amyloid

PET Pittsburgh Compound-B (PIB)

LP
CSF measure
Total Aβ 1-42, 1-40
Prion Like Spread of Pathology of AD

- AD might be induced in a prion-like manner
- In prion disease:
  - misfolded proteins (β rich sheet) induce the template misfolding of other proteins
- Seeds of Aβ and tau recruit normal proteins to aggregate and translocate between neurons
- Explanation for the non random spread of neuropathology of AD

Jucker M and Walker LC; Ann Neurol 2011
The Nuns Study: Pathologies that Interact

- The presence of cerebral infarcts (strokes), even if small and scarce, raise the risk of dementia by 20 times for those with Alzheimer type lesions.

Snowdon DS et al JAMA 1997: 277; 813-817
The Pathogenic Cascade of AD

Evolution over Decades

Age, Genes Environment

Amyloid β production, clearance, aggregation

First Hit

Tau and Tangle formation

Brain co-morbidities: infarcts, other protein aggregates,

Second Hit

Synapse dysfunction

Oxidative stress

Inflammation

Calcium dysregulation

Impaired plasticity and neurogenesis

Neurotransmitter imbalances

Pathology of Dementia (ACCORD Study)

<table>
<thead>
<tr>
<th>Pathology Autopsy Series</th>
<th>N=45</th>
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<tbody>
<tr>
<td>Single Pathology</td>
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<tr>
<td>AD</td>
<td>79%</td>
</tr>
<tr>
<td>CVD</td>
<td>8%</td>
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<tr>
<td>PiD</td>
<td>8%</td>
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<tr>
<td>NFT only</td>
<td>5%</td>
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<tr>
<td>Multiple Pathologies</td>
<td>47%</td>
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<tr>
<td>AD+DLB</td>
<td>38%</td>
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<tr>
<td>AD+FTLD TDP</td>
<td>30%</td>
</tr>
<tr>
<td>AD+CVD</td>
<td>9.5%</td>
</tr>
<tr>
<td>AD+FTLD TDP+CVD</td>
<td>4.8%</td>
</tr>
<tr>
<td>DLB +CVD</td>
<td>4.8%</td>
</tr>
<tr>
<td>PSP +CVD+ FTLD TPD</td>
<td>4.8%</td>
</tr>
<tr>
<td>FTLD TDP +AGD</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

Multiple Pathologies

- Older
- More impaired
Now for some good news about the disease......!

Early identification of the pathology of AD before symptoms start
Summary of the Early Events in AD

- Evidence Aβ deposition to plaques prior to clinical symptoms

- Estimation production of Aβ is 0.004 mg per day\(^1\)
  - 10 mg of Aβ 42 is equivalent to 6.8 years of deposition

- Timing of amyloid lowering intervention\(^2\)
  - Gamma secretase inhibitor in TG APP/PSEN1 reduces plaque given < 6 months but not later despite ↓ Aβ 40/42

- Key themes arising in developing effective treatments
  - Assumption that genetic forms of AD are the same as sporadic
  - Timing of the intervention
    - Prior to pathology or prior to symptoms or both
  - Treatment will require years of exposure prior to symptoms
  - Need to consider acceptable risks and benefits

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Alzheimer’s Disease Pathogenesis: An Empiric Model

Cognitively Normal

Abnormal

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

Normal

Clinical disease stage

Asymptomatic

Mild Cognitive Impairment

Dementia

Amyloid Imaging PET Scans

2. Landau S et al *Ann Neurol* 2012
3. Aizenstein HJ et al *Arch Neurol* 2008
5. Sperling R et al *Neurobiol Aging* 2013

- **Florbetapir AV 45 PET**
  - Mean cortical SUVR = 0.87, PET score = 0
  - β-Amyloid burden = 0.15%
  - Low likelihood of AD

- Mean cortical SUVR = 1.17, PET score = 2
  - β-Amyloid burden = 1.63%
  - High likelihood of AD

- Mean cortical SUVR = 1.68, PET score = 4
  - β-Amyloid burden = 7.92%
  - High likelihood of AD

- **14-44% of healthy older adults are amyloid + on PET**
- Associated with lower memory scores
- May also indicate increased risk of cognitive decline

**β-Amyloid antibody 4G8 Immunohistochemistry**
CSF Biomarkers Predicting Progression to AD from MCI

Pathological CSF
low Aβ42 <530 pg/ml
+ high total tau >350 ng/ml

Innogenetics X-Map Luminex Assay

Hansson O et al Lancet Neurol 2006;5:228-34
Focus on Amyloid protein (Aβ) as cause and treatment target to cure AD

A multibillion dollar investment............
Amyloid-Related Approaches as New AD Treatments

- **APP gene**
- **Production**
  - APP
  - Antisense Si RNA
  - Secretase inhibitors & modulators
    - Beta and Gamma Secretase inhibitors & modulators
  - Aβ Monomer
- **Aggregation**
  - Aβ Monomer
  - Aβ Oligomer
  - Aβ Fibril
    - Fibrillogenesis modulators
    - Scylloinositol Tramiprosate
- **Deposition**
  - Diffuse Plaque
  - Senile Plaque
  - Immunotherapy
    - Bapineuzumab
    - Solanezumab
    - Gantenerumab
    - Crenezumab
    - IVIG
    - Fe, Cu^{2+} Chelator
    - PBT2

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Courtesy of Dr. Norman Relkin, Weill Cornell Medical School, New York, NY.
Solanezumab: Expedition 1 Trial  Phase 3 Results

ADAS-cog 11

ADCS-ADL

http://files.shareholder.com/downloads/LLY/2110812184x0x604107/6a7ad129-ff1d-4dbc-9e6e-828f09e7b60b/Solanezumab_ANA_Slides_8-Oct-2012.pdf
Solanezumab: Expedition Trials
Phase 3 Results: Subanalysis of Mild AD

<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>
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<tbody>
<tr>
<td>Cognitive</td>
<td></td>
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<tr>
<td>ADAScog₁₁</td>
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<tr>
<td>ADAScog₁₄</td>
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<tr>
<td>MMSE</td>
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<tr>
<td>Functional</td>
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<tr>
<td>ADCS-ADL</td>
<td>0.931</td>
<td>0.302</td>
<td>0.062</td>
<td>0.076</td>
<td>0.217</td>
<td>0.057</td>
</tr>
<tr>
<td>ADCS-iADL</td>
<td>0.919</td>
<td>0.319</td>
<td>0.080</td>
<td>0.029</td>
<td>0.250</td>
<td>0.045</td>
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</table>

Mild AD subanalyses, MMSE 20-26

http://files.shareholder.com/downloads/LLY/2110812184x0x604107/6a7ad129-ff1d-4dbc-9e6e-828f09e7b60b/Solanezumab_ANA_Slides_8-Oct-2012.pdf
The bad news about the disease......

No evidence that removing amyloid pathology benefits symptoms
Bapineuzumab

- PET study showing significant reduction in aggregated amyloid with bapineuzumab
  \( n = 19 \) bapi and 7 placebo

- No clinical benefits
  - Cognitive, functional or behavioral

Rinne J et al *Lancet Neurol* 2010
Results of active amyloid immunotherapy AN 1792

- Early death
- No Aβ ab
- Intermediate Aβ ab
- Near complete Aβ removal

What you need to believe to continue with amyloid lowering therapy

- There is a time window where intervention will be effective
  - ? Before or after amyloid plaques but before symptoms
  - Genetically at risk

- There are stages of AD where an effective treatment will not work
  - Hard to find diseases like this........
  - Pathology is not fully distinguishable by stage

- Amyloid treatment will ultimately be one part of effective treatment regimens
  - Need to test with other interventions
## Trials to Prevent AD with Amyloid Immunotherapy

<table>
<thead>
<tr>
<th>AD Prevention Trials</th>
<th>Bateman DIAN</th>
<th>Reiman/Tariot API</th>
<th>Sperling/Aisen A4 RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approach</strong></td>
<td>Intervention in AD mutation carriers; parallel biomarker studies transition to larger outcome studies</td>
<td>Intervention in AD mutation carriers; PS1 280 A and other EAOD mutation carriers</td>
<td>Secondary Prevention RCT in HC with Alzheimer pathology</td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td>Mutation positive -15 to +10 years of expected age of onset in family</td>
<td>Age &gt;30 (within 15 years of estimated age of clinical onset</td>
<td>Age&gt; 70 Clinically normal by memory criteria amyloid +</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Gantenerumab Solanezumab ? BACE inhibitor</td>
<td>Crenezumab</td>
<td>Solanezumab</td>
</tr>
</tbody>
</table>
If it is not Amyloid and Plaques it must be Tau and Tangles…….

Another multibillion dollar investment............
Treatments Directed at Microtubules and Tau Pathology

Finding a Cure for AD

- Amyloid may be necessary but not sufficient to cause or treat the disease
- Tau might be necessary but not sufficient to cause or treat the disease
- Intervention will need to be early and possibly before protein aggregates trigger downstream effects
- Likely to require multipoint interventions to arrest the biology as there are multiple pathologies
  - Multiple therapy approach needed with advanced methodologies (eg adaptive)
“Delaying the onset of AD by 5 years would be associated with a reduction in AD prevalence of 50%”

Brookmeyer R et al Am J Publ Health 1988 (9), 1337-1342
Risk and Protective Factors for Cognitive Impairment and Dementia/AD

Risk Factors
- Age
- Genetics
  - Apo E4 and others
  - Rare familial mutations
- Vascular disease
- Low education
- Gender
- Head injury
- Weight

Protective Factors
- Diet
- Exercise
- Vocation/social
- Treatment of vascular factors
- Prevention of stroke
- Cognitive and social activity
- Multimodal intervention
Conclusions: 12 Years to Achieve a Cure

- **Sporadic AD**
  - Amyloid based treatments…..low probability of success
  - Will need more treatment than just amyloid

- **Genetic forms of AD ….could be more interesting**
  - 5-10 years for preliminary evidence of efficacy on prevention approaches with amyloid, tau treatments

- **Current approaches need widening**
  - Multitargeted approach

- **Focus on prevention to delay onset is entirely justified**

- **Development costs at present rate of success is unsustainable**
  - Need for all out multinational collaboration with unprecedented engagement industry, academia, regulatory and community
“Hope is tenacious. It goes on living and working when science has dealt it what should be its deathblow.”

PAUL LAURENCE DUNBAR, *The Strength of Gideon and Other Stories*
Acknowledgements

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Michelle Assaly
Emily Dwosh
Neil Cashman
Phil Lee

International Working Group: Research Criteria for the Diagnosis of Alzheimer’s Disease

# IVIG in MCI Due to AD: Initial Findings

<table>
<thead>
<tr>
<th></th>
<th>IVIG Baseline</th>
<th>IVIG 1 year</th>
<th>Placebo Baseline</th>
<th>Placebo 1 year</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>26.4±2.3</td>
<td>25.4±3.9</td>
<td>26.4±2.6</td>
<td>25.8±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>CDR SB</td>
<td>1.9±0.9</td>
<td>1.8±1.9</td>
<td>1.7±0.9</td>
<td>2.4±2.0</td>
<td>?</td>
</tr>
<tr>
<td>MRI ventricular volume</td>
<td>5.2%±3.3%</td>
<td></td>
<td>8.1%±4.2%</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Conversion rates</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **N= 51 subjects aged 50-84 NIA AA criteria MCI due to AD**
- **RCT dbl blind plac controlled**
- **0.4 g/kg 10% Newgam IVIG or 0.9% saline q 2 weeks x 5 doses**
- **Safety without SAEs (n=43) N=18 completed 1 yr followup.**