A perspective on preclinical Alzheimer's disease trials

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Co-Director, API
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University of Arizona
I have an interest in relation to one or more organizations that could be perceived as a possible conflict of interest in the context of this presentation. The relationships are summarized below:

<table>
<thead>
<tr>
<th>Interest</th>
<th>Name of organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consulting fees</td>
<td>Acadia, Abbott Laboratories, AbbVie, AC Immune, Auspex, Boehringer-Ingelheim, Brain Test Inc., California Pacific Medical Center, Chase Pharmaceuticals, CME Inc., GliaCure, Insys Therapeutics, Pfizer, T3D</td>
</tr>
<tr>
<td>Consulting fees &amp; research support</td>
<td>AstraZeneca, Avanir, Lilly, Lundbeck, Merck &amp; Co., Roche, Takeda</td>
</tr>
<tr>
<td>Research support only</td>
<td>Amgen, Avid, Biogen, Elan, Functional Neuromodulation (f(nm)), GE, Genentech, Novartis, Targacept</td>
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<tr>
<td>Other research support</td>
<td>National Institute on Aging (RF1 AG041705, 1UF1AG046150, R01 AG031581, R01 AG055444, P30 AG19610), Arizona Department of Health Services, Alzheimer’s Association, Banner Alzheimer’s Foundation, FBRI, GHR, Nomis Foundation, Flinn Foundation, Geoffrey Beene Foundation</td>
</tr>
<tr>
<td>Patents</td>
<td>Contributor to a patent owned by the University of Rochester, “Biomarkers of Alzheimer’s disease”</td>
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<tr>
<td>Stocks</td>
<td>Stock options in Adamas Pharmaceuticals</td>
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</table>

This presentation contains information on treatment options that are not approved for dementia in all countries
Alzheimer’s Disease Statistics

- Most common cause of dementia
- About 5.3 million people affected now in US
- A leading cause of death in older people
- By 2050, up to 16 million Americans are expected to have Alzheimer’s
- Estimated annual cost $1.2 trillion by 2050
- 50% of caregivers will become ill or depressed

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Hypothetical Course of Memory and Thinking Ability in a Person Destined to Develop Alzheimer’s Dementia
“Preclinical” Alzheimer’s Disease (conforms with 2018 FDA Guidance on early AD, stage 1 and 2)

“….individuals (with) evidence of early AD pathological changes (who) .... do not meet clinical criteria for MCI or dementia....

“...a continuum from completely asymptomatic individuals with biomarker evidence suggestive of ...risk for progression to AD dementia (FDA Stage 1) to biomarker-positive individuals who are already demonstrating very subtle decline but not yet meeting ...criteria for MCI....” (FDA Stage 2)

“(we) considered ... “asymptomatic,” “presymptomatic,” “latent,” “premanifest,” and “preclinical.” The term “preclinical” ..best encompass(ed) this conceptual phase of ...disease.”

The Main Changes in the Brain in Alzheimer’s Disease

- Shrinkage of the brain (atrophy)
- Amyloid plaques
- Neurofibrillary tangles (tau)
- Inflammation
A Proposed Temporal Progression Of Alzheimer’s Disease(s)

Genetic Factors
- APP mutations
- Presenilin 1,2 mutations
- APOE4 alleles
- Family history
- APOE2 alleles protect
- APP/BACE mutation protects

Environmental Factors
- Head Injury
- toxins

Endogenous Factors
- Diet
- Cardiovascular risk factors
- Diabetes
- Smoking
- Education
- Menopause
- Physical/Mental Activity

Protective Factors
- Estrogen?
- Anti-inflammatory Drugs?

Net effect = stress and vulnerability to stress

The figure depicts apparently continuous processes, though they are likely to be asynchronous. Yaari and Tariot 2008
A Proposed Temporal Progression Of Alzheimer’s Disease(s)

**Genetic Factors**
- APP mutations
- Presenilin 1,2 mutations
- APOE4 alleles
- Family history
- APOE2 alleles protect
- APP/BACE mutation protects

**Environmental Factors**
- Head Injury
- Toxins

**Age**

**Endogenous Factors**
- Diet
- Cardiovascular risk factors
- Diabetes
- Smoking
- Education
- Menopause
- Physical/Mental Activity

**Protective Factors**
- Estrogen?
- Anti-inflammatory Drugs?

Net effect = stress and vulnerability to stress

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**Molecular Phenotype**

**INITIAL STRESSORS**
- Proximal Apoptosis
- APP dysregulation
- Impaired neurotrophic function
- Oxidative stress
- Excitotoxicity

**FAILED STRESS RESPONSE**
- Cell cycle dysregulation
- Kinase/phosphatase dysfunction
- Protein misfolding
- Altered DNA repair
- Vascular/membrane dysfunction

**CELL INJURY**
- Inflammation
- Cytoskeletal dysfunction
- Synaptic dysfunction
- Mitochondrial damage

**CELL DEATH**
- Distal apoptosis
- Neurotransmitter failure

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**Neuropathology**

- Normal

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**Clinical Phenotype**

- Normal

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Tangles, Plaques

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Mild Cognitive Impairment

Dementia

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The figure depicts apparently continuous processes, though they are likely to be asynchronous. Yaari and Tariot 2008
The New Drug Pipeline

1. RA2 defined Phase II drugs as drugs that are in Phase 2, Phase 2/3 and Phase 1/2

- **57 Drugs In Phase 2**
  - 4% Inflammation
  - 2% Neuronal Growth
  - 2% Tau
  - 5% Vascular
  - 7% Metabolic Dysfunction
  - 14% Neurotransmission
  - 23% Amyloid
  - 44% Unknown/Multiple Mechanisms

- **23 Drugs In Phase 3**
  - 39% Amyloid
  - 35% Neurotransmission
  - 13% Unknown/Multiple Mechanisms
  - 4% Insulin/Glucose
  - 9% Tau

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**Researchers Against Alzheimer's**

**US Against Alzheimer's**

**September 2016**
We can use information from multiple sources to improve diagnosis and assess treatment.

**Diagnosis Treatment**

- Neuronal Activity
  - FDG PET

- Fluid Biomarkers

- Cognitive Reserve
  - fMRI

- Amyloid (Tau) Load
  - PET

- Brain Atrophy
  - Structural MRI

- Genetic Risk Profile

- Cognitive, Functional Profile
Revised dynamic biomarkers of the AD pathological cascade model from C. Jack (McDade and Bateman, 2018 (based on API and DIAN findings)
Why Start Prevention Clinical Trials Now? (Why, who, when, what, how)

• The urgent need
• A “preclinical stage” of Alzheimer’s exists during which silent brain changes occur
• We have plausible experimental therapies and can demonstrate target engagement
• We have clinical and biomarkers of Alzheimer’s disease progression
• Earlier treatment may slow the progression of Alzheimer’s
Alzheimer’s Prevention Initiative plan to accelerate the study of “preclinical” treatments for Alzheimer’s disease

Alzheimer’s disease prevention trials in people with normal memory who, based on their age & genetic background, are at very high risk for showing Alzheimer’s symptoms soon

1. Early onset mutation carriers within 15 years of their estimated mean age at clinical onset
   i. *This is where we began, in partnership with Dr. Francisco Lopera and the Neurosciences Group of Antioquia, Colombia*

2. Apolipoprotein E (APOE) ε4 homozygotes carriers close to their estimated age at clinical onset (Generation Study 1)

3. APOE ε4 carrier study (Generation Study 2)

4. More trials to follow!

API Autosomal Dominant AD Trial in Colombia

Cognitively unimpaired, age 30-60
Double-blind, placebo-controlled trial for up to 60 months
Crenezumab injections SC every 2 weeks

Primary endpoint: change in the API composite cognitive score
Also florbetapir PET, FDG PET, MRI, CSF & other cognitive/clinical endpoints

Planned n=300 PSEN1 E280A kindred participants from Colombia

Launched late 2013, closed enrollment Feb. 2017
Clinicaltrials.gov NCT01998841
## Origins of the API APOE4 trials: Corder et al, Science 1993

<table>
<thead>
<tr>
<th>APOE4 copies</th>
<th>Prevalence</th>
<th>AD risk*</th>
<th>Dementia onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>73%</td>
<td>10-15%</td>
<td>84 yo</td>
</tr>
<tr>
<td>1</td>
<td>24%</td>
<td>20-25%</td>
<td>75 yo</td>
</tr>
<tr>
<td>2</td>
<td>3%</td>
<td>30-55%</td>
<td>68 yo</td>
</tr>
</tbody>
</table>
Randomized, double-blind, placebo controlled trial in cognitively unimpaired 60-75 yo’s
# Evolution of the Generation Program (n about 4350): Overview of Clinical Study Designs

*(differences in italics)*

<table>
<thead>
<tr>
<th></th>
<th><strong>Generation Study 1</strong>¹</th>
<th><strong>Generation Study 2</strong>²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>Global, randomized, double-blind, placebo-controlled, parallel-group studies</td>
<td><strong>APOE4 carriers (homozygote or heterozygote)</strong></td>
</tr>
<tr>
<td><strong>Inclusion: genetic risk</strong></td>
<td>APOE4 homozygote</td>
<td><strong>None</strong></td>
</tr>
<tr>
<td><strong>Inclusion: amyloid biomarker</strong></td>
<td>None</td>
<td><strong>Amyloid positive in heterozygotes based on PET scan or CSF</strong></td>
</tr>
<tr>
<td><strong>Age at entry</strong></td>
<td>60–75 years</td>
<td><strong>Cognitively normal</strong></td>
</tr>
<tr>
<td><strong>Clinical status</strong></td>
<td>Cognitively normal</td>
<td><strong>Cognitively normal</strong></td>
</tr>
<tr>
<td><strong>Primary endpoints (dual; success required on either)</strong></td>
<td>1. TTE (conversion to MCI or dementia)  2. Cognition (change from baseline in APCC)</td>
<td><strong>CNP520 50 mg/day vs 15 mg/day vs placebo</strong></td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td>CAD106 450 µg/CNP520 50 mg/day vs placebo</td>
<td><strong>CNP520 50 mg/day vs 15 mg/day vs placebo</strong></td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td>5 years minimum (up to 8 years; event driven)  Based on longitudinal cohorts, at least 30% of events expected</td>
<td><strong>~2,000</strong></td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>1,340</td>
<td><strong>~2,000</strong></td>
</tr>
</tbody>
</table>

APCC = Alzheimer’s prevention initiative preclinical composite cognitive test; APOE = apolipoprotein E; CSF = cerebrospinal fluid; MCI = mild cognitive impairment; PET = positron emission tomography; TTE = time to event.

Recruitment occurs in multiple ways, including via:

1. The web-based [Alzheimer’s Prevention Registry GeneMatch](#) program
2. Local recruitment efforts at sites
3. Centralized recruitment campaign (generationprogram.com)
4. 23andMe
Alzheimer’s Prevention Registry: www.endALZnow.org

WHY NOW?

Scientists are making great progress in the fight against Alzheimer’s, but 80% of studies are delayed because too few people sign up. Will you help end Alzheimer’s?

289,150 people have signed up to help end Alzheimer’s. THE NEXT STEP IS YOURS.

1. Sign Up to help end Alzheimer’s
2. Receive Emails about prevention study opportunities and research news
3. Participate in studies you choose and qualify for

Why Join | Find a Study | Spread the Word | Alzheimer’s Prevention 101 | About the Registry
GeneMatch enrollment >52,000
www.endALZnow.org/GeneMatch

GeneMatch Eligibility Requirements

- Between 55 and 75 years old
- Live in the United States
- Do not have a diagnosis of dementia or other cognitive impairment syndrome
1st API 1 trial in Colombia
At risk for early onset, familial AD
Enrollment complete

2nd API trial in APOE 4 homozygotes; 3rd API trial in homozygotes or AB+ APOE4 heterozygotes
At risk for late onset AD
Age 60-75

A4 (current)
At risk for late onset AD because of positive amyloid brain scan, age 65-85
Enrollment complete (1150+)

TOMMORROW
Age, APOE4, TOMM40 AD risk algorithm and trial of pioglitazone
Trial terminated for futility 1/18
Some recent findings

• Termination of Merck BACE inhibitor trial
  – Details unknown, “unlikely that a positive benefit/risk could be established if the trial continued”

• Decision to increase sample size in Biogen aducanumab program

• Lack of benefit seen with Lundbeck and Axona 5HT6 antagonists
  – Suven Phase 2 trial continuing

• Termination of TOMMORROW program: trial of low dose pioglitazone plus study to validate biomarker risk assessment algorithm
  – Details unknown
Some thoughts re recent findings...

- Merck program:
  - Is a BACE inhibitor “too little, too late” in persons with symptoms, elevated brain amyloid, and/or in this age range (with high likelihood of other age-related brain changes?
  - Could a different BACE inhibitor be successful?
Conclusion

- Anti-amyloid therapies: intervene earlier? Combined anti-amyloid MOA’s?
- Anti-tau therapies, alone or as part of cocktail?
- Outreach and recruitment for Alzheimer’s trials, especially prevention studies, is a new global challenge and priority
- US enrollment in the Generation Program mainly via the Alzheimer’s Prevention Registry and GeneMatch, with national, international, and local efforts to expand both
- We hope that you can help us spread the word about all prevention studies!

www.endALZnow.org/GeneMatch
API Team at Banner Alzheimer’s Institute

- Eric M. Reiman & Pierre N. Tariot, PI’s
- Jessica B. Langbaum, co-PI

- Kewei Chen
- David Gordon
- Nellie High
- Laura Jakimovich
- Carolyn Langlois
- Jodie Nichols
- Helen Street
- Trisha Walsh

- Bill Burke, Stead Family Memory Center Director
- Ed Zamrini, Banner Sun Health Research Institute Memory Center Director
Acknowledgements of Support to API

National Institute on Aging
RF1 AG041705-01A1, UF1 AG046150, R01 AG031581, R01 AG055444-01, P30 AG19610, AMP (pending)

Industry
Genentech/Roche, Avid/Eli Lilly, Novartis, Amgen

Foundations
Banner Alzheimer’s Foundation, Alzheimer’s Association, anonymous international foundation, FBRI, Flinn Foundation, Forget Me Not Initiative, GHR, Geoffrey Beene Foundation, Nomis Foundation

Colciencias and U de A
1115-545-31651, 1115-657-4185

State of Arizona
Arizona Alzheimer’s Consortium

Our colleagues, collaborators, & supporters
Our valued research participants
Robust Alzheimer’s Pipeline Offers Promise for Treatment – Despite Recent Track Record

MORE THAN A DECADE SINCE A NOVEL ALZHEIMER’S DRUG WAS APPROVED

Namenda was approved by the FDA in 2003, marking the last time a novel Alzheimer’s therapy reached the market.¹

PIPELINE OUTLOOK

There are approximately 50 drugs in Phase 2 trials and about a dozen drugs in Phase 2/3 trials.²

ROUTE OF ADMINISTRATION

Several of these new, innovative treatments will be administered by infusion – requiring new requirements for settings of care.

<table>
<thead>
<tr>
<th>Phase 3 Drugs in Development That Could Launch in the Next Five Years</th>
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</thead>
<tbody>
<tr>
<td><strong>2016</strong></td>
</tr>
<tr>
<td>Brexpiprazole</td>
</tr>
<tr>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Solanezumab</td>
</tr>
<tr>
<td>Masitinib</td>
</tr>
<tr>
<td>TauKine</td>
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<tr>
<td>Sodium Oligo</td>
</tr>
<tr>
<td>Azeliragon</td>
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<tr>
<td>Nilvadipine</td>
</tr>
<tr>
<td>ALZT-01</td>
</tr>
<tr>
<td>AVP-786</td>
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<tr>
<td>ALZ-801</td>
</tr>
<tr>
<td>Aducanumab</td>
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<tr>
<td>Abaloside</td>
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<tr>
<td>Verubecestat</td>
</tr>
<tr>
<td>Pioglitazone</td>
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</tbody>
</table>

**KEY**
- Red: Estimated Trial Completion
- Blue: Estimated Regulatory Filing
- Red: Estimated Launch Date
Pharmacologic Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Dementia

- 51 trials. 3 studied dementia medications, 16 antihypertensives, 4 diabetes medications, 2 NSAIDs or aspirin, 17 hormones, and 7 lipid-lowering agents.
- In persons with normal cognition:
  - Estrogen and estrogen–progestin increased risk for dementia or combined outcome of MCI/dementia
  - High-dose raloxifene decreased risk for MCI but not dementia
  - Antihypertensives (4 trials), NSAIDs (1 trial) and statins (1 trial) did not alter dementia risk
- In persons with MCI, cholinesterase inhibitors did not reduce dementia risk
- “Evidence does not support use of these pharmacologic treatments for cognitive protection in persons with normal cognition or MCI.”

Revised dynamic biomarkers of the AD pathological cascade model. C. Jack et al 2013
DIAN-TU NexGen:
- 4+ years of treatment
- Novel biomarkers
- Uses DIAD-specific Disease Progression Model based on DIAN Obs. data.
- Cognitive interim analysis
- Dose for maximal effect
- Home-based cognitive testing
- Population: with or at-risk for a DIAD mutation; -15 to +10 years of EYO; CDR 0, 0.5, 1.
Dominantly Inherited Alzheimer Network (DIAN)*

1. Establish an international registry of participants at risk for dominantly inherited AD (mutation carriers and non-carriers; presymptomatic and symptomatic).

2. Evaluate clinical and cognitive measures with imaging, CSF, and blood biomarkers in a uniform manner at entry and longitudinally thereafter.

3. Determine the temporal order and rate of change of AD changes in clinical, cognitive, neuroimaging, and biomarker indicators.

4. DIAN Treatment Unit (TU) launched subsequently, sites worldwide

✓ Current DIAN observational cohort > 500.

*UF1 AG032438, RJ Bateman, PI; German Center for Neurodegenerative Diseases (DZNE); Government Agency for Scientific Research from Argentina (Agencia- Mincyt - CONICET); Japan’s Health and Labour Sciences Research Grant (Research and Development Project on Dementia); National Grants from Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (since 2013)
DIAN Resources

Websites:
• DIAN Observational www.dian-info.org
• DIAN Expanded Registry www.dianexr.org
• DIAN-TU www.dian-tu.org

Contact Information:
• DIAN-EXR email: dianexr@wustl.edu
• DIAN Expanded Registry Coordinator 1-844-DIAN-EXR (844-342-6397)
• DIAN Global Coordinator, 1-314-286-2643