A Family Matter: Genetics & Alzheimer’s Disease

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The first case of Alzheimer’s disease

Auguste Deter was first seen by Dr. Alois Alzheimer when she was 51.

Dr. Alzheimer reported Auguste had a “peculiar disorder of the cerebral cortex” and admitted her to his hospital unit due to her substantial forgetfulness and hallucinations.

Dementia progressed rapidly and she died 5 years later, in 1906, at age 56.
Hereditary (autosomal dominant) Alzheimer’s disease

A parent with an autosomal dominant Alzheimer’s causing gene has a **50%** chance of passing down the mutated gene to their biological child.
## Genes involved in autosomal dominant Alzheimer’s

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th># of mutations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSEN1</td>
<td>14</td>
<td>150</td>
</tr>
<tr>
<td>PSEN2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>APP</td>
<td>21</td>
<td>50</td>
</tr>
</tbody>
</table>


Nearly all these mutations lead to the overproduction of a longer, toxic version of amyloid-β peptide. Copies of this protein fragment stick together and build up in the brain, forming clumps called amyloid plaques that are a characteristic feature of Alzheimer disease. A buildup of toxic amyloid-β peptide and the formation of amyloid plaques likely lead to the death of neurons and the progressive signs and symptoms of this disorder.
Genetics and Alzheimer’s

- **Alzheimer’s disease-causing genetic mutations**
  - PSEN1, PSEN2 & APP

- **Alzheimer’s disease protective genetic mutations**
  - A673T (on APP gene)

- **Alzheimer’s disease susceptibility genes**
  - APOE ε4 allele
  - Trisomy 21
  - Others
Colombia: Home to World’s Largest ADAD Population
Founder effect and common ancestry of 14 families

Individual II 1: originates families C2, C5, C7, C12, C21
Individual II 2: originates families C1, C9, C13
Individual II 3: originates families C3, C4, C6, C8, C11
Field work to identify the families
People Registered 5846

- E280A Population
  - 25 Families
  - >6000 Members

- People Registered
  - 5846

- 4619 Non-Carriers
- 1192 Carriers
- 35 No genotype

GNA, Banner and Genentech
Progression of Disease in PSEN1 E280A Carriers

Acosta-Baena et al, Lancet Neurol 2011
Kindred ~ 25 known families with common ancestry

- N = 5000 living individuals
- 1000 with the E280A (Glu280Ala) PSEN1 mutation
- Autosomal dominant, 100% penetrance
- Median age of MCI = 44 years old, dementia = 49 years old
Fleisher et al, Lancet Neurol 2012

25 years before kindred’s median age at clinical onset

mutation carriers, healthy

Fibrillar Aβ deposition

Age
Rationale for Launching the API Program in 2008

- The public health need
- A “preclinical stage” of Alzheimer’s disease exists during which silent brain changes occur
- We had plausible experimental therapies
- We had biomarkers of Alzheimer’s disease progression
- We needed to develop improved cognitive/clinical endpoints
- Earlier treatment may have a better chance to slow the progression of the disease

Reiman et al., 2010 Biomarkers Med
API ADAD Trial: “A top 10 world changing idea”

Early Treatment for Alzheimer’s

A drug trial of 300 Colombians could reveal a way to prevent the disease from ever starting.

Alzheimer’s disease remains virtually untreatable. More than 100 experimental drugs have failed to halt the condition that robs people of their memories, their relationships, and, ultimately, their identity. Now scientists will be testing a new strategy for preventing the horrific condition from starting in the first place, just as people use statins to lower their cholesterol and avoid heart disease. People at risk for Alzheimer’s could someday pop pills to keep the disease away.

Researchers will be investigating a drug that destroys an elusive protein called amyloid, suspected as a primary contributor to Alzheimer’s. Until recently, amyloid plaques could only be seen by dissecting the brain after death. Yet advanced positron-emission tomography scans of living people’s brains, a recent innovation, have shown that by the time symptoms appear, amyloid has been silently accumulating for up to 20 years. Perhaps, if the brain is reversibly damaged, making any drug useless. No one knows for sure, however, whether amyloid causes Alzheimer’s or is merely a by-product of the disease. The new study may provide an answer to the mystery.

Set to start early in 2018, the approval process could involve 300 members of dementia-related families in Colombia whose age and particularly devastating form of Alzheimer’s begins in the prime of life. By testing 300 and 80, many or no helpless at least. Normally it is impossible to predict who will...
Study design and inclusion/exclusion criteria

**Study Duration**
5-8 years in the double-blind study period A (common-close design; all participants stay on treatment until the last randomized participant reaches 5 years (w260))

**Treatment**
Crenezumab vs placebo (720 mg* SC q2w or 60 mg/kg IV q4w)

**Primary Outcome Family**
Annualized rate of change in (1) API ADAD composite score and (2) episodic memory assessed by the Free and Cued Selective Reminding Test (FCSRT) cueing index (both outcomes assessed every 6 months)

**Key Secondary Outcomes**
Amyloid PET SUVr → Time to MCI/dementia due to AD → CDR-SB → Time to non-zero in CDR-GS → RBANS total score

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**Key Inclusion/Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Member of PSEN1 E280A kindred</td>
<td>Sig medical, neurologic, or psychiatric condition</td>
</tr>
<tr>
<td>30-60 years old</td>
<td>Body weight &lt; 45 or &gt; 120 kg</td>
</tr>
<tr>
<td>Does not meet criteria for MCI or dementia</td>
<td>Medications that impair cognition</td>
</tr>
<tr>
<td>MMSE ≥ 24 (&lt; 9 yrs educ) or ≥ 26 (≥ 9 yrs educ)</td>
<td>Strokes, ARIA-E or &gt;4 microhemorrhages</td>
</tr>
<tr>
<td>Study partner</td>
<td>Pregnancy</td>
</tr>
</tbody>
</table>

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*Initially 300 mg; see next slide*

- AD, Alzheimer's disease; ADAD, autosomal dominant Alzheimer’s disease; API, Alzheimer’s Prevention Initiative ARIA-E, amyloid-related imaging abnormalities-edema; CDR-GS, Clinical Dementia Rating – Global Score; CDR-SB, Clinical Dementia Rating – Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Evaluation; PET, positron emission tomography; PSEN1, presenilin-1; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SUVr, standard uptake value ratio; q2w, every two weeks; q4w, every four weeks.
The evolving science of AD led to modifications to the API trial where the dose of crenezumab increased more than 7-fold over the duration of the study, from 300 mg every 2 weeks to ~4200 mg a month.
Pre-screening and screening of the API Colombia participant recruitment

- Launched in December 2013
- Last randomization in February 2017
## Baseline characteristics

Baseline characteristics were generally well balanced across the arms

<table>
<thead>
<tr>
<th></th>
<th>Crenezumab - Carrier (n = 85)</th>
<th>Placebo - Carrier (n = 84)</th>
<th>Placebo - Non-carrier (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)*</td>
<td>36.8 (5.3)</td>
<td>36.9 (6.3)</td>
<td>43.3 (7.2)</td>
</tr>
<tr>
<td>Female sex</td>
<td>51.8%</td>
<td>70.2%</td>
<td>68.7%</td>
</tr>
<tr>
<td>Education &gt;=9 years*</td>
<td>56.5%</td>
<td>56.0%</td>
<td>45.8%</td>
</tr>
<tr>
<td>&gt;=1 APOE4 allele*</td>
<td>22.4%</td>
<td>20.2%</td>
<td>22.9%</td>
</tr>
<tr>
<td>CDR-GS=0*</td>
<td>90.6%</td>
<td>88.1%</td>
<td>94.0%</td>
</tr>
<tr>
<td>CDR-SB, mean (SD)</td>
<td>0.16 (0.38)</td>
<td>0.14 (0.43)</td>
<td>0.05 (0.17)</td>
</tr>
<tr>
<td>API Composite, mean (SD)</td>
<td>81.9 (8.8)</td>
<td>80.4 (11.3)</td>
<td>83.7 (9.8)</td>
</tr>
<tr>
<td>FCSRT CI, mean (SD)</td>
<td>0.78 (0.16)</td>
<td>0.76 (0.20)</td>
<td>0.83 (0.14)</td>
</tr>
<tr>
<td>MMSE Total Score, mean (SD)</td>
<td>28.9 (1.3)</td>
<td>28.8 (1.5)</td>
<td>29.2 (1.0)</td>
</tr>
<tr>
<td>NPI, mean (SD)</td>
<td>0.26 (0.89)</td>
<td>0.64 (2.16)</td>
<td>0.37 (1.95)</td>
</tr>
<tr>
<td>FAST, mean (SD)</td>
<td>1.09 (0.29)</td>
<td>1.13 (0.37)</td>
<td>1.01 (0.11)</td>
</tr>
<tr>
<td>^Amyloid PET Positive, Amyloid PET SUVr, mean (SD)</td>
<td>61.2% (1.15)</td>
<td>48.8% (1.11)</td>
<td>0% (0.96)</td>
</tr>
</tbody>
</table>

Data on file. *Stratification variables, ^Whole cerebellum used as the reference region; threshold > 1.1 defined as positive

API, Alzheimer’s Prevention Initiative; APOE4, apolipoprotein E4; CDR-GS, Clinical Dementia Rating – Global Score; CDR-SB, Clinical Dementia Rating – Sum of Boxes; FAST, Functional Assessment Staging Tool; FCRST, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Evaluation; NPI, Neuropsychiatric Inventory; PET, positron emission tomography; SD, standard deviation; SUVr, standard uptake value ratio.
Baseline Aβ PET measurements

Chance to explore treatment effects in A+ and A- carriers and inform the design, size, selection criteria, and endpoints in future secondary and primary prevention trials.

55% A+ and 45% A- using a 1.10 SUVR (24.3 Centiloid) Threshold

Aβ, amyloid-beta; AD, Alzheimer's disease; PET, positron emission tomography; SUVR, standard uptake value ratio.
## Participant disposition

Excellent adherence and retention rates over 8-year study

<table>
<thead>
<tr>
<th></th>
<th>Crenezumab - Carrier (n = 85)</th>
<th>Placebo - Carrier (n = 84)</th>
<th>Placebo - Non-carrier (n = 83)</th>
<th>All Participants (N = 252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed study period A</td>
<td>79 (92.9%)</td>
<td>78 (92.9%)</td>
<td>80 (96.4%)</td>
<td>237 (94.0%)</td>
</tr>
<tr>
<td>Completed treatment in period A</td>
<td>76 (89.4%)</td>
<td>75 (89.3%)</td>
<td>77 (92.8%)</td>
<td>228 (90.5%)</td>
</tr>
</tbody>
</table>

The primary reason for treatment discontinuation was participant decision (n = 12)
Treatment exposure
Mean 6.1 years of treatment, up to 7.9 years, low impact of COVID-19

- Average SC treatment duration 4.3 years
- Average IV treatment duration 2 years
- Average SC dose intensity 99%
- Average IV dose intensity 88%

All participants including both carriers and non-carriers who received at least 1 dose of study drug are included in this plot. IV, intravenous; SC subcutaneous.
Main outcomes

- Analyzed using random coefficient regression model (RCRM)\(^1\) in mutation carriers receiving at least 1 dose of study drug
  - Provides a simple and holistic measure of average clinical benefit over full duration of trial
- **Dual primary outcomes**
  - API ADAD Composite Test total score assessing overall cognitive function ($\alpha=0.04$) **and/or**
  - Free and Cued Selective Reminding Task (FCSRT) Cueing Index assessing episodic memory ($\alpha=0.01$)
  - Trial positive if either or both were significant
- **Key secondary outcomes**
  - Amyloid PET SUVr
  - Time to MCI or dementia due to AD
  - Change in Clinical Dementia Rating Sum of Boxes (CDR-SB)
  - Time to CDR Global >0
  - RBANS Total Score

The RCRM adjusts for age, education, APOE4 and CDR-GS at baseline and adjusts for treatment assignment for slope; both random intercept and slope terms are added to the model.

AD, Alzheimer's disease; ADAD, autosomal dominant Alzheimer's disease; API, Alzheimer's disease; APOE4, apolipoprotein E4; CDR-GS, Clinical Dementia Rating – Global Score; CDR-SB, Clinical Dementia Rating – Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; MCI, mild cognitive impairment; PET, positron emission tomography; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCRM, random coefficient regression model; SUVr, standard uptake value ratio.

## Results for primary outcomes

Mutation carriers only

<table>
<thead>
<tr>
<th></th>
<th>API Composite (Range 0 – 100)</th>
<th>FCSRT Cueing Index (Range 0 – 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crenezumab (n = 84)</td>
<td>Placebo (n = 84)</td>
</tr>
<tr>
<td>Annualized rate of change (SE) points per year</td>
<td>-1.10 (0.29)</td>
<td>-1.43 (0.29)</td>
</tr>
<tr>
<td>Difference in annualized rate of change, 95% CI</td>
<td>0.33, (-0.48, 1.13)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.43</td>
<td>0.16</td>
</tr>
<tr>
<td>Relative reduction, 95% CI*</td>
<td>22.9%, (-53.1%, 61.1%)</td>
<td></td>
</tr>
</tbody>
</table>

API, Alzheimer’s Prevention Initiative; CI, confidence interval; FCSRT, Free and Cued Selective Reminding Task; SE, standard error.

*95% CI for relative reduction is based on the bootstrap method with replacement.
## Dual primary and key secondary outcomes

Results numerically favor crenezumab across primary and secondary outcomes in relative reduction scale.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Carrier</th>
<th>Relative Effect</th>
<th>P value*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>API ADAD Composite</td>
<td>168</td>
<td>22.9%</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>FCSRT Cueing Index</td>
<td>168</td>
<td>19.9%</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Amyloid PET SUVr</td>
<td>168</td>
<td>3.6%</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Time to MCI/dementia due to AD</td>
<td>168</td>
<td>20.8%</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>CDR Sum-of-Boxes</td>
<td>168</td>
<td>8.8%</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Time to non-Zero in CDR-GS</td>
<td>150</td>
<td>8.1%</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>RBANS Total Score</td>
<td>168</td>
<td>43.8%</td>
<td>0.55</td>
<td></td>
</tr>
</tbody>
</table>
**Biomarker outcomes**

<table>
<thead>
<tr>
<th>Biomarker outcome</th>
<th>Carriers</th>
<th>Relative reduction</th>
<th>P value*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ PET (Florbetapir SUVR)</td>
<td>168</td>
<td>3.6%</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Tau PET (ERC GTP1 SUVR)</td>
<td>83</td>
<td>51.1%</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>FDG PET (sROI FDG SUVR)</td>
<td>168</td>
<td>18.1%</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>CSF pTau181</td>
<td>84</td>
<td>37.4%</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>CSF tTau</td>
<td>90</td>
<td>28.7%</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>CSF NfL</td>
<td>90</td>
<td>18.2%</td>
<td>0.46</td>
<td></td>
</tr>
</tbody>
</table>

* P-values are uncorrected for multiple comparisons.

Continuous outcomes were modeled by the RCRM. Models were stratified for age, group, education, APOE4 and CDR-GS.

Forest plots show mean reductions in biomarker progression in the crenezumab carrier group compared to those in the placebo carrier group and 95% CIs.

Aβ, Alzheimer’s disease; APOE4, apolipoprotein E4; CI, confidence interval; CSF, cerebrospinal fluid; ERC, entorhinal cortex; FDG, fluorodeoxyglucose; GTP1, Genentech Tau Probe 1; NfL, neurofilament light chain; PET, positron emission tomography; pTau, phosphorylated Tau; RCRM, random coefficient regression model; sROI, statistical region of interest; SUVR, standard uptake value ratio; tTau, total Tau.
Where do we go from here?

Why Didn’t She Get Alzheimer’s? The Answer Could Hold a Key to Fighting the Disease

Researchers have found a woman with a rare genetic mutation that has protected her from dementia even though her brain has developed major neurological features of the disease.
Brain Imaging and Fluid Biomarkers in ADAD Carriers

**Figure 1:** Longitudinal change rates of plasma p-tau and neurofilament light chain levels by age. Log transformed longitudinal data. Shaded areas represent 95% probability intervals. (A) Change in p-tau by age in carriers and non-carriers. Age is the x-axis between the carrier and non-carrier mean values at any given age. Non-carrier sets are nested in a log transformation data nested model using linear mixed-effects models, a robust control group, and Bayesian Mark chain Monte Carlo analysis. The underlying models procedures used in the generation of these representations of the longitudinal change rates of plasma p-tau are very similar to those used to generate the representations in Figure 1 (p-tau versus plasma p-tau between mutation carriers and non-carriers) to the dependent variable (p-tau, the rate of change in plasma p-tau concentrations) of the models was different between the analysis.”

Acknowledgments

National Institute on Aging
RF1 AG041705, 1UF1AG046150, R01 AG055444, R01 AG058468, R43 AG055218, R01 AG063954, R01 AG069453, R01 AG070349, 1R33 AG070604-01A1, P30 AG072980

Industry Partners for API Trials
Genentech/Roche, Avid/Eli Lilly, Novartis, Amgen

Foundations
Alzheimer’s Association, Banner Alzheimer’s Foundation, FBRI, Flinn Foundation, GHR Foundation, Nomis Foundation

Colciencias
1115-408-20512, 1115-408-20543

State of Arizona
Arizona Alzheimer’s Consortium

Our colleagues, collaborators, & supporters
Our valued research participants
Thank you!