Disclosure: Randall J. Bateman, M.D.

Sources of Research Support:
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Alzheimer’s Association, American Health Assistance Foundation, Glenn Foundation, Ruth K. Broadman Biomedical Research Foundation, Anonymous Foundation, Merck research collaboration

DIAN Pharma Consortium: AIP, Biogen, Eisai, Elan, Forum, Genentech, Lilly, Mithridion, Novartis, Pfizer, Roche, Sanofi
Companies: Co-founder C2N Diagnostics
Invited Speaker: BMS, Lilly, Merck, Pfizer, Elan, Wyeth, Novartis, Abbott, Biogen, Takeda Foundation
Editorial Duties: ad-hoc reviewer
Consulting Relationships: DZNE, IMI, Forum (SAB), Merck, Roche, Sanofi
Disclosure – Eric M. McDade, D.O.

Sources of Research Support: -
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Alzheimer’s Association, GHR Foundation, Anonymous Foundation
DIAN Pharma Consortium: Amgen, AstraZeneca, Biogen, Eisai, Elan, Eli Lilly, Forum, Genentech, Roche, Janssen AIP, Mithridion, Novartis Pharm AG, Pfizer, Sanofi-Aventis
Invited Speaker: Alzheimer Association
Consulting: American College of Physician (MKSAP18)
DIAD Family Conference
July 18th, 2015 AAIC, Washington, D.C.

• Historic, first-time meeting of DIAD families
  • 98 DIAD individuals and family members attended
  • a family networking opportunity
• Dialogue with researchers, pharmaceutical companies, foundations and donors, NIH, members of Congress and regulators (FDA, EMA).
• Discussions:
  – Scientific, medical, regulatory, advocacy and disease burden
  – Support sessions for asymptomatic and symptomatic individuals and their families
• Sponsored by the DIAN-TU and Alzheimer’s Association
• “It is really cutting edge, and it is the right thing to do – the trial, the observational study……” Janet Woodcock, 2015 DIAD Family Conference, https://dian-tu.wustl.edu/en/2015-family-conference/

Next DIAD Family Conference:
July, 2016 AAIC, Toronto, Canada
2016 DIAD Family Conference

Too Young To Forget

Saturday, July 23rd, 8:00am-2:00pm ET

Fairmont Royal York Hotel (Ballroom) • Toronto, Ontario

Agenda Overview

• Family Presentations
• AD Research Updates (DIAN, DIAN-TU, field)
• Advocacy and Public Policy
• Panel Discussion
  – Advocacy and Pharma
  – Drug Re-purposing for AD
• Non-pharmacological & Pharmacological Approaches and Modifiable Risk Factors
• Caregiving and Long-Term Care
• Legal and Financial Matters
• Ethical Issues in Risk Disclosure
• Support Sessions
Family Presentation

Living with early onset AD
STATE OF ALZHEIMER DISEASE RESEARCH

Serge Gauthier, C.M., MD, FRCPC
McGill University Research Center for Studies in Aging
Douglas Mental Health University Institute
Montréal, Canada
DIAN and DIAN-TU Update
Dominantly Inherited Alzheimer’s Disease Family Meeting
July 23rd, 2016
Toronto, Ontario, Canada

Randall Bateman, M.D.
DIAN Trials Unit Director
Washington University School of Medicine
Dominantly Inherited Alzheimer’s Disease

• A rare form of Alzheimer’s disease
• Caused by an inherited gene mutation
• 50% chance of passing the gene to children
• Early onset
• Mutations cause predictable age of onset
Dominantly Inherited Alzheimer’s Disease (DIAD)

• Less than 1% of AD cases result from autosomal dominant mutations in three genes directly involved in amyloid beta (Aβ) production
  • Amyloid precursor protein (APP)
  • Presenilin 1 (PSEN1)
  • Presenilin 2 (PSEN2)

• Auguste D., the first AD patient ever described by Alois Alzheimer, was later found to carry an DIAD mutation in presenilin 1 (F176L)
Participant Interaction and Partnership

**DIAN Expanded Registry**

Serves as a key information and referral source for the DIAN Observational and DIAN-TU trials

Register: [www.dianexr.org](http://www.dianexr.org)
Call: 1-844-DIAN-EXR (342-6397)
Email: dianexr@wustl.edu
DIAN Observational and DIAN-TU Trial sites

- DIAN Observational ONLY
- DIAN-TU ONLY
- DIAN Observational & DIAN-TU
- Potential Future Sites
Dominantly Inherited Alzheimer Network (DIAN) Observational Study*

The DIAN Study is a multi-center, international, observational, longitudinal study of individuals with or at risk for autosomal dominant AD.

- The DIAN has currently enrolled more than 445 participants
- Site expansion in Argentina, Japan and Korea
- Over 20 DIAN-related presentations at 2016 AAIC
- 20 journal publications in 2015

*UF1 AG032438, RJ Bateman, PI; the German Center for Neurodegenerative Diseases (DZNE) completely supports German DIAN sites.
DIAN amyloid deposition by years to estimated age of onset

Estimated Age of Onset = -25

Courtesy of Tammie Benzinger; Bateman et. al NEJM 2012
Tau PET: DIAD and Sporadic AD

DIAN CDR 0.5
Sporadic AD CDR 0.5

ACCELERATING MEDICINES PARTNERSHIP (AMP)
Progression of dominantly inherited AD

1° prevent
2° prevent
Cog decline
Prodromal
Mild-Moderate dementia

The DIAN; Bateman et al NEJM 2012
Comparison of Autosomal Dominant and Sporadic Alzheimer’s Disease

<table>
<thead>
<tr>
<th></th>
<th>Autosomal Dominant AD</th>
<th>Sporadic AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>Amnestic</td>
<td>Amnestic</td>
</tr>
<tr>
<td>Cognitive deterioration</td>
<td>Memory, frontal/executive, generalized cognitive decline</td>
<td>Memory, frontal/executive, generalized cognitive decline</td>
</tr>
<tr>
<td>MRI</td>
<td>Hippocampal atrophy and whole brain atrophy</td>
<td>Hippocampal atrophy and whole brain atrophy</td>
</tr>
<tr>
<td>PiB PET</td>
<td>Cortex plus basal ganglia</td>
<td>Cortex</td>
</tr>
<tr>
<td>FDG PET</td>
<td>Parieto-occipital hypometabolism</td>
<td>Parieto-occipital hypometabolism</td>
</tr>
<tr>
<td>CSF Aβ 42</td>
<td>Decreased by 50%</td>
<td>Decreased by 50%</td>
</tr>
<tr>
<td>CSF tau</td>
<td>Increased by 2-fold</td>
<td>Increased by 2-fold</td>
</tr>
</tbody>
</table>
DIAN Obs Impact on DIAN-TU Therapeutic Trials

- **Proof of principle:** DIAN studies can be performed globally to the highest standards
- **Trial development:** participation provides crucial data used to design and develop DIAN-TU trial
- **Novel mutations:** Enables families to be eligible for DIAN-TU trials
Through public/private support and partnership, the DIAN-TU has launched trials to provide advancement of treatments, scientific understanding and improvements in the approach to Alzheimer’s disease drug developments.

*Financial support has also been provided by anonymous sources.
DIAN-TU-001 Trial

• Placebo controlled, **double-blinded**, cognitive outcome trial with biomarker interim analysis

Three-arm trial:

  Gantenerumab, Solanezumab, Pooled Placebo

• ~210* enrolled to reach 138 mutation carriers (52 per active drug arm, 34 pooled placebo)  *Estimated 72 non-carriers (placebo)

• Drug treatment duration = **4 years** (2 years for biomarker endpoint with an additional 2 years for cognitive endpoint)

• **Trial has now completed enrollment of all participants**
DIAN-TU-001: Current Status

DIAN-TU-001 Enrollment Metrics

- Randomized: 81%
- Screen Fail: 19%

DIAN-TU-001: Participant Status

- Active: 92%
  - Early Term ('True'): 4%
  - Early Term (Other): 4%

Recruitment Sources

- DIAN Observational: 47%
- DIAN Expanded Registry: 38%
- Sites/Other: 15%
## DIAN-TU Trial Data

<table>
<thead>
<tr>
<th>Test Measure</th>
<th>Assessments per participant</th>
<th>Quantity</th>
<th>Compliance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR, CDR-SB, MMSE, FAQ, GDS, NPIQ</td>
<td>5</td>
<td>≈1000</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Cognitive Measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CogState, Pencil / Paper</td>
<td>5-10</td>
<td>≈ 1000-2000</td>
<td>99%</td>
</tr>
<tr>
<td><strong>Fluid Biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma, Serum, CSF</td>
<td>4</td>
<td>≈ 800</td>
<td>99%</td>
</tr>
<tr>
<td><strong>Imaging Biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PiB, AV-45, FDG</td>
<td>4</td>
<td>≈ 800</td>
<td>99%</td>
</tr>
</tbody>
</table>

### Imaging Modality / Tracer

<table>
<thead>
<tr>
<th>Imaging Modality / Tracer</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 4</th>
<th>Total # Scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV-1451</td>
<td>30</td>
<td>107</td>
<td>141</td>
<td>141</td>
<td>419</td>
</tr>
</tbody>
</table>
The Next Generation of DIAN-TU Trials (DIAN-TU NexGen)

Goal: *Accelerate identification and registration of effective drugs for prevention and treatment of AD*

- DIAN-TU Trial Platform
  - **Test multiple drugs in parallel** (efficient use of rare population with shared placebos)
  - **More rapidly determine efficacy or futility** using a DIAD Disease Progression Model
  - **Maximal dose**
  - Maximal collection and use of data
    - pooled placebo, minimizes numbers of placebo
    - Composite for cognitive endpoint (compared to single measures)
    - Home-based cognitive testing
    - Observational data
  - Develop surrogate biomarkers to accelerate future AD trials
  - **Future aim: combination therapy**
DIAN-TU NexGen Trial Design

DIAN-TU NexGen:
- 2 new drug arms
- 4 years of treatment
- Uses DIAD-specific Disease Progression Model based on DIAN observational data.
- Cognitive interim analysis at 2 and 3 years
- Dose adjustment for maximal effect
- Home-based cognitive testing

22 July 2016
A selected brief history of Alzheimer’s disease modifying prevention

1906 - Dr. Alois Alzheimer describes first Alzheimer’s disease patient – disease of brain – plaques and tangles

1991 - Mutations discovered that cause early onset Alzheimer’s in families – later discovered in Alzheimer’s first patient

2012 - Aβ lowering mutation discovered which dramatically protects against Alzheimer’s

2012 – first prevention trial against amyloid-beta is launched

2014 - Prevention trials targeting at risk individuals

2000’s – first drugs targeting Aβ - A cause of Alzheimer’s are developed

Senility known throughout history

1906 - Dr. Alois Alzheimer describes first Alzheimer’s disease patient – disease of brain – plaques and tangles
DIAN EXPANDED REGISTRY
Expanded Registry

• Single location to identify researchers and those with/at risk of DIAD
  – Coordination with registrants and DIAN sites
  – Coordination across large geographic regions
  – Outreach for communication

• Expand the identification of families with DIAD mutations
  – Evaluate families for risks consistent with DIAD
  – Identify new genetic mutations of DIAD
    - Expands access to DIAN-TU and DIAN Observation

• Increase awareness of DIAD
  – DIAD Family Conference
PRIMARY PREVENTION
Primary Prevention

• DIAN-TU and other secondary prevention platforms are well established

• Population ( >90% of recently surveyed stated they are willing to stay in trials > 5 years; majority agree that those >15 years before EYO should be able to be in trials)

• Improved understanding of temporal ordering of biomarkers (1st phase of primary prevention), particularly in DIAD

• Improved therapeutic target engagement (PK/PK & Safety)
Primary Prevention in DIAN-TU

• Challenges -
  – Duration of trial
  – Starting point
  – Design of intervention
  – Discussion of Industry perspective (previous experience) and Regulatory considerations
Primary Prevention

• Next steps
  – Grant Funding for Start up
    • Trial design
    • Operational Considerations
    • Engagement of key partners
  – Wednesday June 27th, NexGen Meeting
  – CTAD San Diego, December 2016

• Interest from DIAN Steering Committee Members?
Discussion Points

• Importance of being in DIAN obs
• Open label extension
• DIAN-TU Primary Prevention trial
• Impact of potential positive readout of ongoing trials in sporadic Alzheimer’s disease
The DIAN (NIH UF1AG032438)
The DIAN participants and family members
The Alzheimer’s Association, ADAD Forum, DIAN Pharma Consortium

Admin – RJ Bateman
Clinical – JC Morris
Biomarkers – AM Fagan
Biostatistics – C Xiong

Genetics – AM Goate
Imaging – T Benzinger
Informatics – D Marcus
Neuropathology – NJ Cairns

Performance Sites

• **United States:** Washington Univ (Bateman), MGH/BWH (Sperling), Butler Hosp/Brown Univ (Salloway), Columbia Univ (Mayeux), Indiana Univ (Ghetti), UCLA (Ringman), U of Pittsburgh (Klunk), Mayo Clinic, Jacksonville (Graff-Radford), UCSD (Galasko)

• **Europe:** Institute of Neurology, Univ College London (Rossor), Ludwig-Maximilians-Universität München (Danek), University of Tübingen (Jucker)

• **Australia:** Prince of Wales Medical Research Institutes, Sydney (Schofield), Mental Health Health Research Institute, Melbourne (Masters), Edith Cowan Univ, Perth (Martins)

• **Japan:** DIAN-Japan (Mori): University Hirosaki (Shoji), Niigata (Ikeuchi), Tokyo (Suzuki), Osaka (Shimada)

• **Argentina:** Beunas Aires (Allegri) – FLENI

• **Korea:** DIAN-Korea (JH Lee): Asan Medical Center (JH Roh)
DIAN-TU Administrative and Clinical Operations Team

Randall Bateman – Director and PI
Stephanie Belyew, Virginia Buckles, Matt Carril, David Clifford, Mary Downey-Jones, Kathy Fanning, Amanda Fulbright, Angela Fuqua, Ron Hawley, Dottie Heller, Michelle Jorke, Denise Levitch, Jacki Mallmann, Tayona Mayhew, Eric McDade, Susan Mills, John Morris, Angela Oliver, Katrina Paumier, Monique Romeo, Anna Santacruz, Jessi Smith, Joy Snider, Annette Stiebel, Shannon Sweeney, Guoqiao Wang, Ellen Ziegemeier

DIAN-TU Cores

Administrative: Randall Bateman and team
Biomarkers: Anne Fagan and team
Biostatistics: Chengjie Xiong, Guoqiao Wang and team
Genetics: Alison Goate, Carlos Cruchaga and team
Imaging: Tammie Benzinger and team
Cognition: Jason Hassenstab and team

DIANTU Collaborators

Project Arm Leaders: Steve Salloway, Martin Farlow
Consultants: Berry Consultants, Univ. of Rochester – Cornelia Kamp, Cardinal Health Regulatory Sciences, Granzer Regulatory Consulting
DIAN-TU Therapy Evaluation Committee: Paul Aisen, Randall Bateman, Dave Clifford, David Cribbs, Bart De Strooper, Kelly Dineen, David Holtzman, Jeffrey Kelly, William Klunk, Cynthia Lemere, Eric McDade, Susan Mills, John Morris, James Myles, Laurie Ryan, Raymond Tait, Robert Vassar
DSMB Members: Gary Cutter, Steve Greenberg, Karl Kieburtz, Scott Kim, David Knopman, Allan Levey, Dave Clifford, Randall Bateman, Kristine Yaffe
ADCS: Ron Thomas and Paul Aisen
University of Michigan: Robert Koeppen
Mayo Clinic: Clifford Jack

We gratefully acknowledge the DIAN and DIAN-TU participants and family members, DIAN Team, DIAN Steering Committee, Knight ADRC, Alzheimer’s Association, ADAD Forum, NIH U01AG042791, NIH R01AG046179, DIAN-TU Pharma Consortium, GHR, Anonymous Foundation, Pharma Partners (Eli Lilly, Hoffman-LaRoche, Avid Radiopharmaceuticals, CogState), and Regulatory Representatives.
DIAN-TU Sites

United States
Columbia University, Lawrence Honig
University of Puerto Rico, Ivonne Jimenez-Velazques
Indiana University, Jared Brosch
University of Pittsburgh, Sarah Berman
Washington University, Joy Snider
University of Alabama, Erik Roberson
Butler Hospital, Ghulam Surti
Emory University, James Lah
Yale University, Christopher Van Dyck
UCSD, Doug Galasko
University of Washington, Seattle, Suman Jayadev

Canada
McGill University, Serge Gauthier
UBC Hospital, Robin Hsiung
Sunnybrook Health Sci Centre, Mario Masellis

Italy
IRCCS Centro San Giovanni di Dio Fatebenefratelli, Giovanni Frisoni
Azienda Ospedaliera Universitaria Careggi, Sandro Sorbi

United Kingdom
The National Hospital for Neurology & Neurosurgery, Catherine Mummery

Australia
Neuroscience Research Australia, William Brooks
The McCusker Foundation, Roger Clarnette
Mental Health Research Institute, Colin Masters

France
Hopital Roger Salengro, Florence Pasquier
Hopital Neurologique Pierre Wertheimer, Maité Formaglio
CHU de Rouen, Didier Hannequin
CHU de Toulouse, Jérémie Pariente
Groupe Hospitalier Pitie, Bruno Dubois

Spain
Hospital Clinic I Provincial de Barcelona, Raquel Sanchez Valle
Resources

Websites:
• DIAN Observational [http://www.dian-info.org](http://www.dian-info.org)
• DIAN Expanded Registry [http://www.dianexr.org](http://www.dianexr.org)
• DIAN-TU [http://www.dian-tu.org](http://www.dian-tu.org)

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