NAPA Scientific Research Sub-committee: Scientific Advances to 2025 goal

Randall Bateman, M.D.
Charles F. and Joanne Knight Distinguished Professor of Neurology
DIAN and DIAN-TU PI and Director
Washington University School of Medicine

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Dr. Randall J. Bateman – Disclosure

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NIH U01AG042791-S1 (DIAN-TU)
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NIH R56AG053267 (DIAN-TU NexGen)
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DIAN-TU Pharma Consortium: (Active: Biogen, Eisai, Eli Lilly & Co., Janssen, Roche/Genentech, United Neuroscience. *Previous: AbbVie, Amgen, AstraZeneca, Forum, Mithridion, Novartis, Pfizer, Sanofi*)
DIAN-TU Trial Companies: Eli Lilly and Co., Roche, Janssen, Avid Radiopharmaceuticals

Invited Speaker (12 months): Roche, Novartis, USC
Editorial Board: Alzheimer's and Dementia, Alzheimer's Research and Therapy, The Journal of Prevention of Alzheimer's Disease
Consulting Relationships (12 months): AC Immune, Eisai, Roche

Companies:

- Drs. Randall J. Bateman and David M. Holtzman are co-founders of C2N Diagnostics. Washington University has equity ownership interest in C2N Diagnostics.
  - Dr. Bateman, Dr. Holtzman, and Dr. Kwasi Mawuenyega are co-inventors of the stable isotope labeling kinetics and blood plasma assay technology licensed by Washington University to C2N Diagnostics. Through these relationships, Washington University, Drs. Bateman, Holtzman, and Mawuenyega are entitled to receive royalties and/or equity from the license agreement with C2N. Drs. Bateman and Holtzman receive income from C2N Diagnostics for serving on the scientific advisory board.
  - Dr. Holtzman is an inventor on a patent licensed by Washington University to C2N Diagnostics on the therapeutic use of anti-tau antibodies. C2N has licensed certain anti-tau antibodies to AbbVie for therapeutic development. Washington University and Dr. Holtzman are entitled to royalties from the sale and distribution of the licensed and sublicensed anti-tau antibodies.
- Dr. Holtzman is an inventor on patents for one of the treatments (solanezumab), currently being tested in the DIAN clinical trials. If solanezumab is approved as a treatment for Alzheimer's disease or Dominantly Inherited Alzheimer's Disease, Washington University and Dr. Holtzman will receive part of the net sales of solanezumab from Eli Lilly, which has licensed the patents related to solanezumab from Washington University.

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Alzheimer's disease – the challenge

- The most common form of dementia
- No cure (or disease modifying treatment) currently for Alzheimer's (universally fatal)
- Personal and societal impact
  - >**30 million patients** suffering from Alzheimer's worldwide.
  - **6th leading cause of death** and only increasing major cause of death.
  - **>$200 billion** annual cost in US.
  - Undiagnosed or misdiagnosed in half of all patients

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NAPA 2025 Goals – 10 year anniversary

- *Prevent and effectively treat Alzheimer's disease by 2025*
- *Optimize care quality and efficiency*
- Expand supports for people with Alzheimer's disease and their families
- Enhance public awareness and engagement
- *Track progress and drive improvement*

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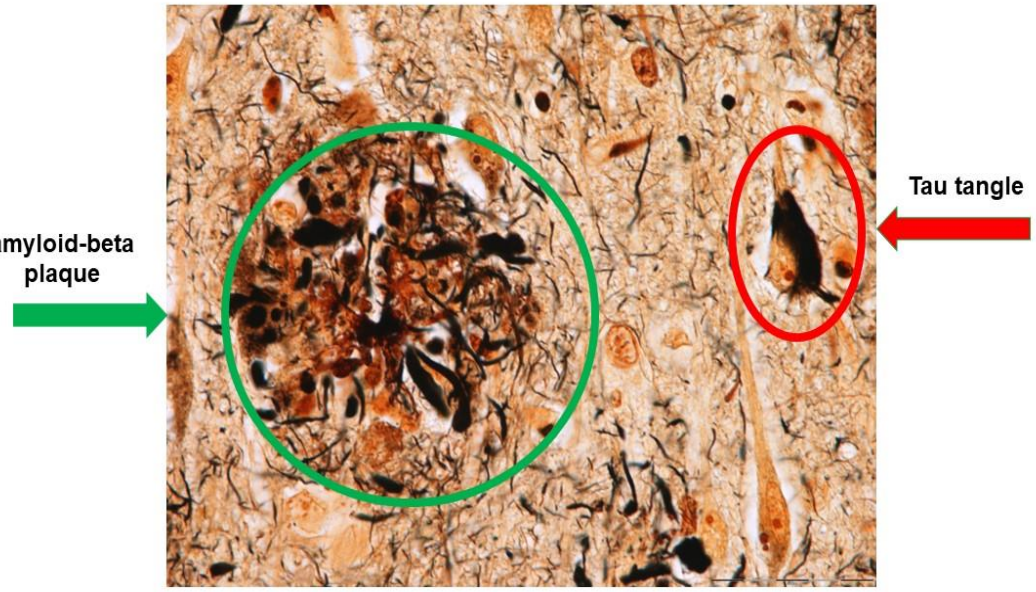
Signature Lesions of Alzheimer's Disease : Neuritic amyloid-beta plaque and Neurofibrillary Tau Tangle



Courtesy of Knight ADRC Neuropathology Core

Modified Bielschowsky silver impregnation

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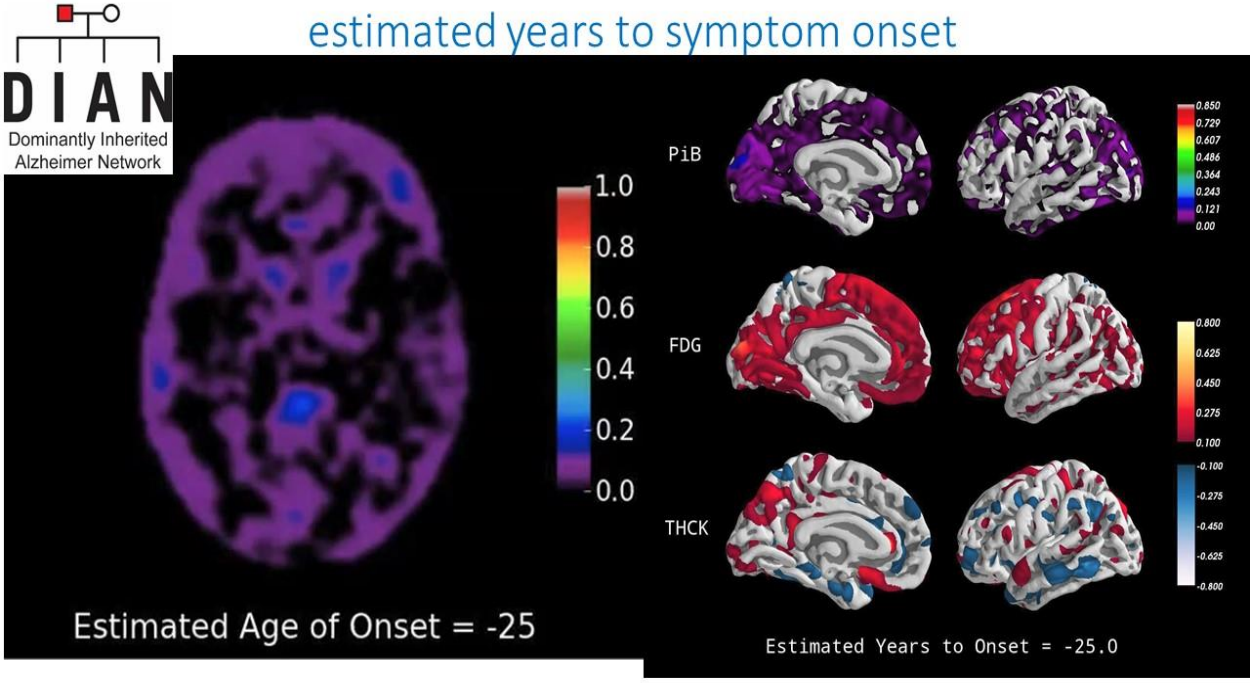
amyloid deposition, hypometabolism, and cortical atrophy by estimated years to symptom onset



Bateman et. al NEJM 2012

Benzinger et. al 2015 PNAS

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A brief history of diagnostic development in Alzheimer's disease

2017 – blood Aβ biomarkers of AD **2018 – blood tau biomarkers of AD** **>2019 – abundant blood biomarkers of AD**

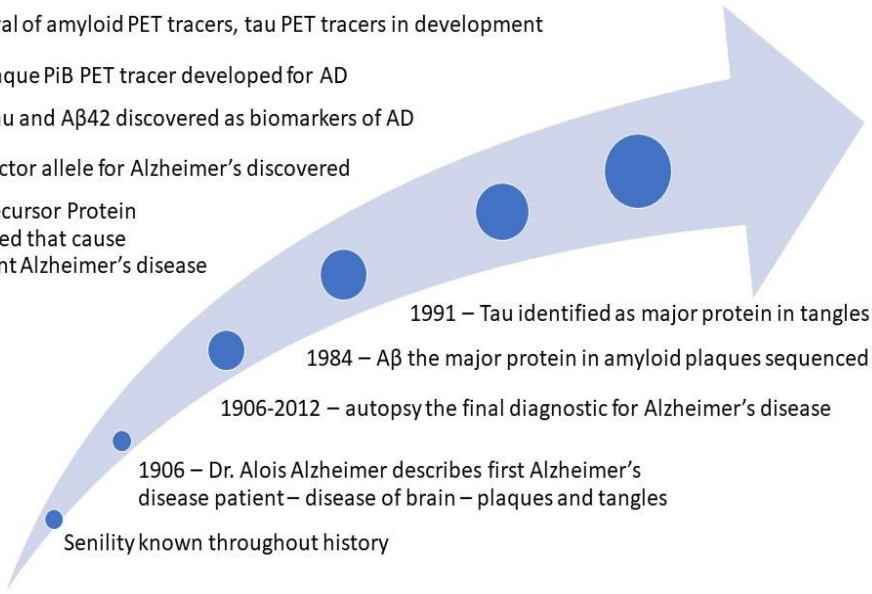
2012 – FDA approval of amyloid PET tracers, tau PET tracers in development

2004 – Amyloid plaque PiB PET tracer developed for AD

1993/1995 – CSF tau and Aβ42 discovered as biomarkers of AD

1993 – ApoE risk factor allele for Alzheimer's discovered

1991 – Amyloid Precursor Protein mutations discovered that cause autosomal dominant Alzheimer's disease



1991 – Tau identified as major protein in tangles

1984 – Aβ the major protein in amyloid plaques sequenced

1906-2012 – autopsy the final diagnostic for Alzheimer's disease

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

Senility known throughout history

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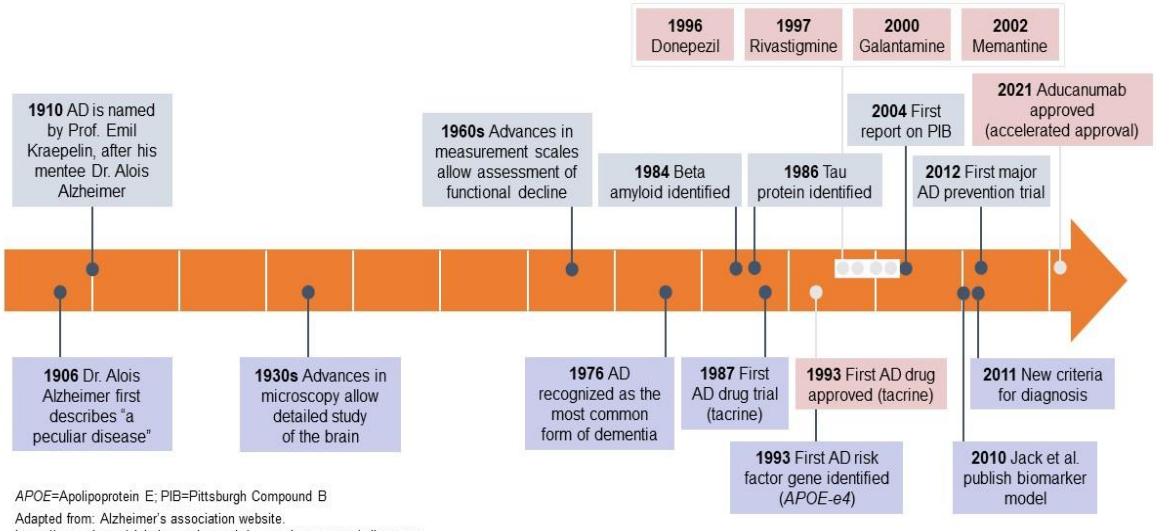
100 years of Alzheimer's disease (AD)



APOE=Apolipoprotein E; PIB=Pittsburgh Compound B

Adapted from: Alzheimer's association website. https://www.alz.org/alzheimers-dementia/research_progress/milestones. Accessed July 2021;
AlzForum website. https://www.alzforum.org/therapeutics/. Accessed July 2021

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Courtesy of Ali Atri

Challenges for disease modification

- **Wrong target?** Which Aβ species, tau species, other? Not all targets may be safe to maximal effect (e.g. general gamma secretase inhibitors)
- **Too little?** Biomarker engagement in the human CNS of the mechanism of action has been inconsistently shown in many trials. No drug has 'normalized' AD biomarkers
- **Too late?** Focus on earlier stages of the disease including secondary prevention.

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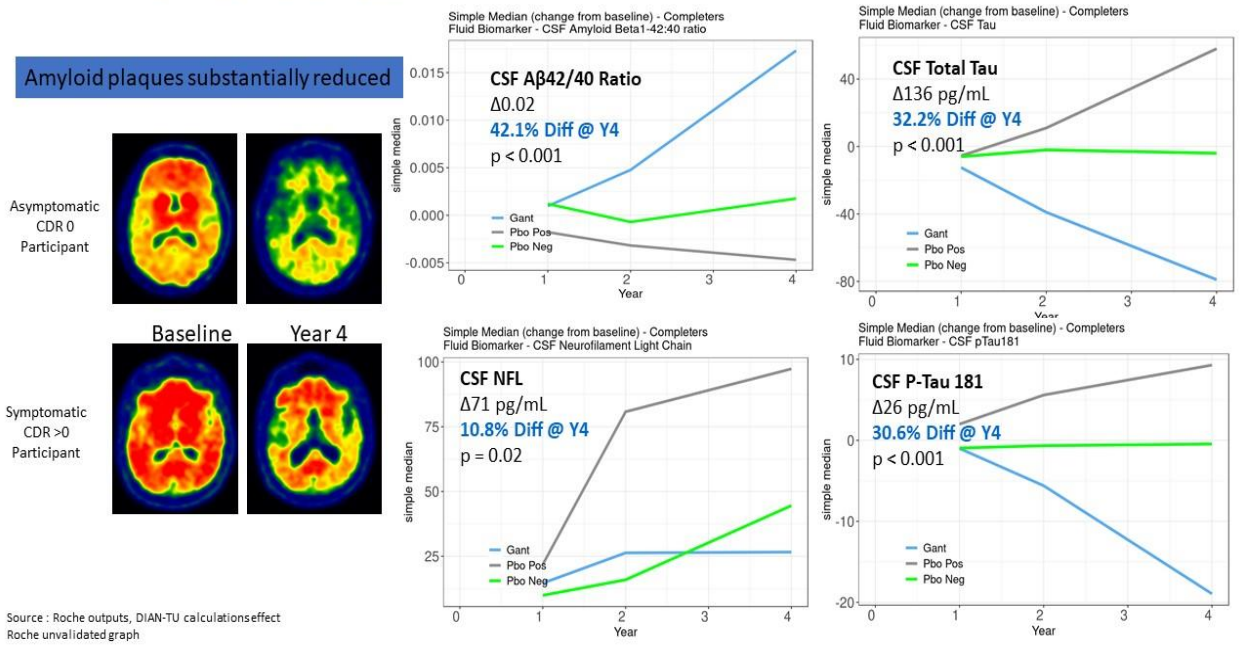
Gantenerumab Affected Biomarkers of Disease Activity



The DIAN-TU, adapted from Salloway et. al, Nature Medicine 2021

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How do we accelerate delivery of scientific advancements to patients sooner and impactfully?

- Discoveries are accelerating due to increased investments from all stakeholders.
- *Unprecedented breakthroughs*: Alzheimer's disease can now be accurately diagnosed at an early stage, predicted with biomarkers and imaging, and drugs can reverse and normalize some Alzheimer's disease pathology.
- There are *limitations* in the speed and scale at which these discoveries can be delivered to patients, families, and medical systems, and *opportunities* to improve processes to deliver on the promise of effective preventions and treatments of Alzheimer's disease by 2025.

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NAPA Advisory Council Research Sub-committee draft recommendations

1. A major area of emphasis by all federal agencies involved in the National Plan should be to increase synergies and translation across research, clinical practice, and implementation of care for diagnostic, treatment, and care paradigms that could improve patient outcomes. Stakeholders should design and implement pipelines for faster translation of research findings to clinical care, accounting for the entire continuum from research studies through regulatory review and approval, payer review and approval, and delivery of improved diagnosis and care.
2. A top priority remains the urgent need for Congress to continue to increase annual federal research and implementation science funding sufficient to meet these goals across biomedical, clinical, LTSS, and public health settings.
3. Representation and diversity in clinical trials should continue to be increased to address health equity and representation in research.
4. Research into implementation of dementia care to provide best care models should continue to be increased.
5. An understudied area that should be prioritized is the impact of stigma on health-seeking behaviors to improve access to health services.
6. A cross-cutting recommendation across all NAPA subcommittees is to increase research into neurological effects of Covid-19 and development of emergency preparedness programs.
7. Research into causes and relationships between delirium (including Covid delirium) and dementia should be increased, with a focus on how to reduce delirium risk.

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