A newsletter distributed by The Dominantly Inherited Alzheimer Network Expanded Registry (DIAN EXR), Washington University School of Medicine, Department of Neurology

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CONTACT US

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The state of AD clinical trials

Randall Bateman, MD

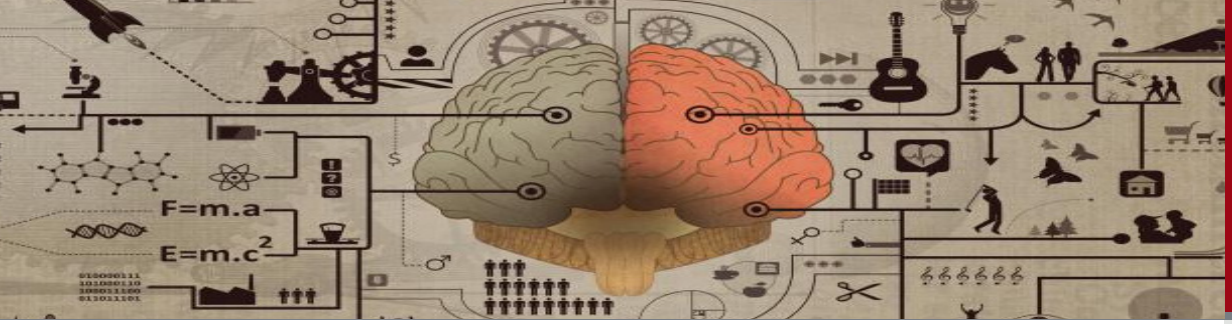
The field of Alzheimer's disease (AD) research has had several recent disappointments in attempts to treat symptomatic AD (after memory loss, neuronal death, and brain damage begin). In January 2019, two Phase 3 trials of crenezumab, an anti-amyloid antibody targeting oligomeric (small clumps) forms of Aβ, were halted. In March 2019, two Phase 3 trials of aducanumab, an antibody targeting plaques (large aggregates) of Aβ, were also terminated early. Trials of both drugs failed to show a benefit in late-onset, sporadic, symptomatic AD participants. In addition, several drugs which decrease the production of Aβ (BACE inhibitors) have also failed to show a benefit, with some reporting negative side effects. These results are disappointing, but because the trials were designed and run well, we have learned a great deal and the field continues to work toward developing and testing treatments for AD.

What does this tell us? Targeting Aβ in the later stages of AD has not been beneficial. The symptomatic stages of AD are the last 7 years of a disease process that spans at least 25 years. Prevention efforts, such as the DIAN-TU, aim to improve drug effectiveness by treating earlier stages of AD, before significant brain damage (neurodegeneration) occurs. Further, in dominantly inherited AD, the cause of AD dementia is a pure form of AD without other significant pathologies, in contrast to late-onset AD where having other diseases such as strokes and other pathologies are the rule, not the exception. In dominantly inherited AD, this means that the effects of trial drugs can be evaluated for AD in the absence of other medical conditions. Further, younger patients may be able to respond better to treatments due to better recovery capabilities.

What should we do? We need to continue prevention efforts and look toward the next generation of approaches and drug targets. The first two secondary prevention drug arms of the DIAN-TU will read out in early 2020, which will provide the first AD prevention trial results. The contributions from the many participants and family members will provide an enormous amount of data and findings to help the field move toward more effective treatment and prevention strategies. In addition, the launch of the cognitive run-in is preparing for the next generation of treatments, now targeting the second AD pathology, tau. In parallel, a primary prevention trial is being planned to target the earliest stages, before AD pathology begins, and prevent AD pathology from forming in the first place in family members up to 30 years before symptom onset.[1]

Hope for the future: The field of AD research has made tremendous advancements. We are testing drugs that are able to stop and reverse AD pathology for the first time in history and show tantalizing hints of potential benefits to thinking and memory. We have a growing armamentarium of treatments which can target different aspects of AD. We are now honing in on the right combination of drugs, targets, and stages of AD that can slow or potentially even stop the disease. Exciting

1. McDade, E. & Bateman, R. J. Stop Alzheimer's before it starts. Nature 547, 153–155 (2017).



progress is also being made in the diagnosis of AD, including blood-based assays that can detect pathology before symptoms begin. These tests can help researchers quickly and inexpensively identify eligible participants for prevention and treatment trials, which means we can enroll and obtain trial results more quickly. We remain hopeful as we continue to work toward a cure, and we thank the participants and families for their dedicated support and partnership toward a day without Alzheimer's.

DIAN-TU Clinical Trial-001: Cognitive Run-In (CRI) update

Susan Mills, Associate Director Research Clinical Trials Operations

We're very excited to announce that the Cognitive Run-In (CRI) period of the DIAN-TU-001 trial is now launching! Enrollment into CRI will be opening on a rolling basis as each site receives their regulatory approvals (from local ethics committees and regulatory authorities). This CRI period is a very important part of the next drug arm(s) to be added to the trial. The data collected during CRI will be used when testing the next drug arm(s) and will contribute to the ability to detect whether a drug is working by providing more data on participants' memory and thinking changes prior to receiving study drug. This will also help participants that have not participated in DIAN related research to become familiar with the study procedures and requirements in preparation for the drug arm to be added. Enrollment in CRI should help identify participants for immediate recruitment into a drug arm once available; we expect this to help decrease the overall timeline for testing the next drug and finding out the result(s)! Participation in CRI will primarily involve cognitive tests of thinking and memory (mostly at home) with some additional study procedures.

The CRI includes participants who are younger than 15 years prior to their parents age of symptom onset (referred to as 'primary prevention'); in addition to those that are 15 years younger to 10 years older than their estimated age of symptom onset (referred to as 'secondary prevention'). Participants in the secondary prevention age range will have a PET scan to measure the amount of aggregated tau tangles at some centers. These tau PET measures are very helpful, as many new drugs targeting these tau proteins are currently being tested in clinical trials and we plan to add as a future drug arm in the DIAN-TU trial.

If you have any questions on your eligibility or when your trial site may have approval and be ready to enroll, please contact the DIAN Expanded Registry (**dianexr@wustl.edu**) and/or your local DIAN-TU site.

Primary Prevention webinar re-cap

Dr. Eric McDade and the DIAN Expanded Registry hosted a webinar focused on the new Primary Prevention study and issues related to family planning on May 4, 2019. To view the webinar in its entirety, please visit our website https://dian.wustl.edu/for-families/webinars/. For your convenience, we provide a recap here.

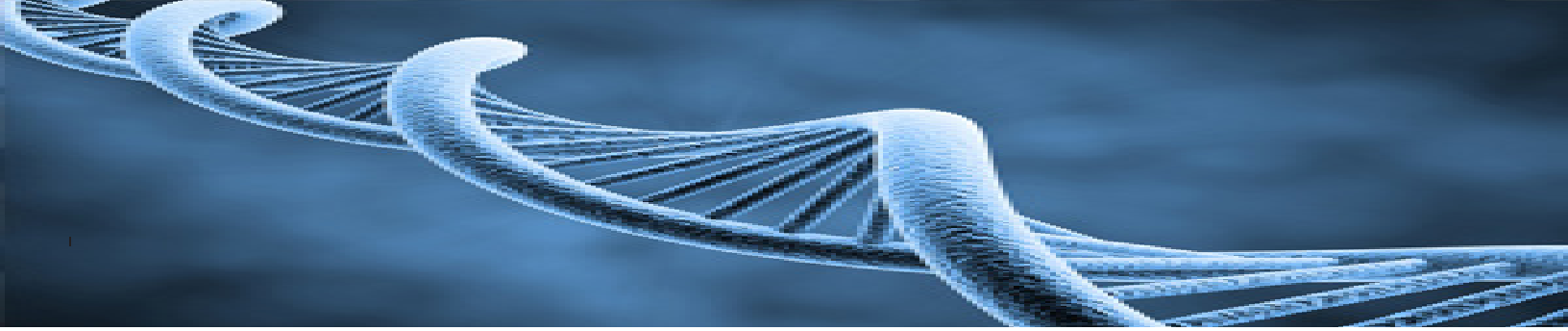
The Primary Prevention trial aims to test drugs that prevent AD pathology from ever beginning in the brains of family members who are younger than 15 years prior to their parent's age of symptom onset. The study will begin enrolling this year into an initial Cognitive Run-In (CRI) period, described elsewhere in this newsletter, in preparation for a drug to be added in 2020.

The webinar provided a forum for discussion on issues of family planning, as participants would be eligible at age 18 and older when many people are considering starting or expanding their family, and a necessary requirement of the trial will be to avoid pregnancy for the duration of the study once a drug arm is added. Dr. McDade discussed points to consider before enrollment, such as genetic counseling and/or testing, and provided links to medical-reproductive resources. He encouraged potential participants to consult with their local DIAN

Upcoming Events:

DIAD Family Conference: 13 July 2019

Fall Webinar: date to be determined



and DIAN-TU sites, genetic counselors and reproductive health specialists. Participants submitted many excellent questions, which are included in the recording of the webinar. We encourage you to contact the DIAN Expanded Registry at dianexr@wustl.edu for any questions you may have regarding the Primary Prevention study.

Dr. Randall Bateman receives Potamkin Award

John C. Morris, MD

Dr. Randall Bateman is the recipient of the 2019 Potamkin Prize presented by the American Academy of Neurology and the American Brain Foundation on May 6, 2019 in Philadelphia, PA. The Potamkin award recognizes major contributions to the understanding of the causes, prevention, treatment, and cure for Pick, Alzheimer and related diseases. Dr. Bateman's accomplishments represent fundamental advances in the understanding of the causes, diagnosis, treatment, and prevention of Alzheimer disease.

His research led to many discoveries in the field of Alzheimer biomarkers such as decreased central nervous system clearance of Aβ in individuals destined to develop late onset Alzheimer disease, over-production of the Aβ42 isoform in dominantly inherited Alzheimer disease, characterization of diurnal patterns of CSF Aβ levels in humans, and the effect of sleep on CSF Aβ kinetics.

Dr. Bateman recently provided the first detection of Aβ in human plasma that reflects cerebral amyloidosis.

From the onset of The Dominantly Inherited Alzheimer Network (DIAN) in 2008, for which Dr. Bateman was the Clinical Core Leader, he was dedicated to analyzing the comprehensive DIAN dataset, with an emphasis on molecular biomarkers of Alzheimer disease via imaging and spinal fluid to characterize the cascade of pathophysiological events throughout the initial preclinical stage on through the symptomatic course. His efforts culminated in a description of the appearance, sequence, and pattern of biomarker changes in the DIAN cohort prior to the symptomatic onset of Alzheimer disease, providing the first ever in vivo data to indicate that the illness begins two decades or more before symptoms appear.

In 2012, Dr. Bateman realized a goal to launch the first ever secondary prevention trials of potential disease-modifying therapies for Alzheimer disease in individuals with or at risk for dominantly inherited Alzheimer disease with the development of the DIAN-Trials Unit (TU). The DIAN-TU is testing 2 therapeutic arms and serves as a model for other prevention trials.

Please join us in celebrating this most deserving recipient.

Recent DIAN publications

Emerging cerebrospinal fluid biomarkers in autosomal dominant Alzheimer's disease.

https://www.sciencedirect.com/science/article/pii/S1552526019300135?via%3Dihub

Seizures as a symptom of autosomal dominant Alzheimer's disease

https://www.sciencedirect.com/science/article/pii/S019745801830424X?via%3Dihub

Tau PET in autosomal dominant Alzheimer's disease: relationship with cognition, dementia and other biomarkers

https://academic.oup.com/brain/article/142/4/1063/5315649

Clinical, pathophysiological and genetic features of motor symptoms in autosomal dominant Alzheimer's disease

https://academic.oup.com/brain/article/142/5/1429/5416202

Comparison of Pittsburgh compound B and florbetapir in cross-sectional and longitudinal studies

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6389727/

Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease

https://stm.sciencemag.org/content/11/474/eaau6550.short

Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease

https://www.nature.com/articles/s41591-018-0304-3

Alzheimer's disease in the news

A simple blood test reliably detects signs of brain damage in people on path to devolping Alzheimer's disease

https://medicine.wustl.edu/news/blood-test-detects-alzheimers-damage-before-symptoms/

Managing cholesterol, triglycerides may reduce Alzheimer's risk, study suggests

https://medicine.wustl.edu/news/cardiovascular-disease-alzheimers-genetically-linked/

The DIAN website is a great place to learn more about our research and find additional information. Please visit the "News" page at https://dian.wustl.edu/news/ for articles related to DIAN and Alzheimer's disease. Family members share their stories on the "Family Voices" page at https://dian.wustl.edu/for-families/family-voices/. If you are interested in research opportunities please contact the DIAN Expanded Registry at **dianexr@wustl.edu.** If you are not part of the registry and would like to be, please visit **dian.wustl.edu** to register.