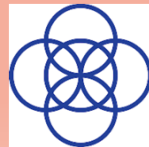


The Future of Prevention and Treatment of Alzheimer's Disease in Down Syndrome

Brad Christian, Ph.D.

Departments of Medical Physics and Psychiatry
Associate Director of Waisman Center IDDRC



Waisman Center

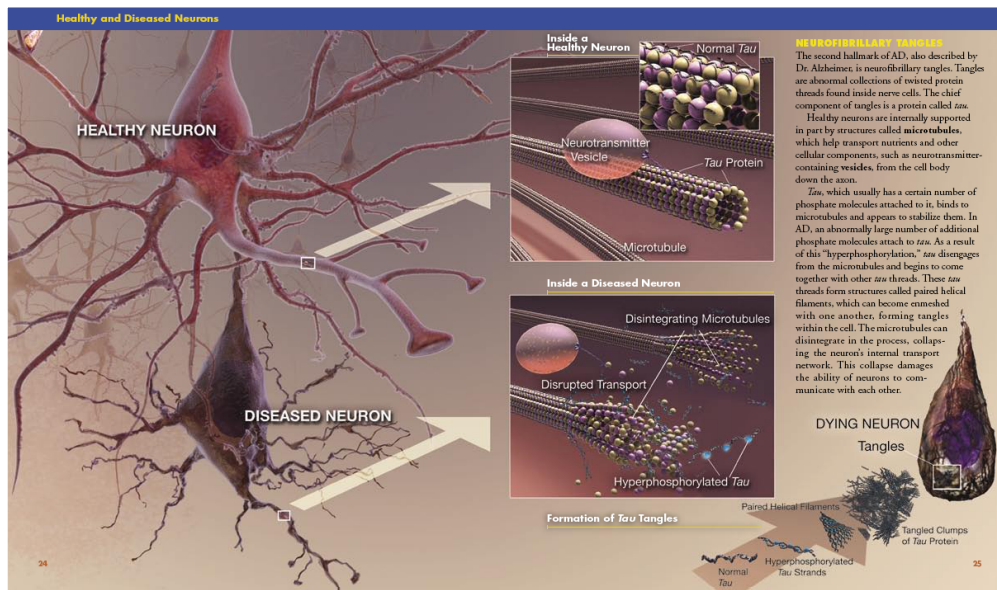
Advancing knowledge of human development, developmental disabilities, and neurodegenerative diseases.



Wisconsin Alzheimer's
Disease Research Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Alzheimer's Disease Pathology

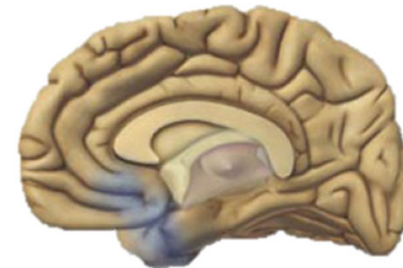
- tangles and plaques



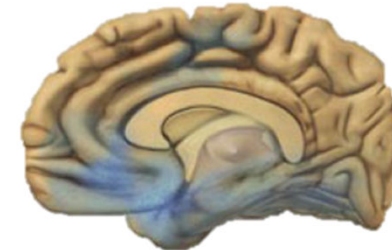
www.nia.nih.gov

Neurofibrillary

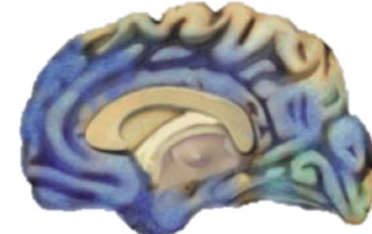
Preclinical

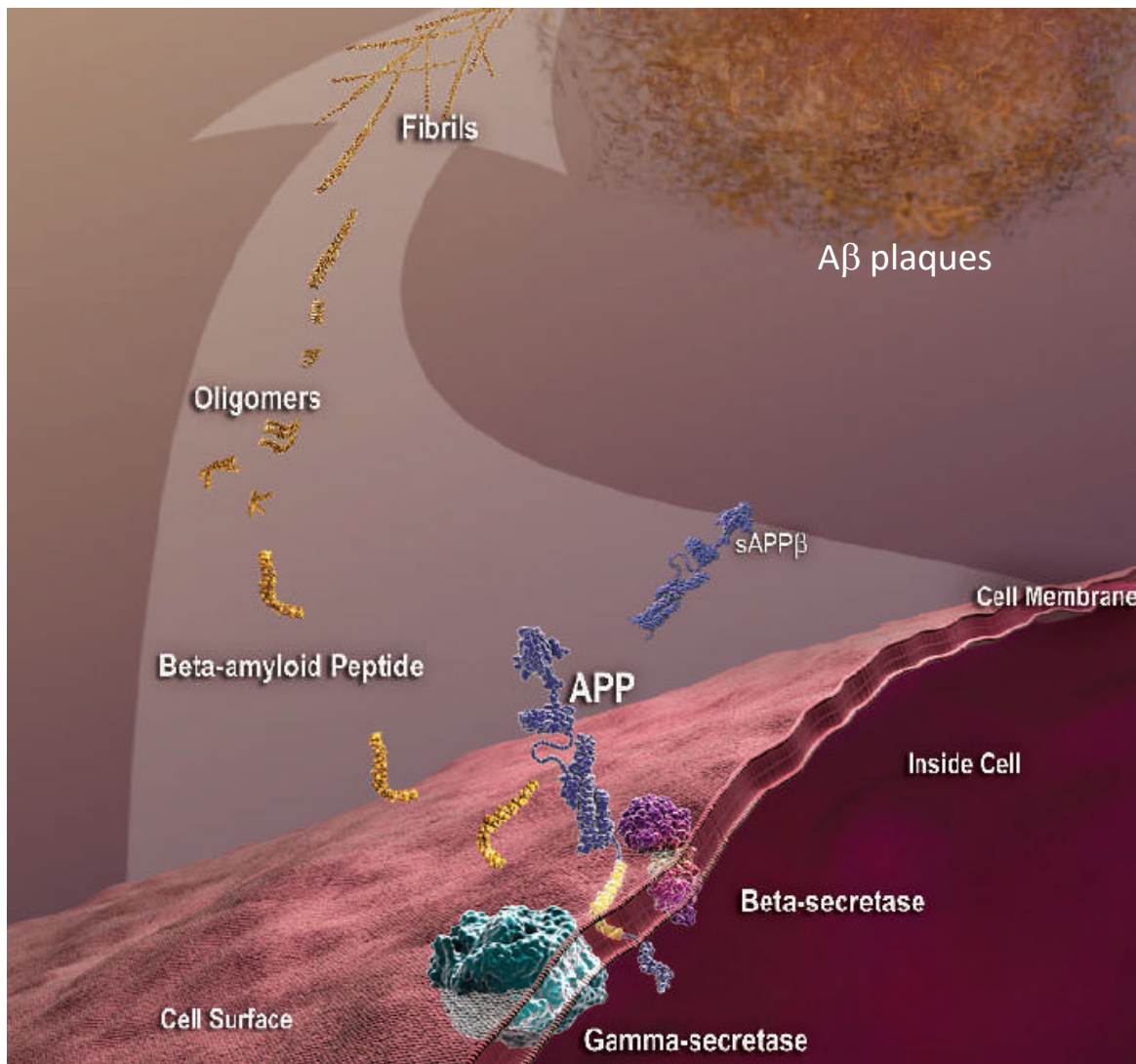


Moderate



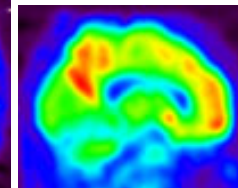
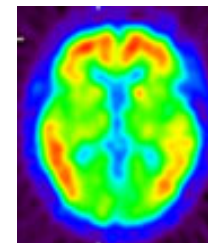
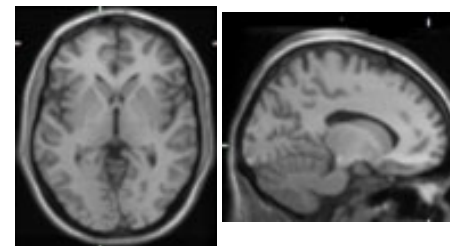
Severe



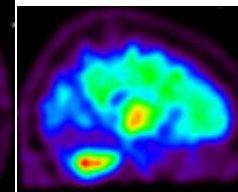
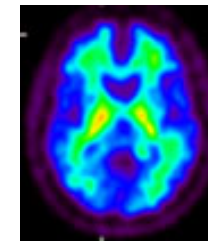


www.nia.nih.gov

β-Amyloid in AD



[¹¹C]PiB binding AD



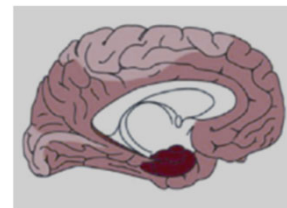
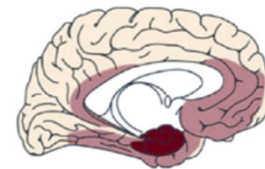
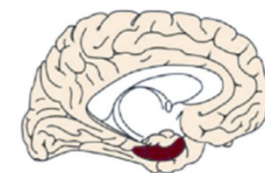
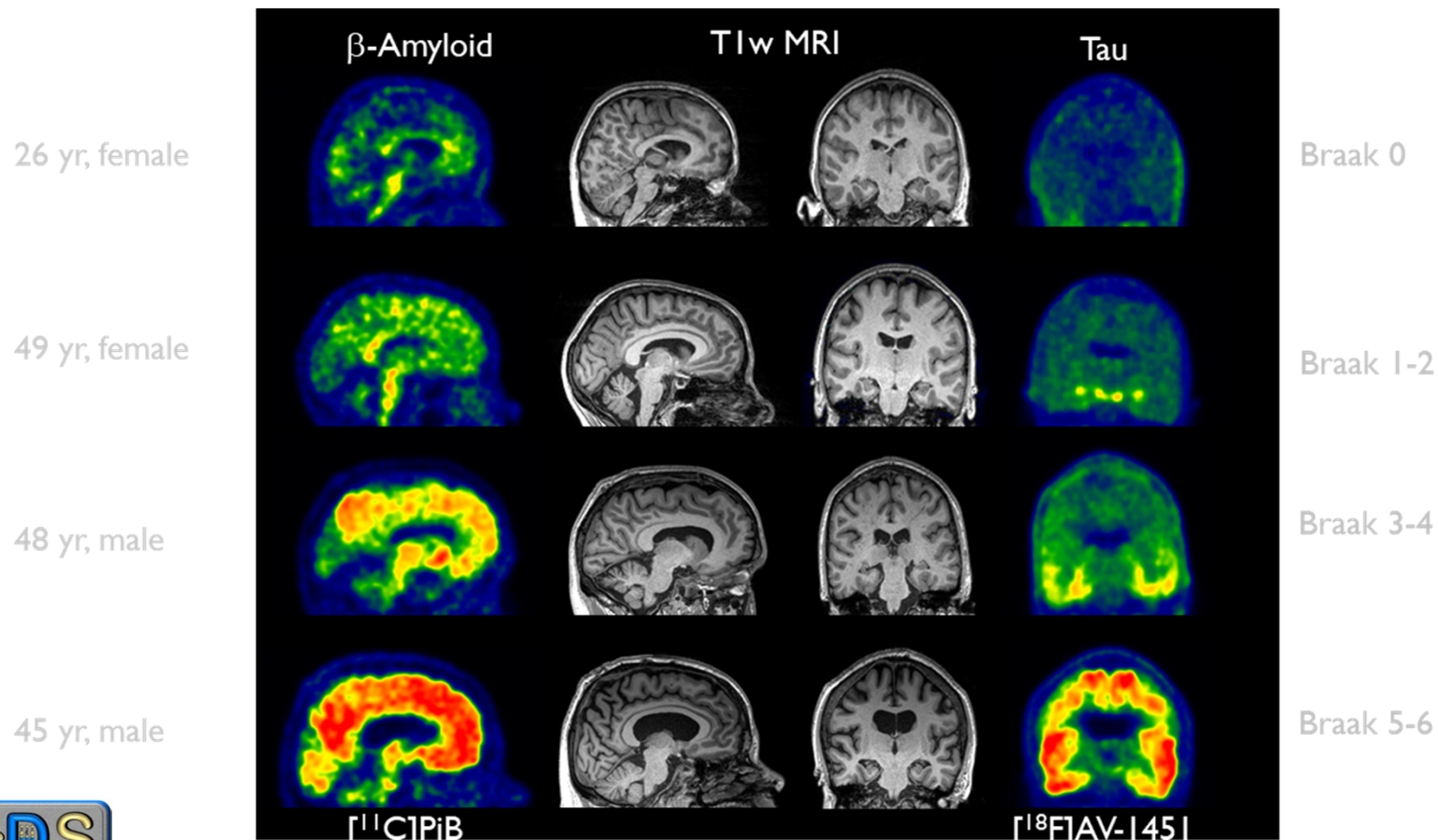
[¹¹C]PiB binding HC



- Goal: This longitudinal study will examine progression of AD related neuroimaging, biofluid, genetic and cognitive/functional biomarkers in **550 adults** with DS (>25 yrs of age) and 50 “biomarker-controls”
- 1. Examine existing and novel biomarkers of DS-AD and determine if they are similar to LOAD.
- 2. Study the direct and downstream effects of genetic variants from whole genome sequencing.
- 3. Develop novel multi-modal biomarkers from genetic, proteomic, metabolomic, imaging, and clinical/cognitive information.
- 4. Provide data and specimen sharing for the broader scientific community.

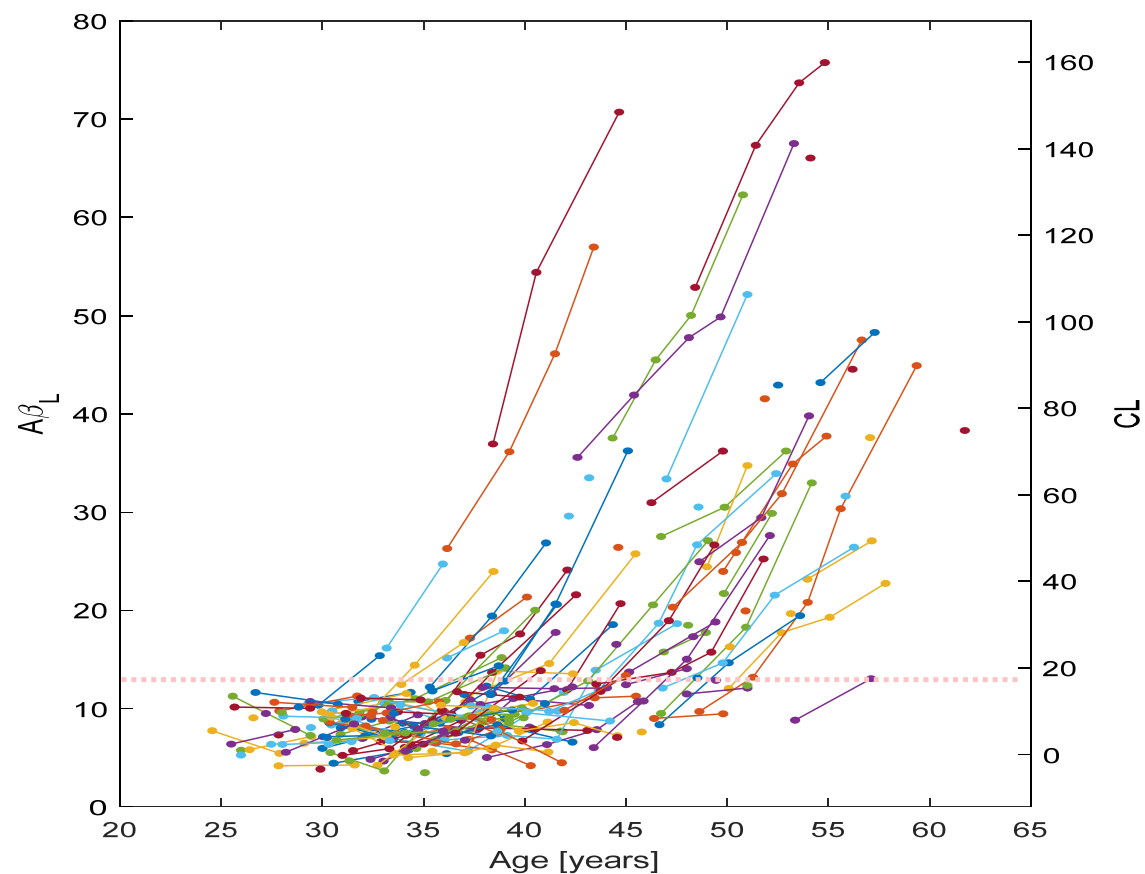
The screenshot shows the official website of the Alzheimer's Biomarkers Consortium of Down Syndrome (ABC-DS). The page is part of the National Institute on Aging's Alzheimer's Disease Education and Referral Center. It features a navigation bar with links to Home, Health and Aging, Research and Funding, Newsroom, About NIA, and Contact Us. Below this, there's a section for the ABC-DS initiative, which includes links for participants and families (What is ABC-DS?, How Can I Participate in the ABC-DS Initiative?, Resources) and for researchers (Biomarkers of Alzheimer's Disease in Adults with Down Syndrome (ABC-DS)). The page also includes a photo of a man with Down syndrome and a woman holding an ABC-DS umbrella. The text describes the initiative's goal to identify biomarkers that indicate and track the Alzheimer's disease process in people with Down syndrome, a joint study by the National Institute on Aging (NIA) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Amyloid and Tau Imaging in Down Syndrome



Adapted from Braak, et al. *J Neuropathol Exp Neurol*. 2011

Estimating A+ duration time and age of A+ onset



- Mean A+ age:
 - APOE E4 carriers: 40.1(4.89) years
 - Non-carriers: 41.6(5.93) years





Alzheimer Disease Treatment Trials

Inclusion of People with Down Syndrome

Disease-Modifying Drugs for Alzheimer's Disease

History of failure...

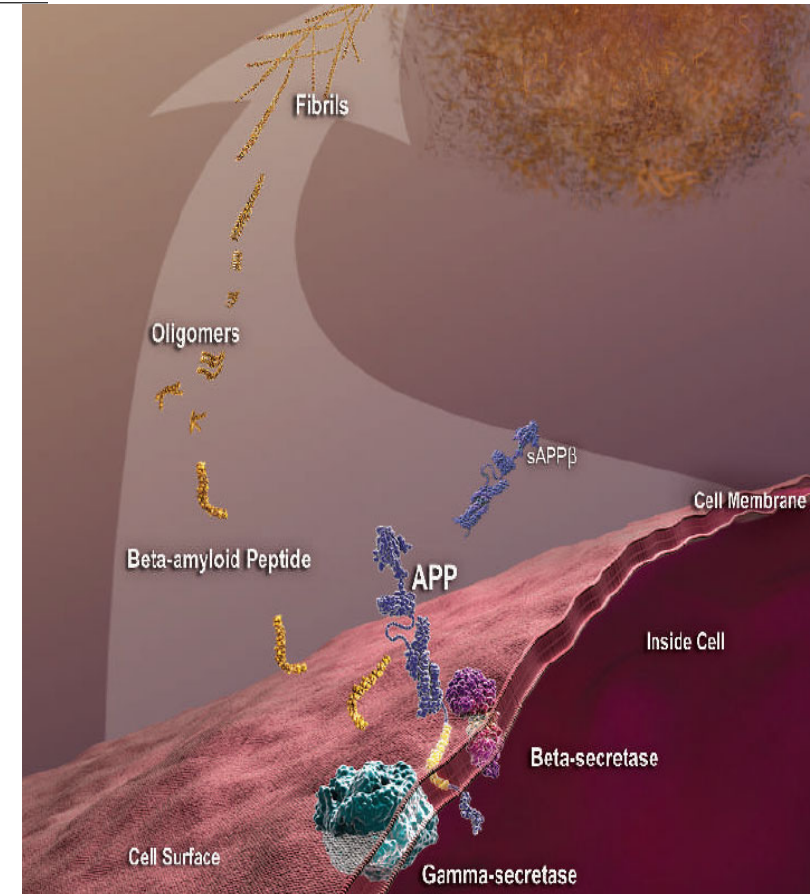
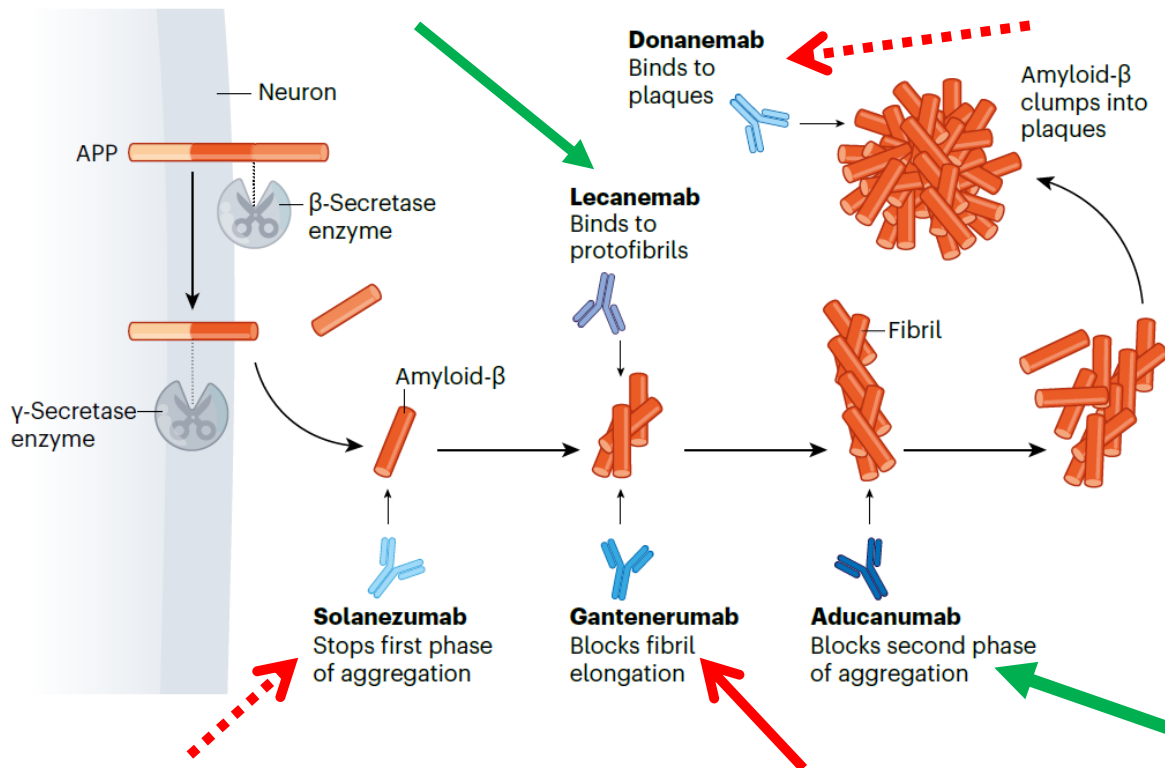


Possible reasons for failures of trials of disease-modifying drugs for Alzheimer's disease:

- inadequate understanding of the biology of Alzheimer's disease
- wrong treatment target
- starting the test of therapies too late in disease development
- incorrect drug doses
- the choice of the clinical endpoint for the trials and associated variability in measurement of endpoints within or between individuals

ANTIBODIES AGAINST AMYLOID

Several clinical trials are testing whether drugs called monoclonal antibodies can stem the symptoms of Alzheimer's by preventing the toxic clumping of amyloid- β proteins. This process starts when enzymes cleave the amyloid precursor protein (APP). Amyloid- β proteins elongate into fibrils and then nucleate into plaques. All of the drugs bind to amyloid- β , but their primary targets in the process are different.

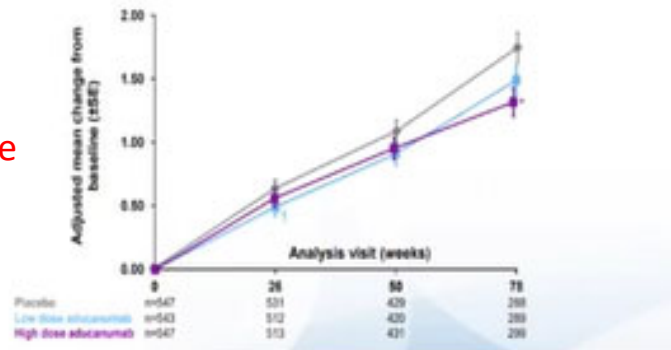


Abbot et al. , Nature 2022; slide provided by Carol Van Hulle, Ph.D.

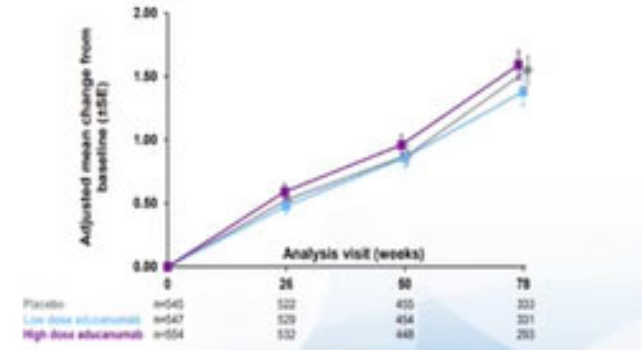
Aducanumab – Accelerated Approval – June 2021

22% slowing in
cognitive decline

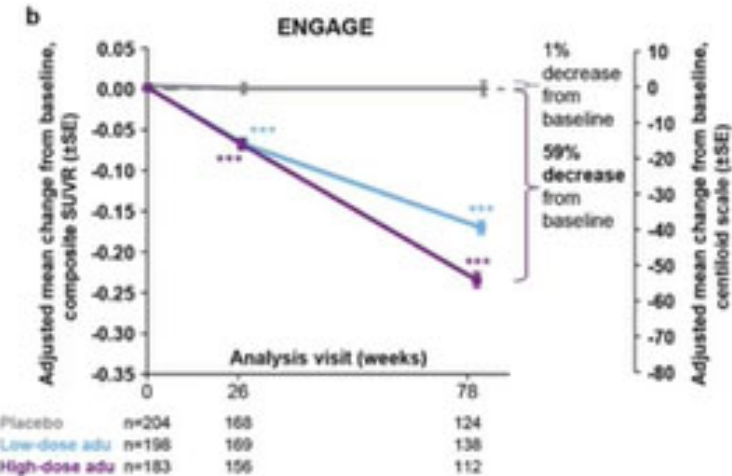
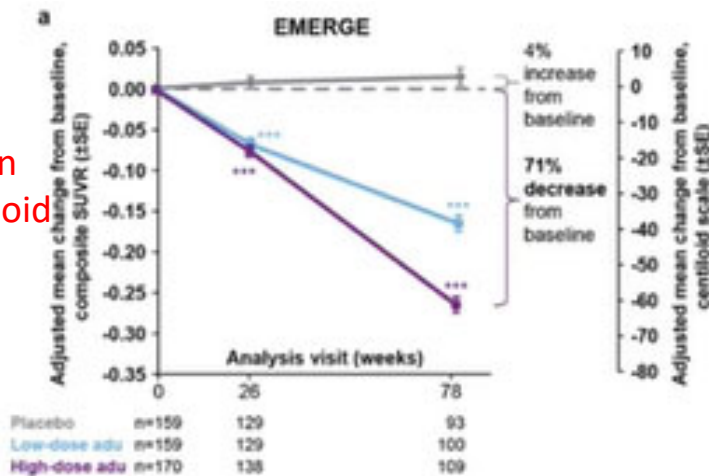
EMERGE: Longitudinal change from baseline in CDR-SB



ENGAGE: Longitudinal change from baseline in CDR-SB



70% reduction
in brain amyloid
at 18 mos

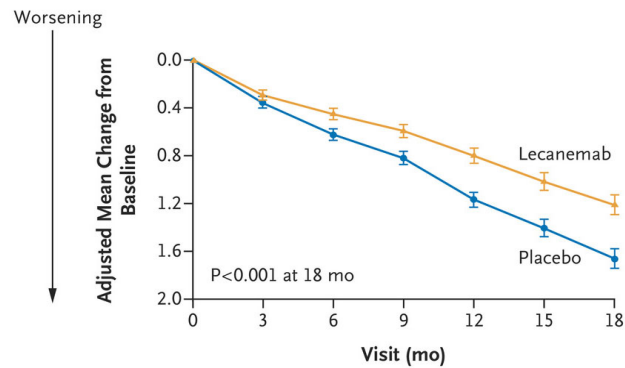


RESEARCH SUMMARY

Lecanemab in Early Alzheimer's Disease

van Dyck CH et al. DOI: 10.1056/NEJMoa2212948

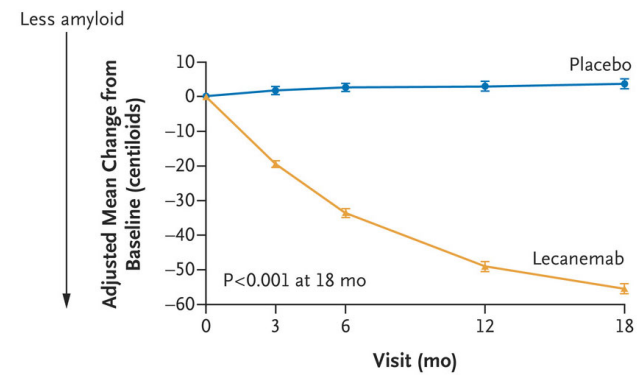
A. CDR-SB Score



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

B Amyloid Burden on PET



No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

27% reduction in rate of cognitive decline

77% reduction β -amyloid PET

Major Progress towards AD Therapeutics

- Aducanumab: accelerated approval based on amyloid removal, but CMS non-coverage
 - Marketing of aducanumab has essentially ceased
 - Phase IV study moving forward
- Lecanemab: accelerated approval, expecting full approval
- In the next 3-6 months expect results for:
 - Phase 3 donanemab in Early AD
 - Phase 3 solanezumab in Preclinical AD

None of the clinical trials enrolled individuals with DS!



Received: 13 July 2021 | Accepted: 13 July 2021
DOI: 10.1002/alz.12444

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

NEWS

Aducanumab: Appropriate use recommendations

Jeffrey Cummings¹ | Steve Salloway²

¹ Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV), Las Vegas, Nevada, USA

² Butler Hospital and Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

Expert Panel recommends against treating amyloid positive patients with Down syndrome, dementia with Lewy bodies, or cerebral amyloid angiopathy with aducanumab. The Expert Panel recommends caution in treating patients with autosomal dominant AD and those with atypical AD syndromes until more data are available; the lack of information in these settings should be disclosed to potential treatment candidates. We are the beginning of the aducanumab era, and more data will inform the range of appropriate use of this agent.

BIOTECH

Alzheimer's meds are here. But for the Down syndrome community, it's still the 1980s

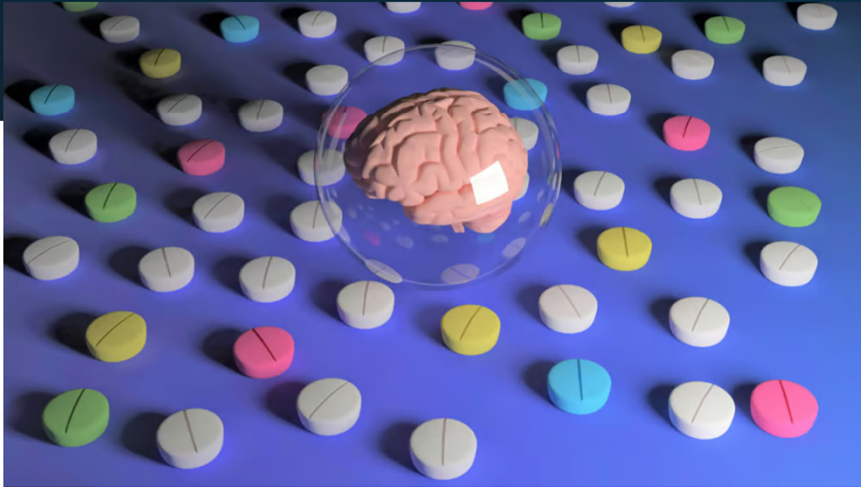
By Annalee Armstrong • Mar 1, 2023 09:25am

Alzheimer's disease

Down syndrome

neurodegenerative diseases

clinical research



Ninety percent of people with Down syndrome, also known as trisomy 21, will develop Alzheimer's disease.
(cosinart/iStock/Getty Images Plus)

<https://www.fiercebiotech.com/biotech/down-syndrome-and-alzheimers-pharma-clinical-trials-safety-lecanemab>

The Down syndrome community hasn't stayed silent. As the Centers for Medicare & Medicaid Services (CMS) considered whether to provide coverage for Eisai and Biogen's controversial medicine Aduhelm back in 2022, the community wrote as many as 3,000 letters asking for coverage or at the very least, safety studies to see if the therapy could be used at all. The original proposal had exclusion criteria for "any neurological or other medical condition (other than AD) that may significantly contribute to cognitive decline." CMS ultimately decided against this exclusion criteria, noting the overwhelming number of comments asking for a rethink of what one letter referred to as discrimination.

Down Syndrome – Alzheimer's Disease: ideal candidates for anti-amyloid trials

- Predictable age range for AD onset
- A genetic form of AD with near full penetrance
- Emergence of AD biomarkers are similar to those in sporadic AD

Things to consider for AD therapeutics for people with DS:

- Safety!!!
- Amount of target engagement
- Timing of therapies
- Types of administration

RESEARCH SUMMARY

Lecanemab in Early Alzheimer's Disease

van Dyck CH et al. DOI: 10.1056/NEJMoa2212948

Table 3. Adverse Events.*

Event	Lecanemab (N=898)	Placebo (N=897)
Overall — no. (%)		
Any adverse event	798 (88.9)	735 (81.9)
Adverse event related to lecanemab or placebo†	401 (44.7)	197 (22.0)
Serious adverse event	126 (14.0)	101 (11.3)
Death	6 (0.7)	7 (0.8)
Adverse event leading to discontinuation of the trial agent	62 (6.9)	26 (2.9)
Adverse event that occurred in ≥5% of participants in either group		
Infusion-related reaction	237 (26.4)	66 (7.4)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)

Amyloid
Related
Imaging
Abnormalities

ARIA and Anti-Amyloid mAbs

	Aducanumab	Lecanemab	Donanemab
Amyloid Clearance	++	++	+++
ARIA-E Incidence %	42.0	12.6	27.5
ARIA-H Incidence %	19.0	14.0	30.5

84% of ARIA-E cases were asymptomatic and self-limiting

Adapted from Withington et al, 2022

Keck School of Medicine of USC
Alzheimer's Therapeutic Research Institute



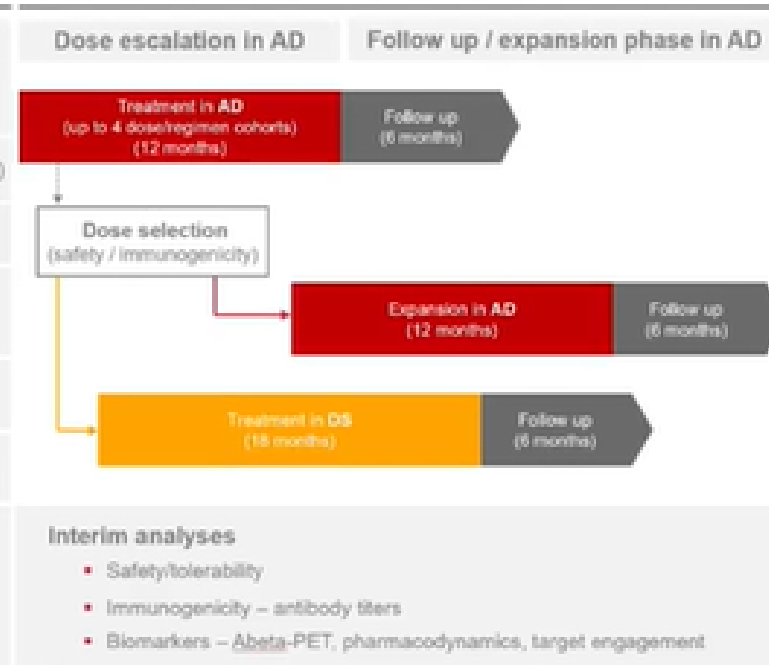
Slide Courtesy of Mike Rafii, M.D., Ph.D.

A phase Ib/2, multicenter, randomized, placebo-controlled study to assess the safety, tolerability, immunogenicity, and pharmacodynamic effects of ACI-24.060 in prodromal Alzheimer's disease and in adults with Down syndrome

Placebo-controlled Phase 1b/2 Study Overview

Inclusion criteria	Both	Multicenter, adaptive, placebo-controlled, dose-escalation, double-blind, randomized Phase 1b/2 study in people with: • <u>Abeta</u> pathology confirmed by PET³ scan
	AD	• Prodromal AD (CDR⁴-Global Score 0.5; age 50-75 years)
	DS	• Non-demented people living with DS (age 35-50 years)
Study design	Both	• IA⁵ of safety/tolerability and immunogenicity • Biomarker analyses including <u>Abeta</u> PET and others
	AD	• Up to 4 different doses and/or dose regimens • Expansion of one cohort to assess effect on <u>Abeta</u> PET
	DS	• Initiation using selected dose identified in AD (based on safety/tolerability and immunogenicity)
Outcome measures	Both	• Safety/tolerability • Pharmacodynamics: Serum anti-<u>Abeta</u> antibody titers • Exploratory biomarkers and clinical endpoints

Trial Schematic



(1) Alzheimer's disease, (2) Down syndrome-related AD, (3) Positron emission tomography, (4) Clinical Dementia Rating, (5) Interim analyses



Slide Courtesy of Mike Rafii, M.D., Ph.D.

Future Directions

- Alzheimer's Clinical Trial Consortium (ACTC) launched in 2017
 - Initiated ACTC – Down Syndrome (DS) in 2019 (PI – Rafii)
 - TRC-DS, a trial-ready cohort for AD treatment trials across 15 ACTC-DS sites using R61 / R33 funding
- TRC-DS Goals
 - Establish a network of infrastructure to conduct AD clinical trials in adults with DS
 - Develop a well-characterized, trial-ready cohort to facilitate enrollment into AD trials for adults with DS
 - Conduct a randomized trial of an anti-amyloid therapeutic utilizing TRC-DS as a run-in cohort.



Thank you!

All the participants & families

