The next generation of Alzheimer research: new reasons for hope

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Marc Busche
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  - JPB
  - Cure Alzheimer Fund
  - FBIR
  - Abbvie

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David Holtzman Wash U
Tom Montine, Stanford
Reisa Sperling Harvard

Martin Ingelsson Canada
Dave Klennerman Cambridge UK
Daniel Muller Basel SW
Luc Buee France

Pubmed contains >170,000 articles that mention Alzheimer's disease

These are the non-controversial facts:

It's a dreadful disease

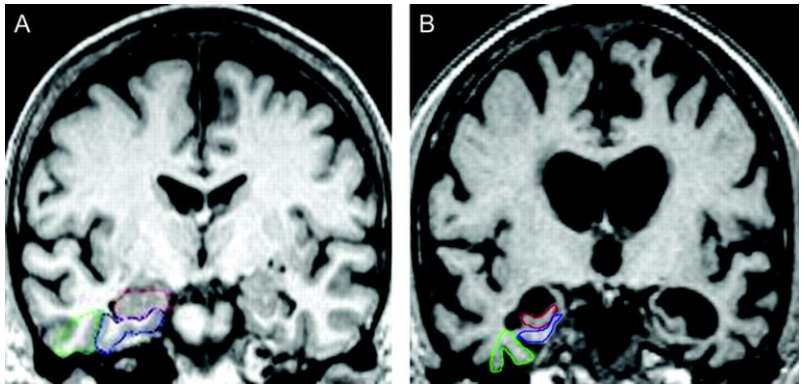
It affects >> ~8 million Americans

We should try to cure it

What happens to the brain in Alzheimer's?

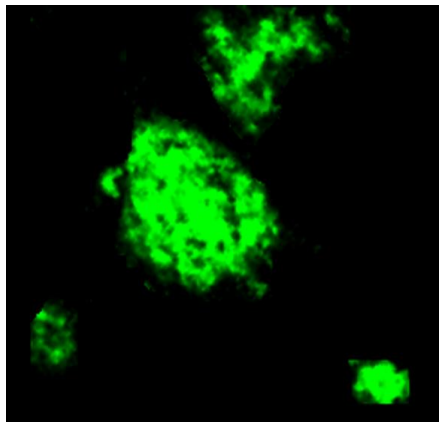
Healthy Brain

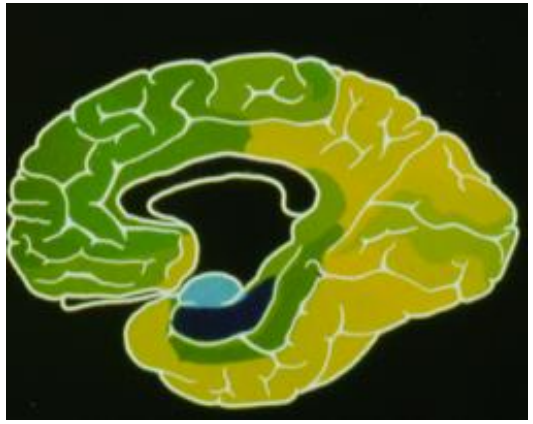
Severe Alzheimer's



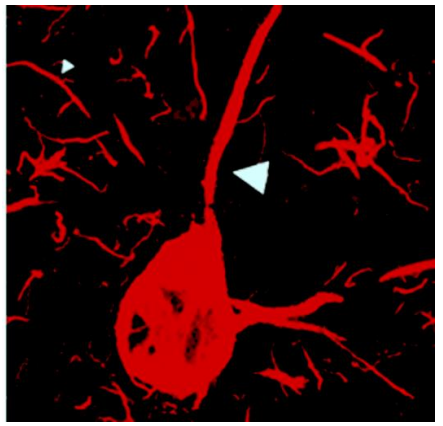
Duara et al 2008

Neuronal loss

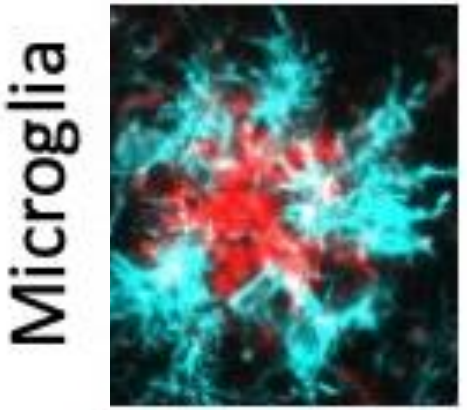


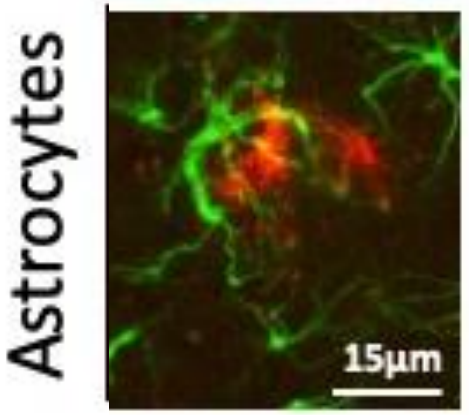


Abeta



tau

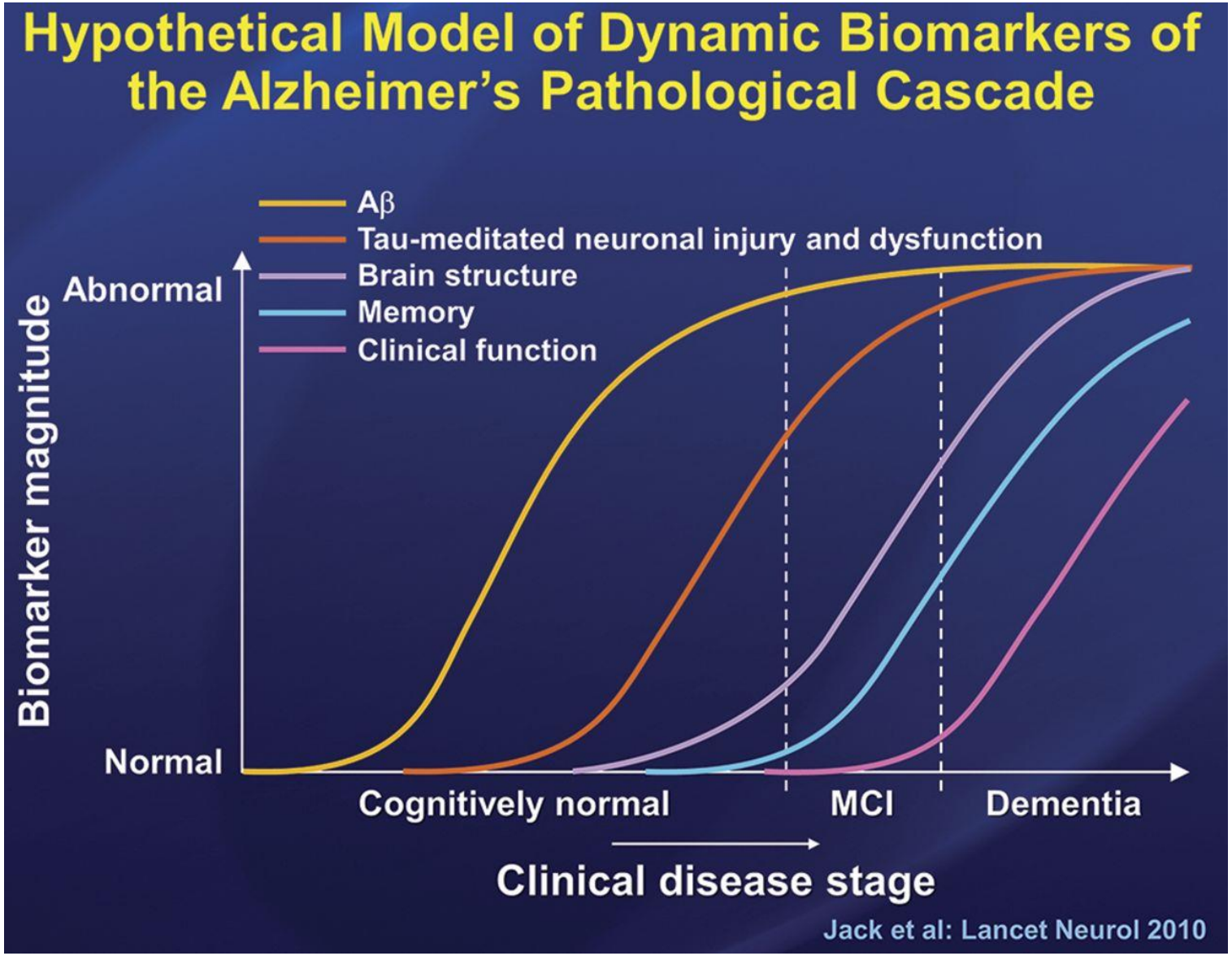




Inflammation

Hyman

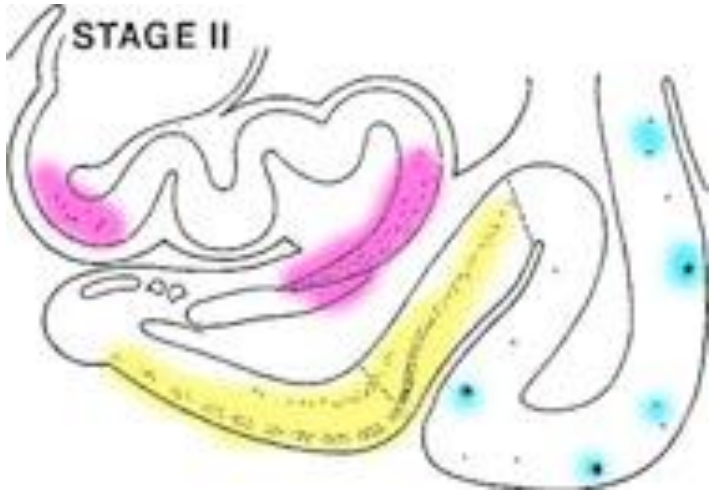
Arnold et al 1991

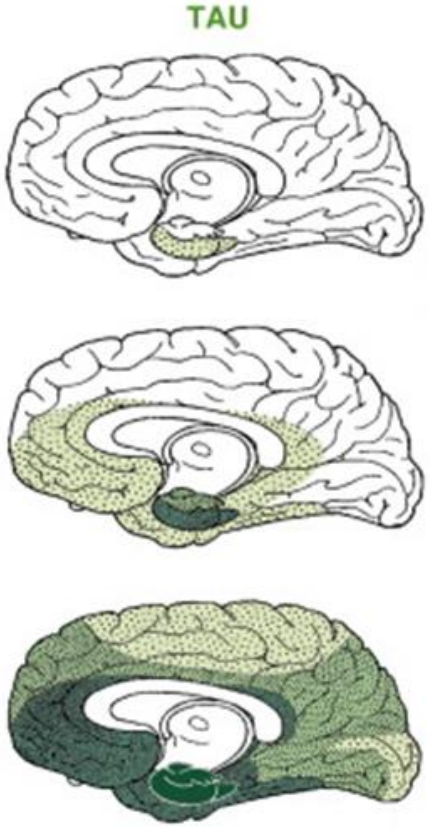

Hypothetical Model of Dynamic Biomarkers of the Alzheimer's Pathological Cascade
Aβ
Tau-meditated neuronal injury and dysfunction
Brain structure
Memory
Clinical function
Abnormal
Normal
Biomarker magnitude
Cognitively normal
MCI
Dementia
Clinical disease stage
Jack et al: Lancet Neurol 2010

20 years? →

Stereotypical Progression of NFTs and plaques

- Entorhinal cortex (EC) is the first part of the brain to develop NFTs





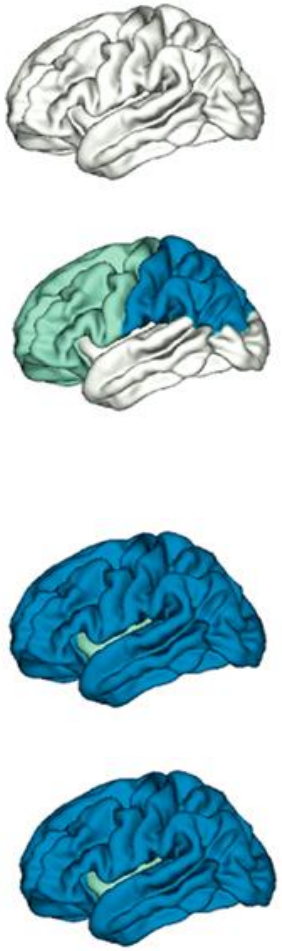
EC
Stages I/II

Hippocampus
Stages III/IV

Neo-cortex
Stages V/VI

~ 20 years

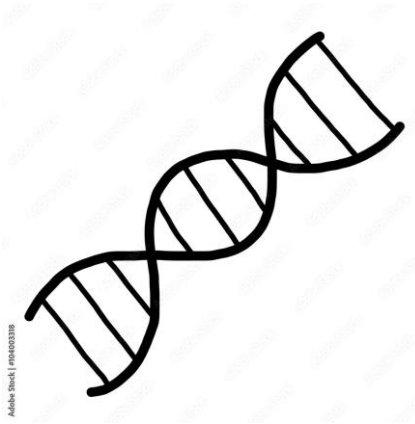
Amyloid



The pattern of progression, and time course, is inferred from cross sectional autopsy studies or PET studies

Adapted from "Neuropathological stageing of Alzheimer-related changes", Braak and Braak, Acta Neuropathol (1991) 82:239-259; Sun et al Trans Psych 2023.

What triggers AD?

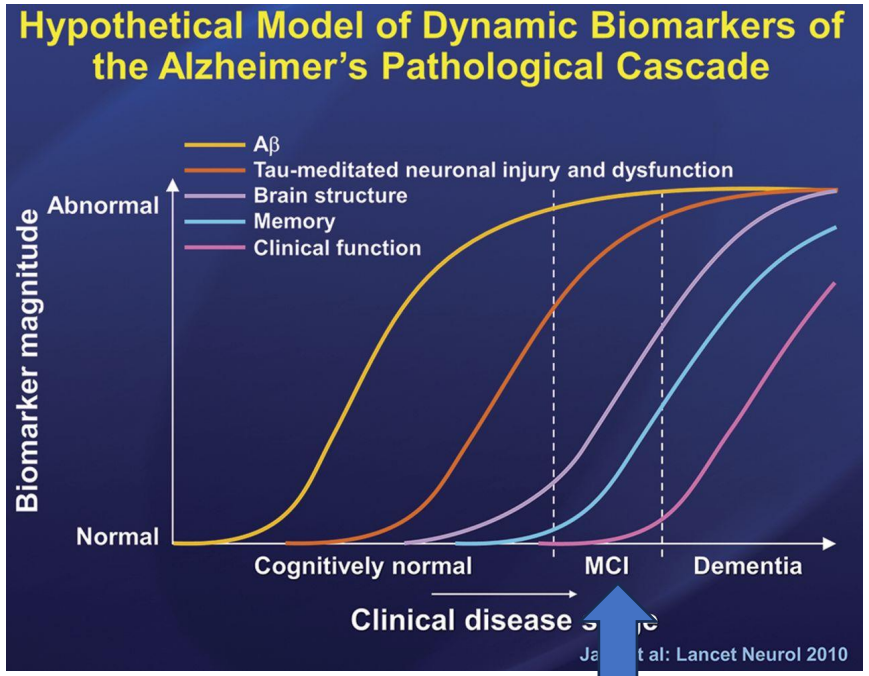


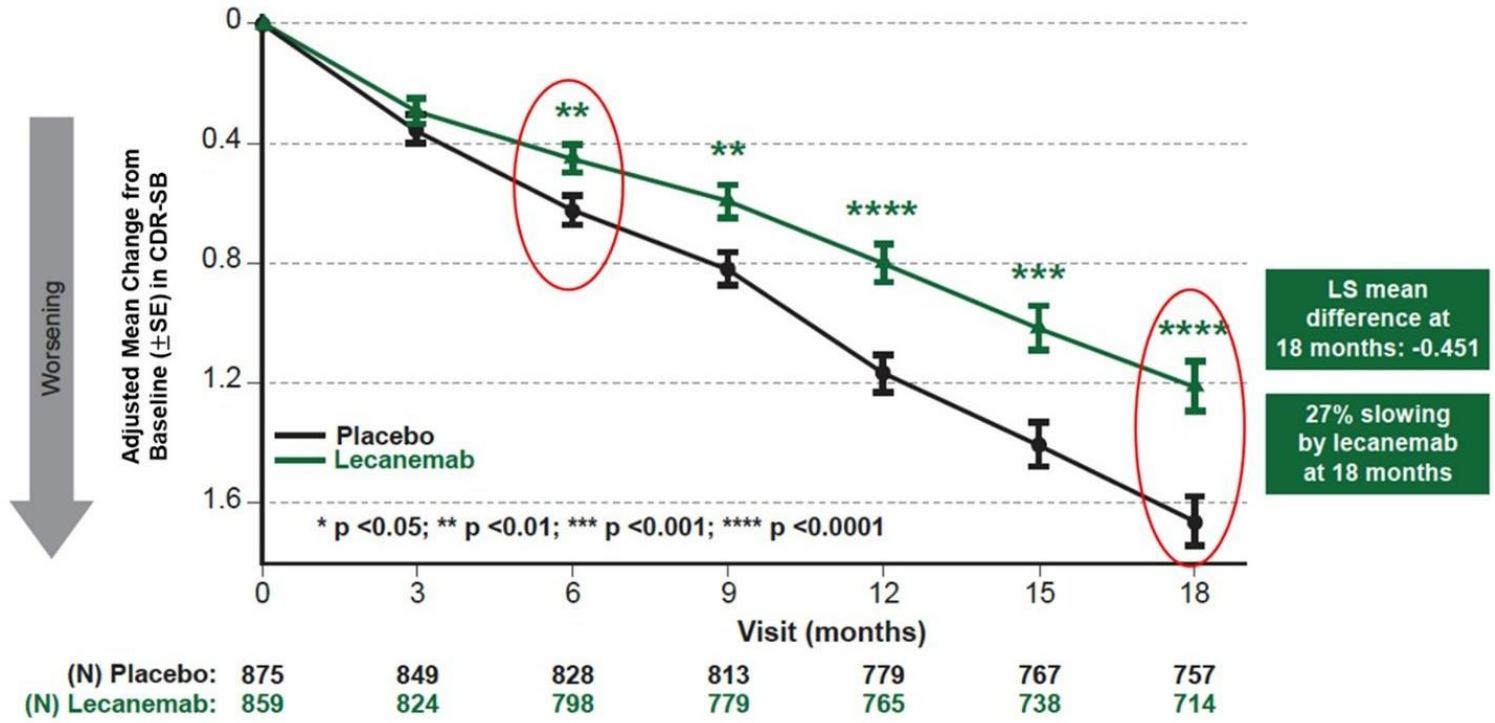
- **Clues from genetics**
  - 3 Autosomal dominant genes all lead to more plaques
  - Tau mutations lead to a very closely related set of diseases
  - Recent genetic data point to neuroinflammation
- **Treatments are derived from understanding the biology**
  - Anti-plaque medications can clear plaques!
  - Very recent anti-Tau agents appear to impact tangles
  - Agents that impact neuroinflammation under development
- **Lessons**
  - Not everything works as well as we hoped
  - It may be difficult to impact ongoing, established disease after neuronal loss

Reasons for hope

1. *anti-amyloid drugs are arriving in 2023*

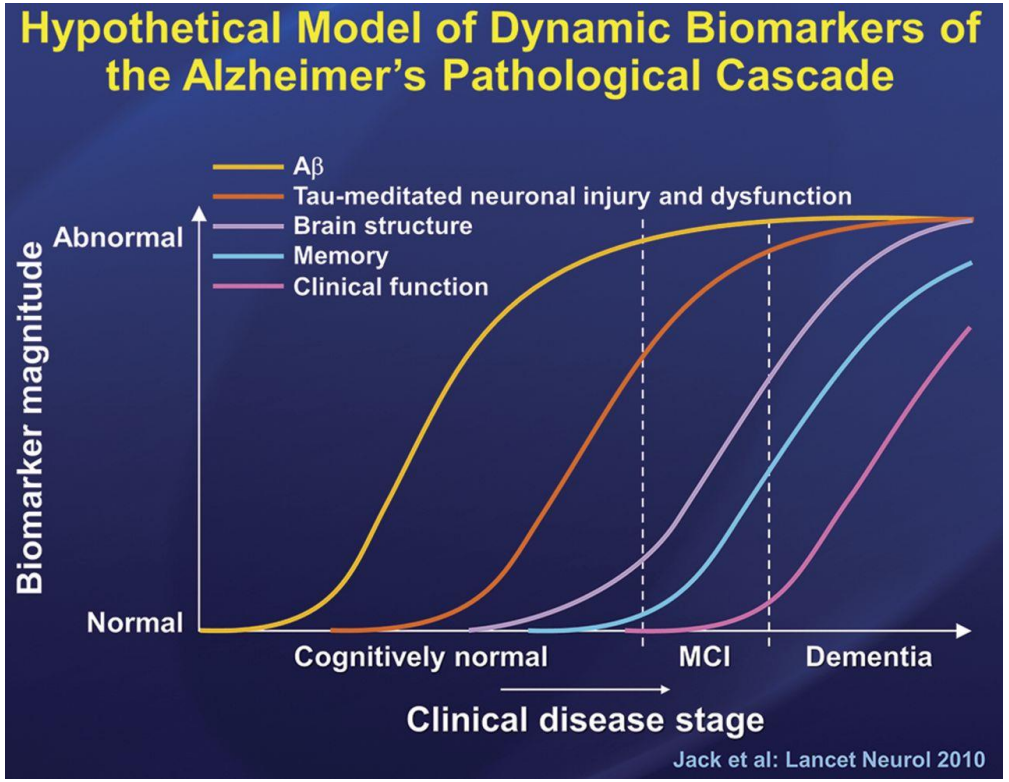
Lecanemab- the first new drug in many decades – is a first step towards helping – a little





Treatment started, lasts for 18 months

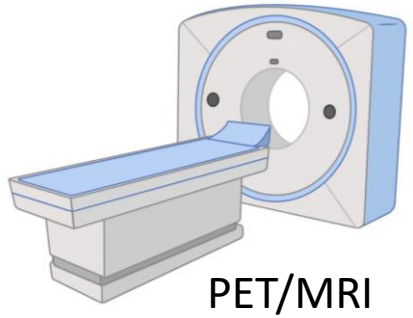
Will drugs based on amyloid work better to prevent or delay symptoms if it is caught early?



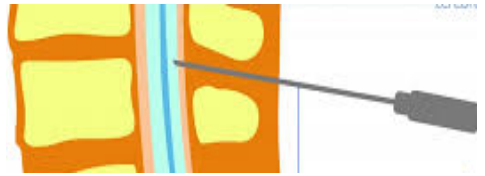
20 years?

Can detect "disease" here

Newest therapies approved for use here



PET/MRI SCANS

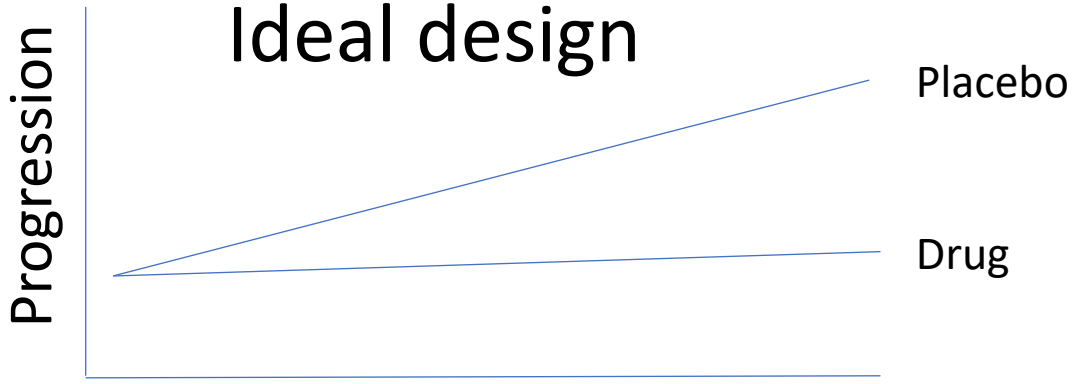


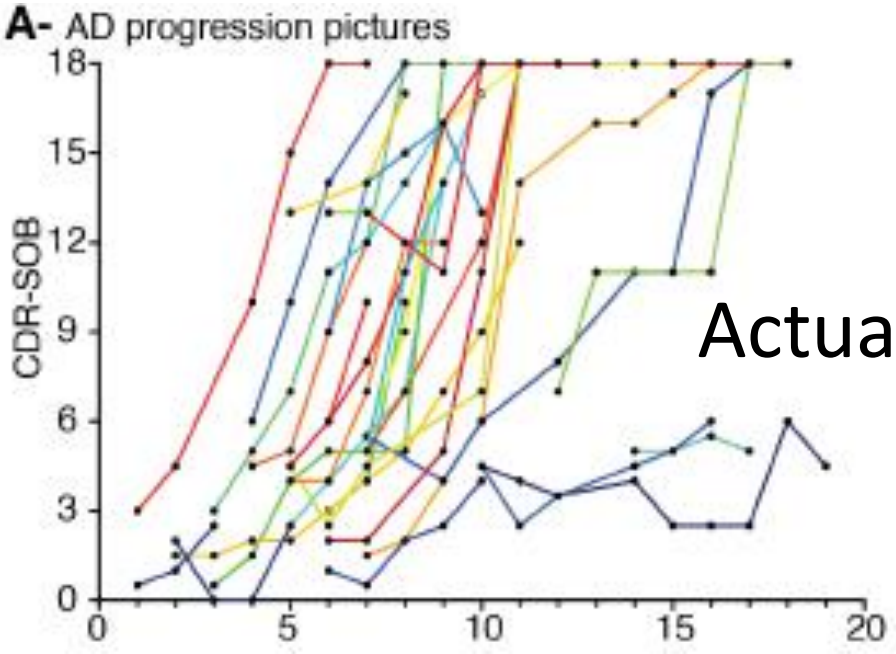
Spinal fluid and Plasma Biomarkers

Key 1: Learn how early we can diagnose the biochemical changes of Alzheimer disease.

Key 2. Learn how to run a clinical trial that tests the idea that an intervention works to prevent AD.

Treating the disease as it gets farther along





Actual data

C. J. Yao Art Gallery

One of our goals: how do patients differ from one another- and how are they the same?

The underlying questions to achieve effective therapeutics after cognitive impairments have become established:

- **Why do patients progress? Why do they have such different rates of progression?**
  1. Differences in the properties of proteopathic **tau** seeds among patients corresponds with their rate of progression
  2. Genetic landscape, including especially **apoE**
  3. Understanding **resilience**

2. REDUCING TAU SPREAD ACROSS THE BRAIN

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ALZHEIMER'S DISEASE

Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy

2017

Sarah L. DeVos,[1] Rebecca L. Miller,[1]* Kathleen M. Schoch,[1]* Brandon B. Holmes,[1] Carey S. Kebodeaux,[1] Amy J. Wegener,[1] Guo Chen,[1] Tao Shen,[1] Hien Tran,[2] Brandon Nichols,[2] Tom A. Zanardi,[2] Holly B. Kordasiewicz,[2] Eric E. Swayze,[2] C. Frank Bennett,[2] Marc I. Diamond,[3] Timothy M. Miller[1†]

SCIENCE ADVANCES | RESEARCH ARTICLE

NEUROSCIENCE

Persistent repression of tau in the brain using engineered zinc finger protein transcription factors

Susanne Wegmann[1,2*†], Sarah L. DeVos[1*], Bryan Zeitler[3*†], Kimberly Marlen[3], Rachel E. Bennett[1], Marta Perez-Rando[1], Danny MacKenzie[1], Qi Yu[3], Caitlin Commins[1], Riley N. Bannon[1‡], Bianca T. Corjuc[1], Alison Chase[1], Lisa Diez[2], Hoang-Oanh B. Nguyen[3], Sarah Hinkley[3], Lei Zhang[3], Alicia Goodwin[3], Annemarie Ledeboer[3], Stephen Lam[3], Irina Ankoudinova[3], Hung Tran[3], Nicholas Scarlott[3], Rainier Amora[3], Richard Surosky[3], Jeffrey C. Miller[3], Ashley B. Robbins[1], Edward J. Rebar[3§], Fyodor D. Urnov[3], Michael C. Holmes[3], Amy M. Pooler[3], Brigit Riley[3], H. Steve Zhang[3‖], Bradley T. Hyman[1†]

2021

HOT OFF THE PRESS!

Biogen and Ionis report positive topline clinical data on investigational Alzheimer's disease treatment at ADPD: in **A HANDFUL OF PATIENTS, TANGLES SEEEM TO HAVE DISAPPEARED**

Hopefully Phase 2, to start 2023

3. Genetic influences: **APOE4** remains the primary risk factor, and **APOE2** THE MOST IMPORTANT PROTECTIVE FACTOR KNOWN: gene therapy –may provide a way to restore synaptic integrity and dampen neuroinflammation

HOT OFF THE PRESS: CTAD Dec 2022, reported in NYT

A Promising Trial Targets a Genetic Risk for Alzheimer's

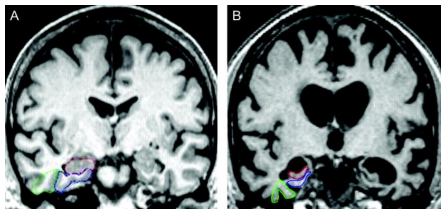
Preliminary results offer hope that gene therapy can protect some people with the brain disease driven by a particular gene variant.

2 patients, treated with apoE2 by AAV
No toxic side effects
Possible improvements in CSF biomarkers
Dr Ron Crystal - ADDF/ Lexeo therapeutics

4. The future: Understanding resilience and neuronal preservation, and the role of processes like senescence as they contribute to neural system reserve or vulnerability

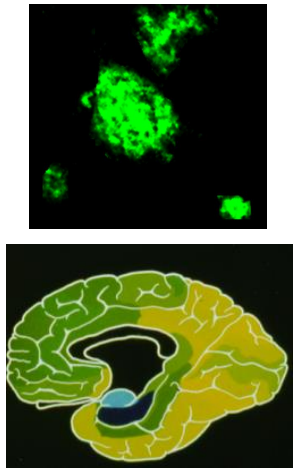
Nature Rev 2022

REASONS FOR HOPE, FOR TOMORROW



Neuronal loss

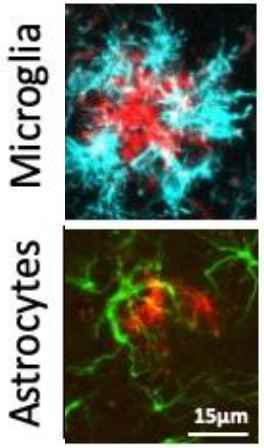
Duara et al 2008



Abeta

Arnold et al 1991

tau



Inflammation Hyman

WHAT TO DO TODAY

KEEP YOUR BRAIN HEALTHY WITH DIET, EXERCISE, BLOOD PRESSURE CONTROL

MAXIMIZE EVERY DAY

PAY FORWARD TO THE PEOPLE YOU LOVE- DIFFICULT DECISIONS, DIFFICULT CONVERSATIONS, BUT YOU DO NOT NEED TO DO IT ALONE

INTERVENTIONS, ALREADY IN DEVELOPMENT OR IN TRIALS, TARGETING EACH OF THESE PROCESSES

Thank you!

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Alzheimer's Disease
Research Center

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