ALZHEIMER'S DISEASE THERAPEUTICS: STATE OF THE FIELD

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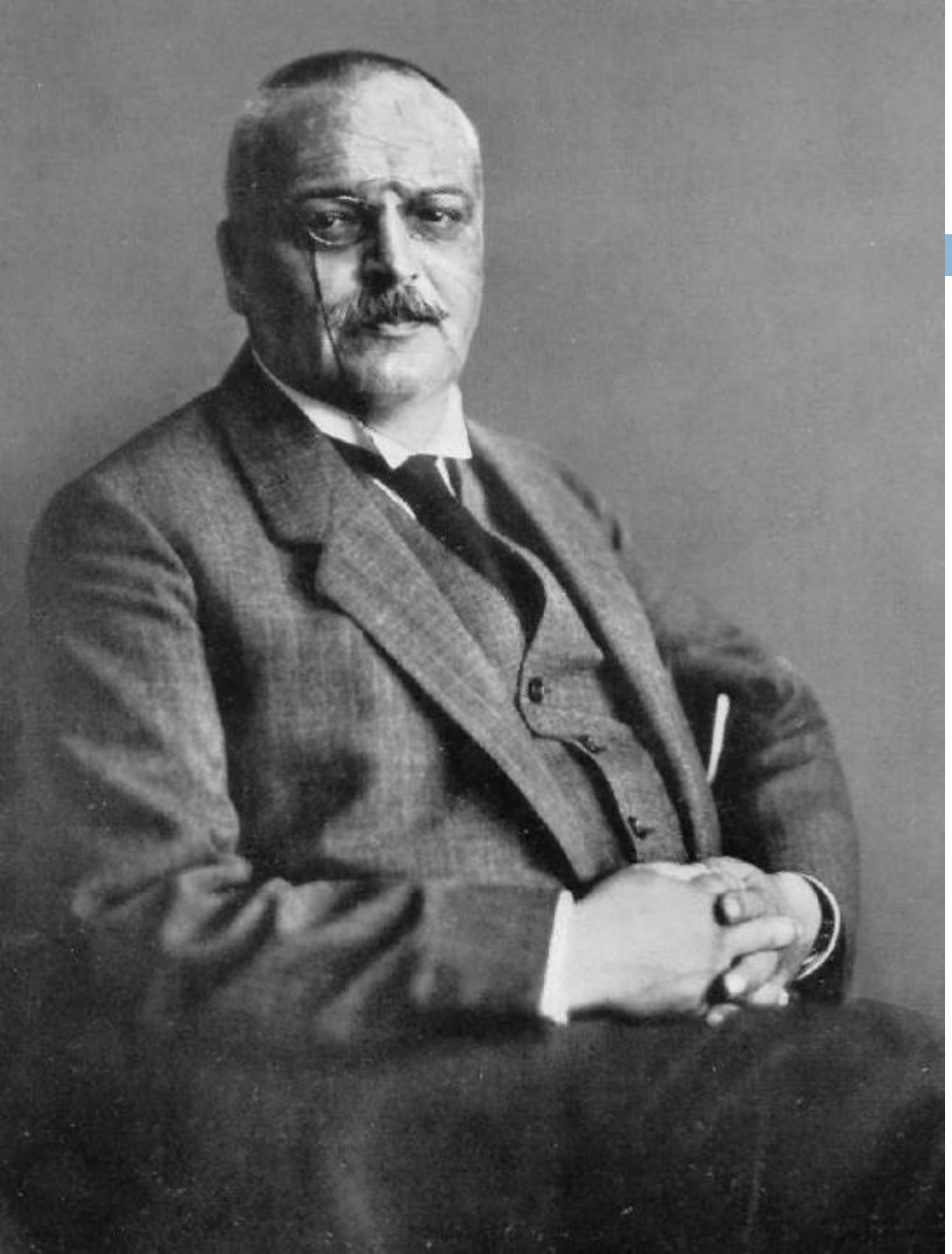
USC Alzheimer's Therapeutic Research Institute in San Diego

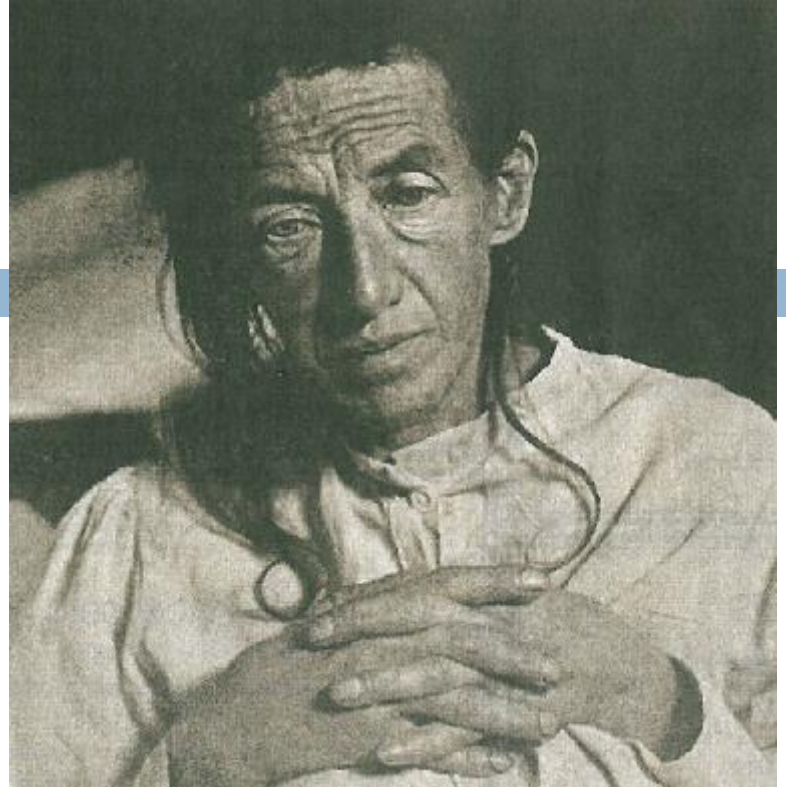
A bit about USC ATRI …

- Our history
- Who we are today
- Our mission
- Our research projects
  - A4
  - A3, A45
  - ADNI
  - ACTC
  - TRC-PAD
  - NIC, INI, DoD-ADNI, LEADS …

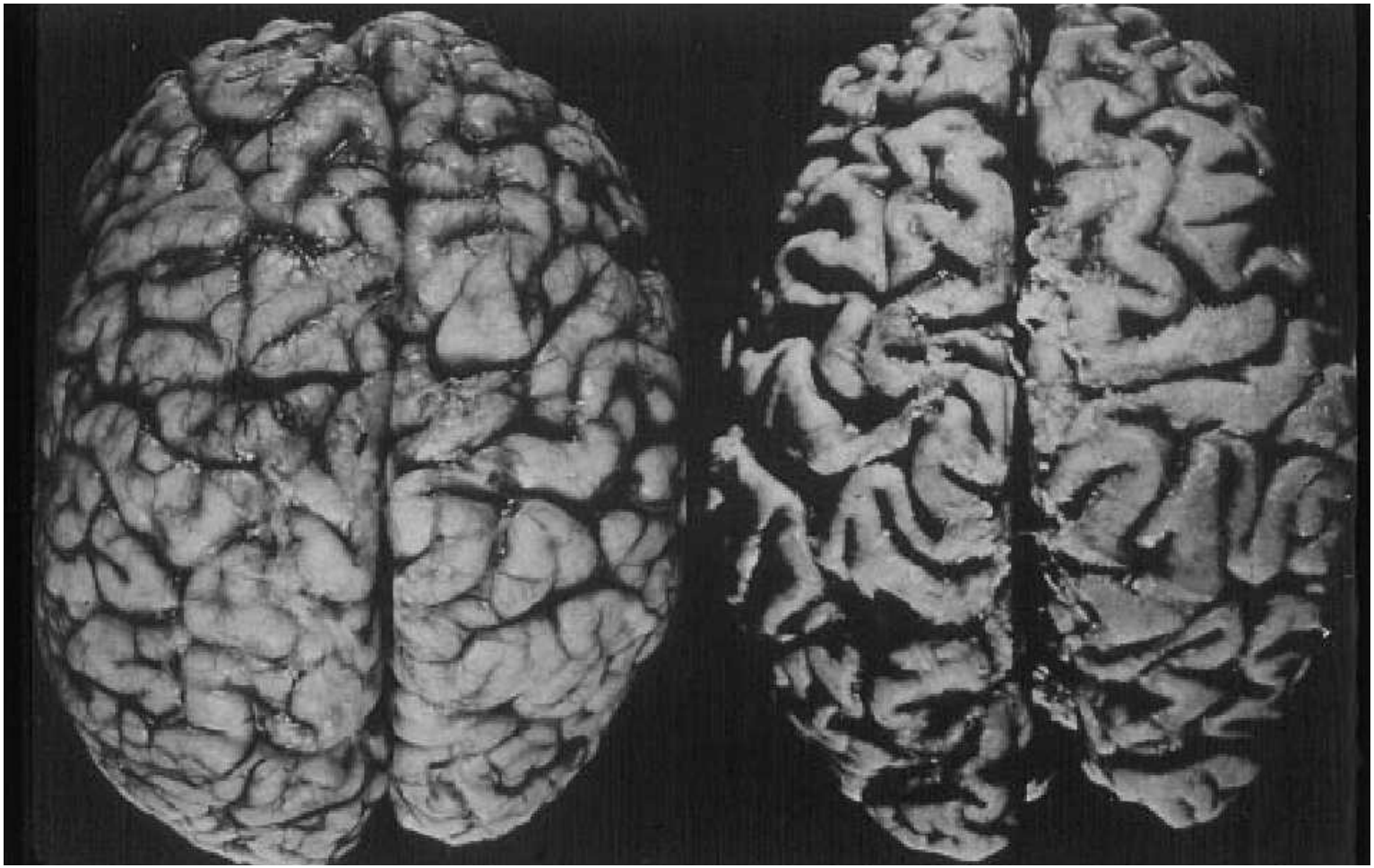
Alzheimer's dementia

- ~50 million people have AD dementia worldwide; 10 million new cases per year
- As populations age, the number of cases of AD dementia will grow to130 million in 2050
- Annual economic impact >US$1 trillion

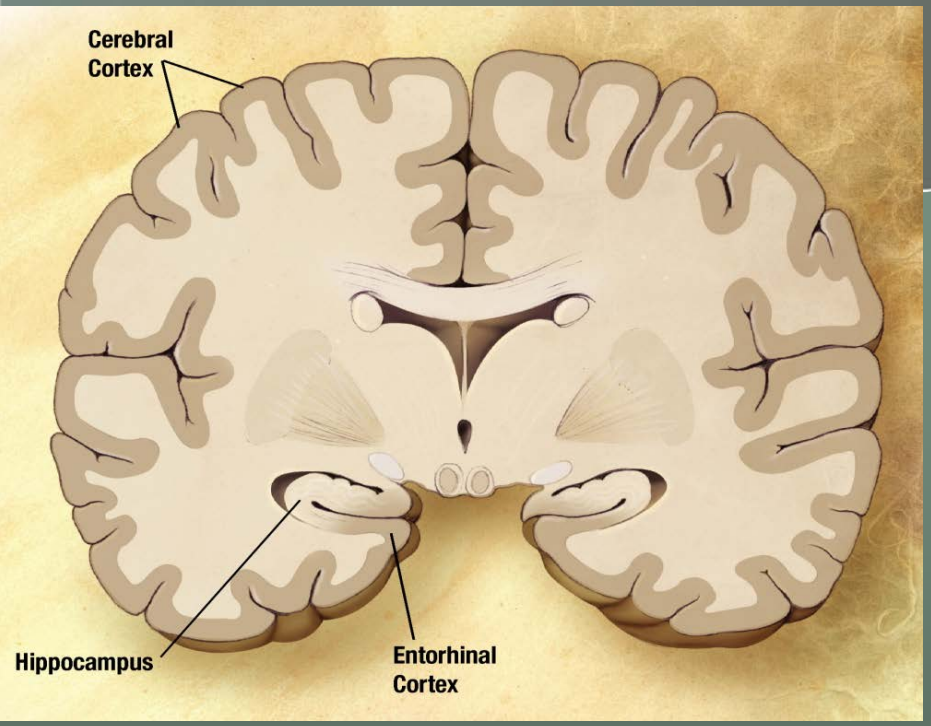


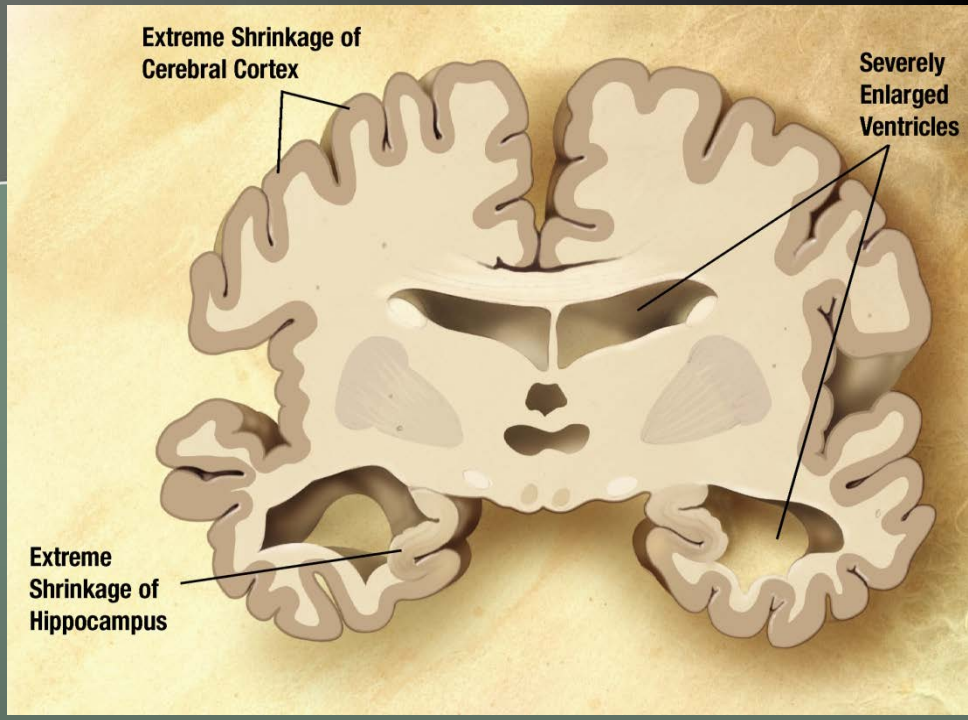


Loss of Brain Tissue with AD



Normal AD

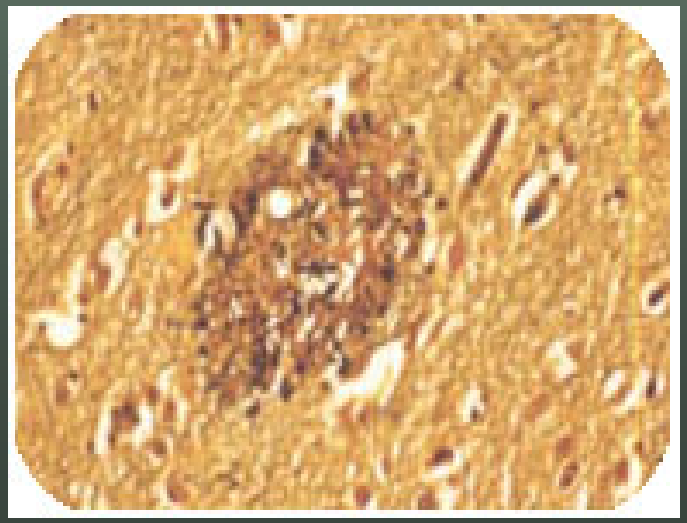


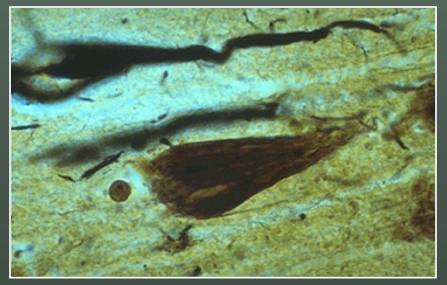


Normal Brain

Alzheimer's Brain

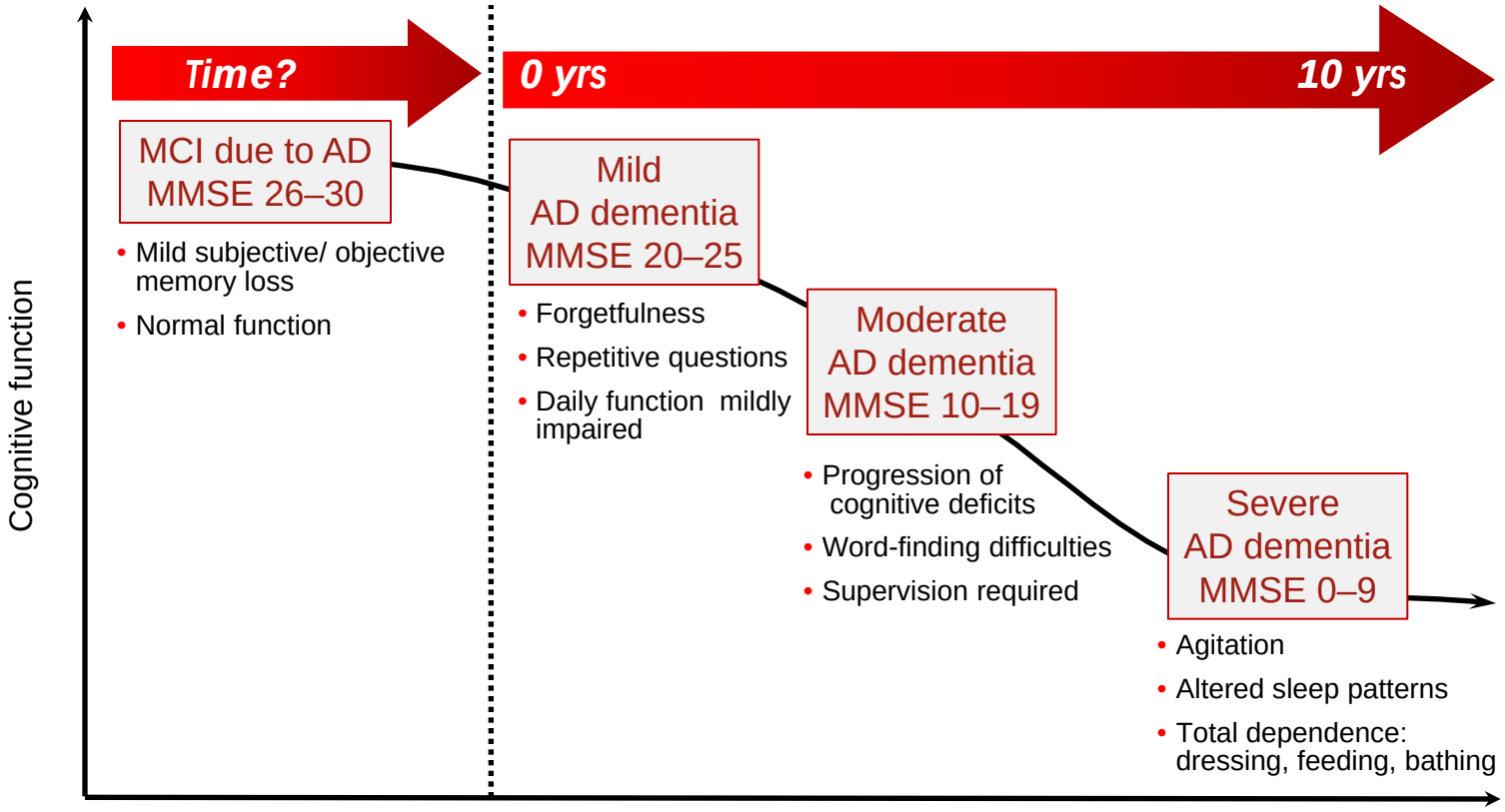
Amyloid plaque





Neurofibrillary tangle

Traditional view:
AD begins with the onset of demenia



Brief History of AD Therapeutics

- 1906: Dr. Alois Alzheimer describes AD
- 1906-1970's: General assumption that this is an unusual and untreatable degenerative disease of middle age
- 1976: Dr. Robert Katzman editorial: The Prevalence and Malignancy of Alzheimer's Disease
- Late 1970's Cholinergic hypothesis suggests treatment possibilities

The beginning of AD therapeutics

- An academic-government partnership is US: National Institute on Aging (NIH) supports the development of AD trial methods, and the first multicenter trial (tacrine)
- Tacrine trialists, led by Thal and Davis, become the Alzheimer's Disease Cooperative Study (ADCS, funded by NIA in 1991)

Early success in AD trials

- 1993: Tacrine is approved; 3 other similar drugs follow
- 2003: Memantine is approved, representing a second therapeutic class for AD
- And then a lost 16 years?

Finding new treatments for AD

- How do we decide what new treatments should be tested in randomized controlled trials?
  - Basic research studies
  - Epidemiology

Epidemiology

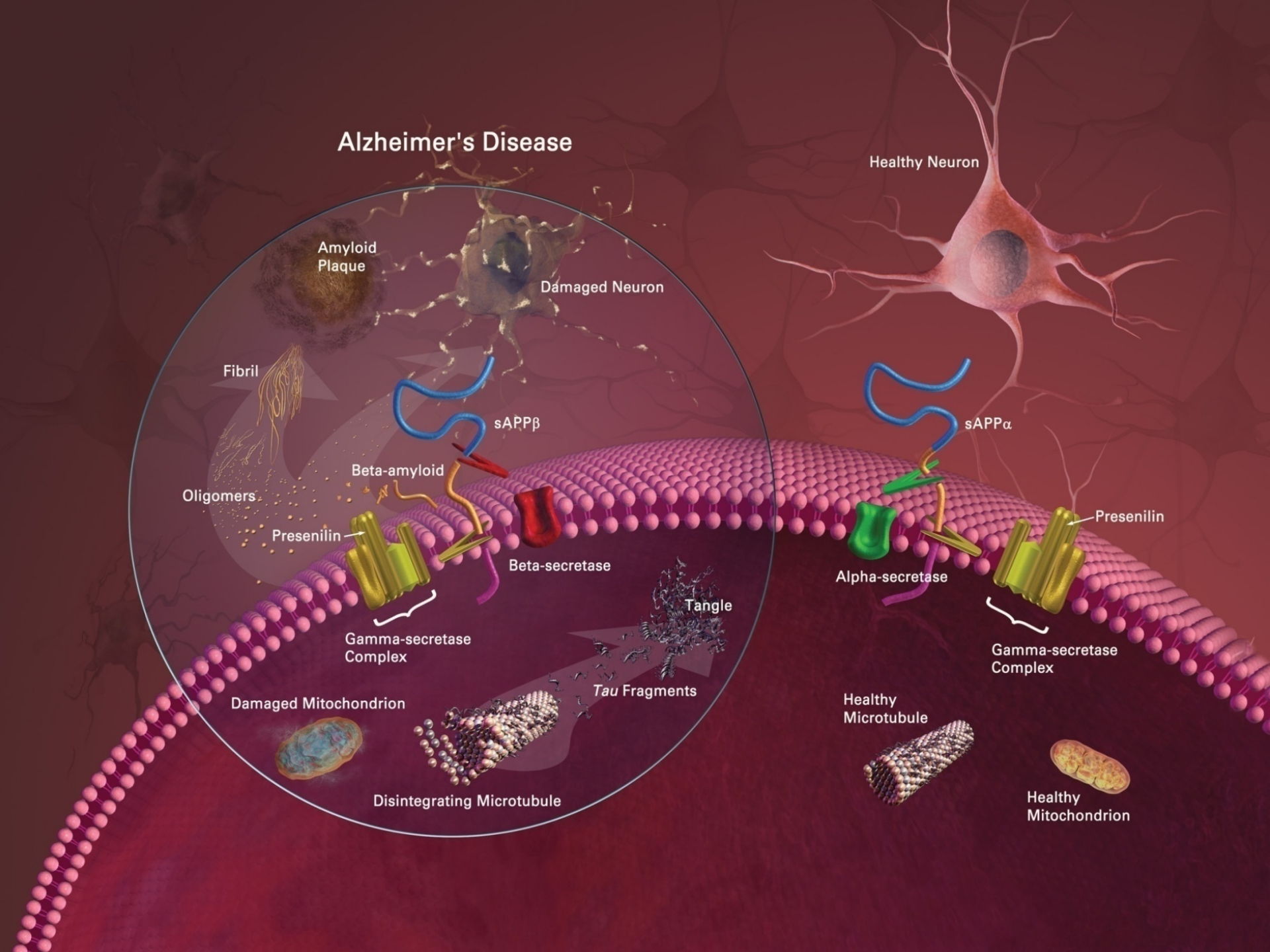
- Pros:
  - real-life observations
  - can examine many issues simultaneously
  - hypothesis-generating
  - expensive, but not nearly as expensive as clinical trials
- Cons:
  - Without random assignment to a treatment condition, studies are never conclusive (biases unavoidable)
  - In the AD field, epidemiology has not been very helpful with therapeutics

Candidate therapies suggested by epidemiology

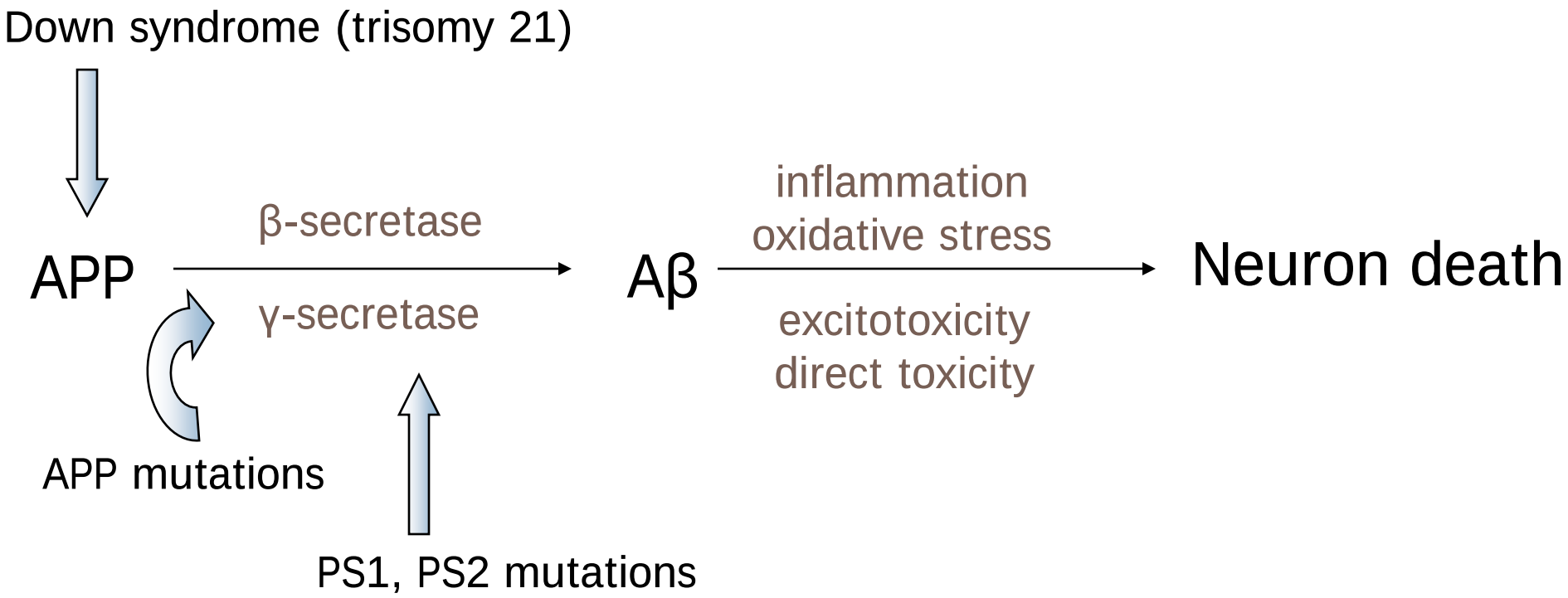
- Anti-inflammatory drugs
- Estrogen
- B vitamins
- Statins
- Docosahexaenoic acid (DHA)

Negative ADCS trials (mainly based on epidemiology)

- Prednisone
- Rofecoxib
- Naproxen
- Estrogen
- Simvastatin
- B vitamins
- DHA


Alzheimer's Disease
Amyloid Plaque
Damaged Neuron
Fibril
sAPPβ
Beta-amyloid
Oligomers
Presenilin
Beta-secretase
Gamma-secretase Complex
Tangle
Tau Fragments
Damaged Mitochondrion
Disintegrating Microtubule
Healthy Neuron
sAPPα
Alpha-secretase
Presenilin
Gamma-secretase Complex
Healthy Microtubule
Healthy Mitochondrion

Moving away from epidemiology: genetics and neurobiology



Industry AD trials (a partial list): promising targets, negative trials

- Xaliproden (neuroprotection)
- Tramiprosate (amyloid anti-aggregation)
- Tarenflurbil (gamma secretase modulator)
- Rosiglitazone (metabolic, anti-inflammatory)
- Leuprolide (endocrine)
- Dimebon (mitchondrial)
- Semegacestat (gamma secretase inhibitor
- Avagacestat (gamma secretase inhibitor)
- Bapineuzumab (anti-amyloid antibody)
- Solanezumab (anti-amyloid antibody)
- Verubecestat (BACE inhibitor)
- Lanabecestat (BACE inhibitor)
- Aducanumab (anti-amyloid antibody)

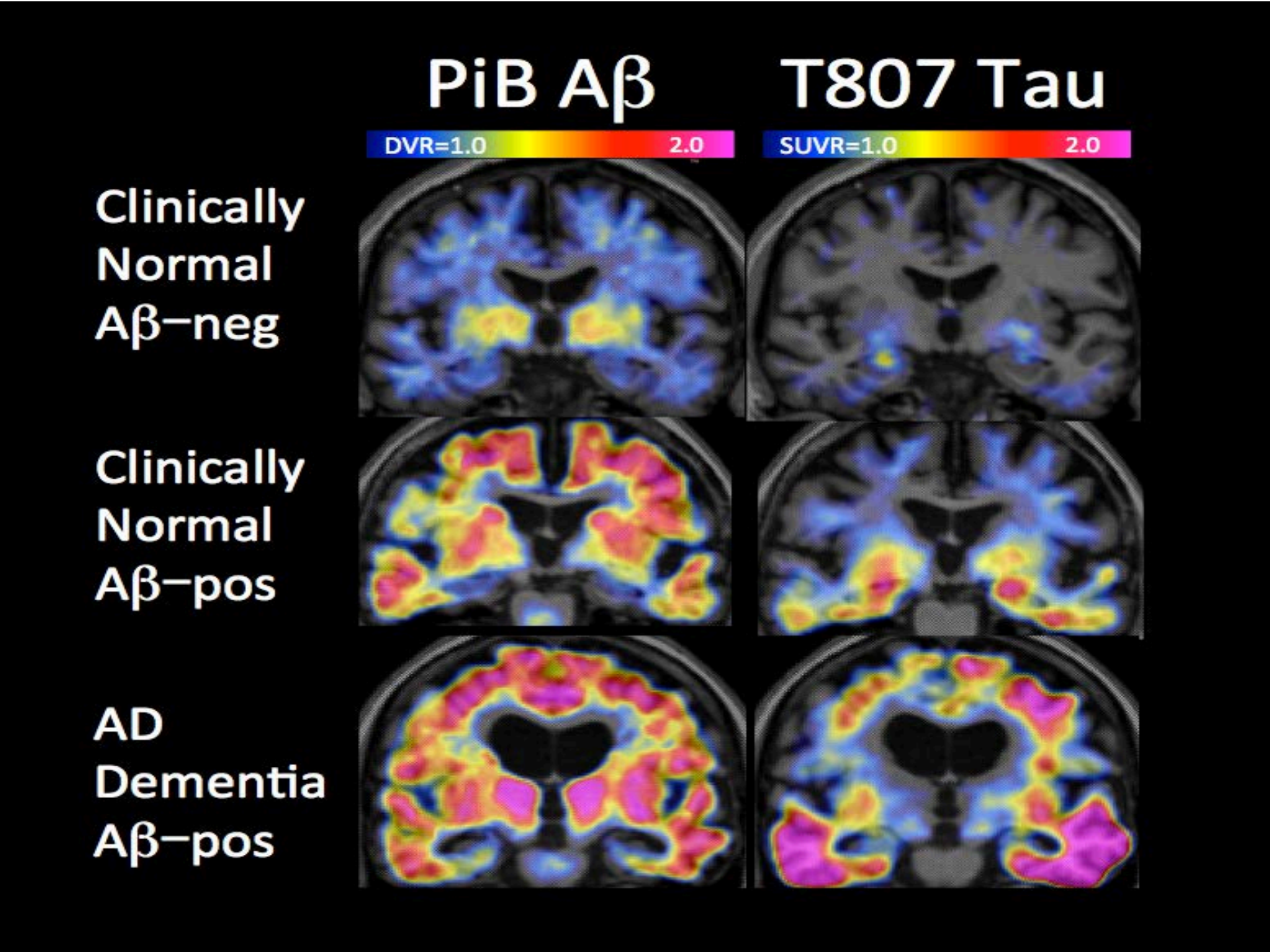
How can we do better?

- Optimize selection of drugs
- Optimize drug doses
- Treat early
- Combination therapy?

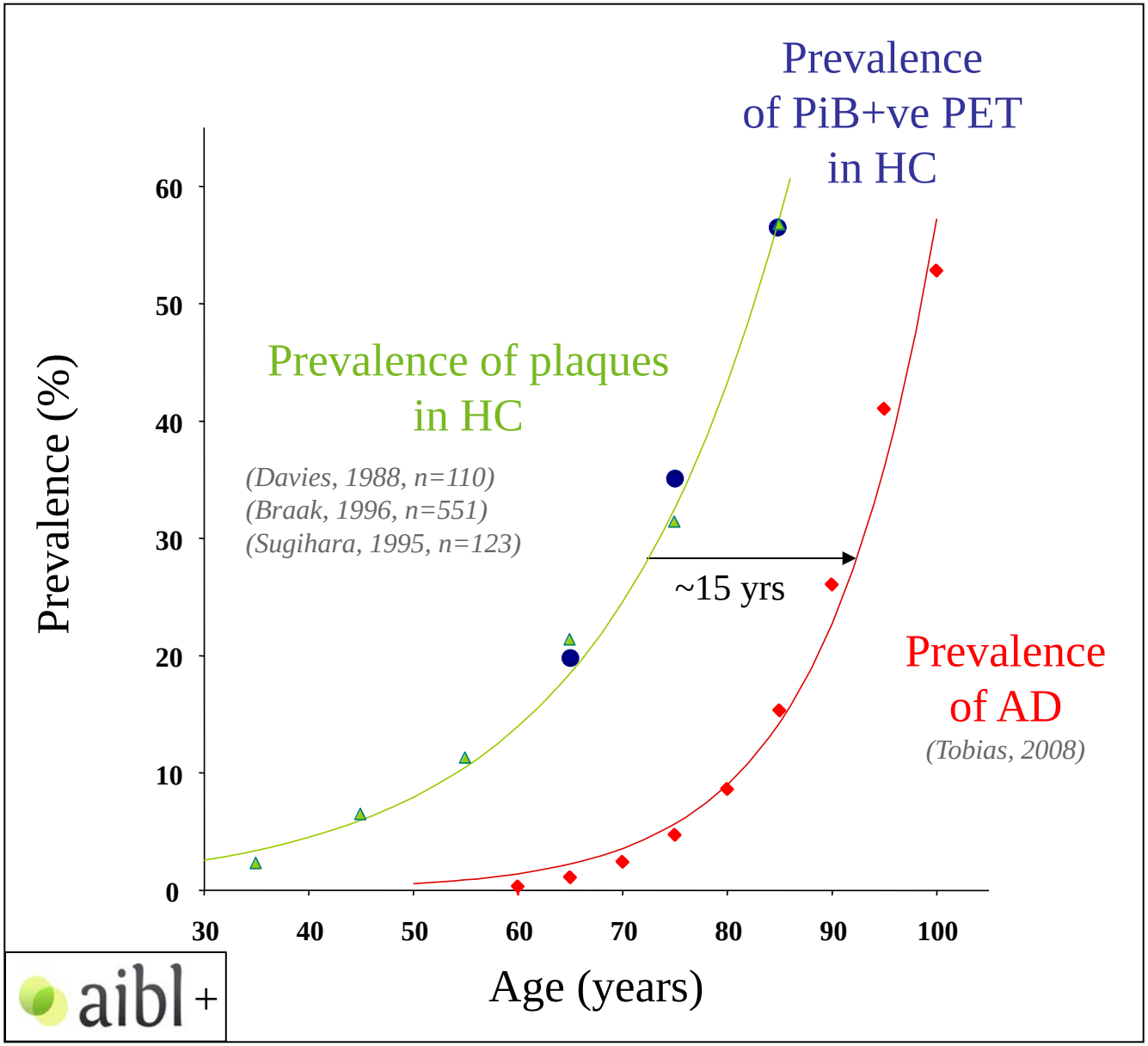
New tools available

- Amyloid PET imaging
- Tau PET imaging
- Other biomarkers: CSF, volumetric MR
- Sensitive measures of cognitive and functional decline
- Large collaborative datasets: ADNI, AIBL …

A paradigm shift in AD trials


PiB Aβ
T807 Tau
DVR=1.0
2.0
SUVR=1.0
2.0
Clinically Normal Aβ−neg
Clinically Normal Aβ−pos
AD Dementia Aβ−pos

Amyloid plaques precede dementia by at least 15 yrs

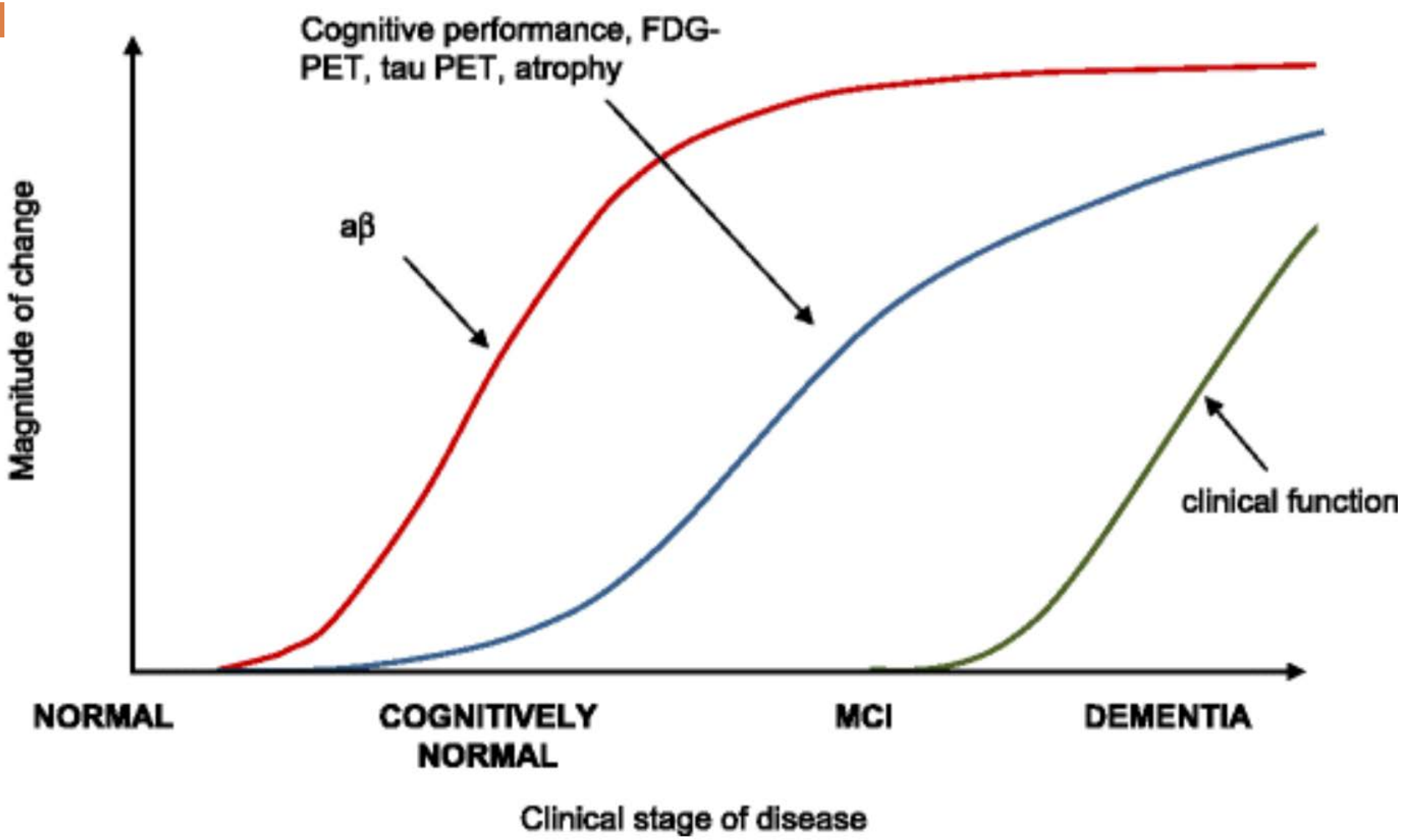


Rowe et al, Neurobiol Aging, 2010

New paradigm

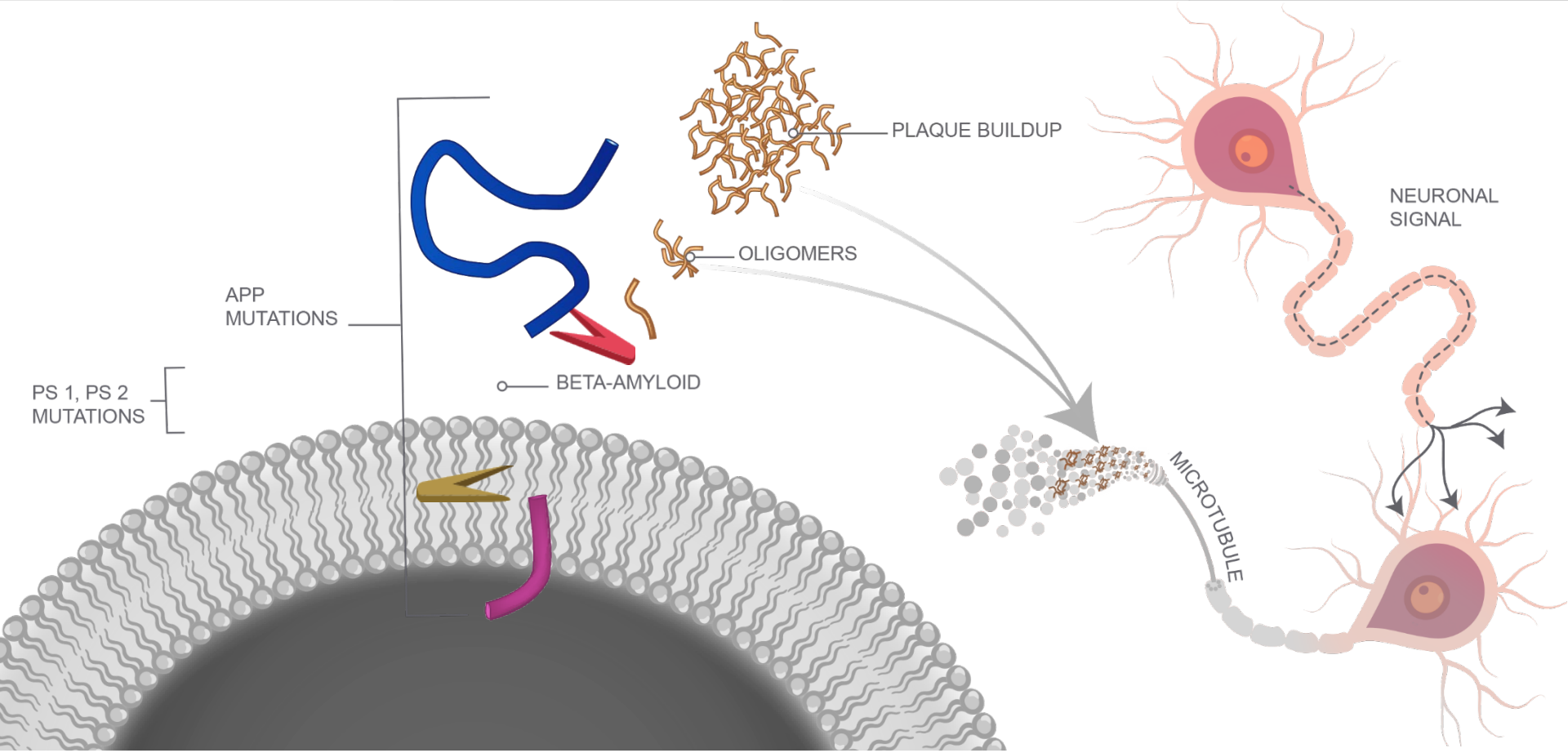
- AD dementia
- Prodromal AD
- Preclinical AD

AD Continuum



- How can we prevent or slow the disease?

PS 1, PS 2, AND APP MUTATIONS DOWN SYNDROME (TRISOMY 21)	β-SECRETASE γ-SECRETASE	OXIDATIVE STRESS; INFLAMMATION DIRECT TOXICITY; EXCITOTOXICITY	SYNAPTIC FAILURE; NEURON DEATH



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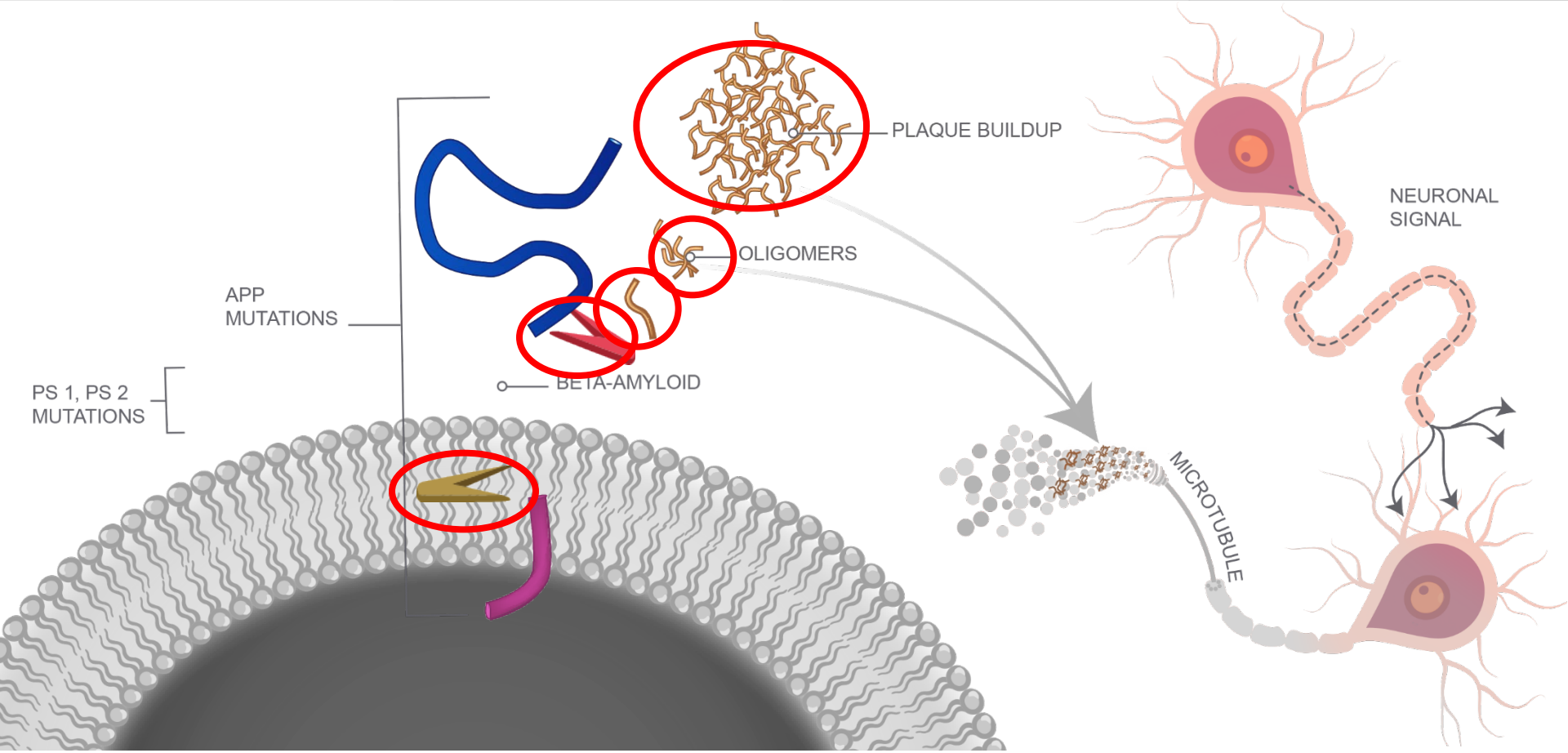
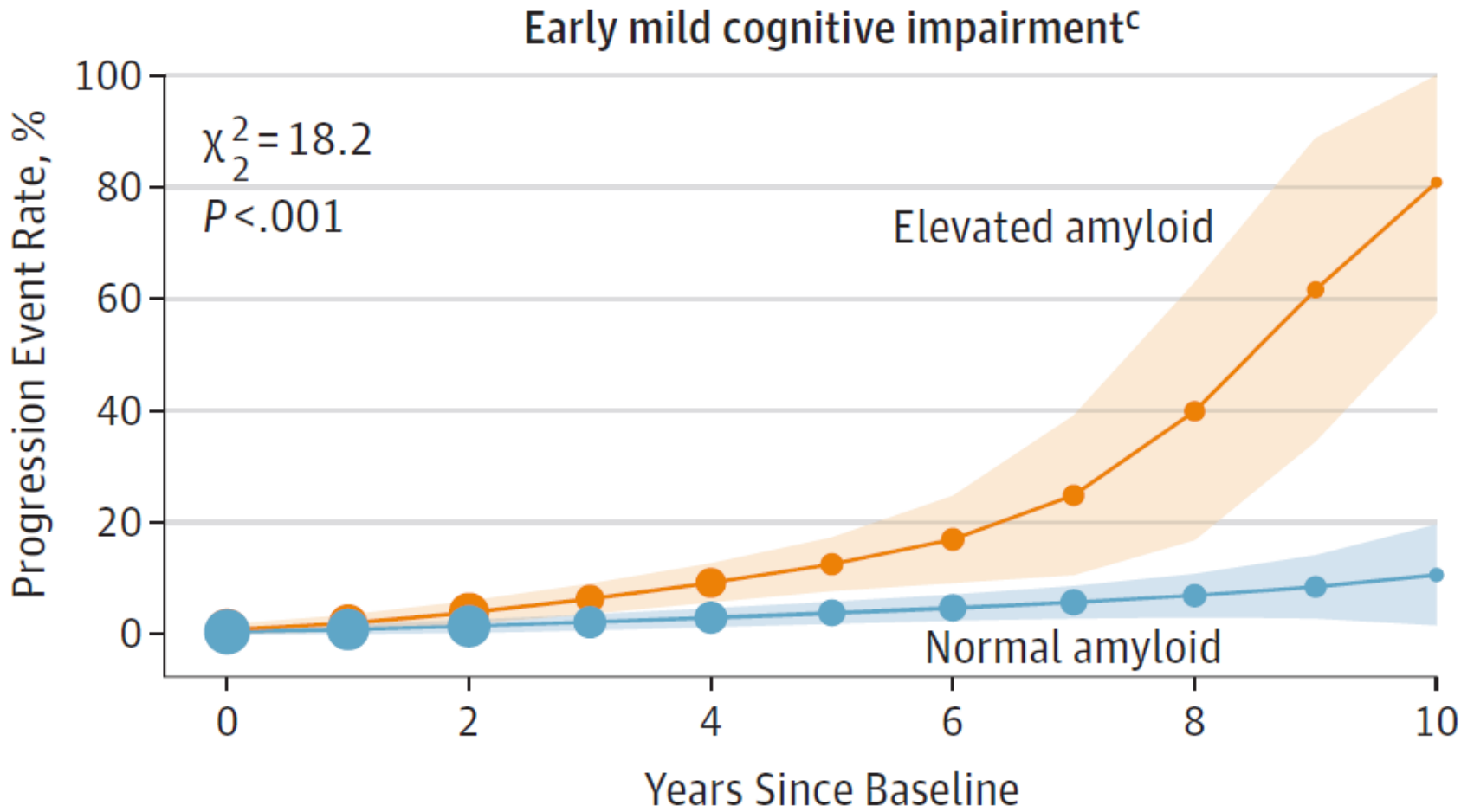


“Preclinical” (asymptomatic) AD

- ADNI data: 30% of clinically normal individuals at least 65 years of age are amyloid positive by CSF or PET

- *Frightening*
- *But this is a therapeutic opportunity*

Preclinical AD progresses to symptomatic AD



No. of patients, by amyloid level

Elevated	196	148	167	65	79	32	35	28	25	14	7
Normal	239	194	198	97	98	56	59	53	36	29	9

Donohue et al, JAMA, 2017

Secondary prevention (very early treatment of AD)

target *amyloid-related cognitive decline* in clinically normal older individuals

ADCS A4 Trial Design

Anti-Amyloid treatment in Asymptomatic AD

- Screen clinically/cognitively normal 65+ year-olds
- Select those with amyloid in brain by PET
- Enroll in a 4 year RCT of an anti-amyloid rx (solanezumab)
- Primary outcome: cognitive composite
- Broad secondaries including computerized cognitive composite, PRO, functional/structural MR, CSF

Current status of the A4 trial

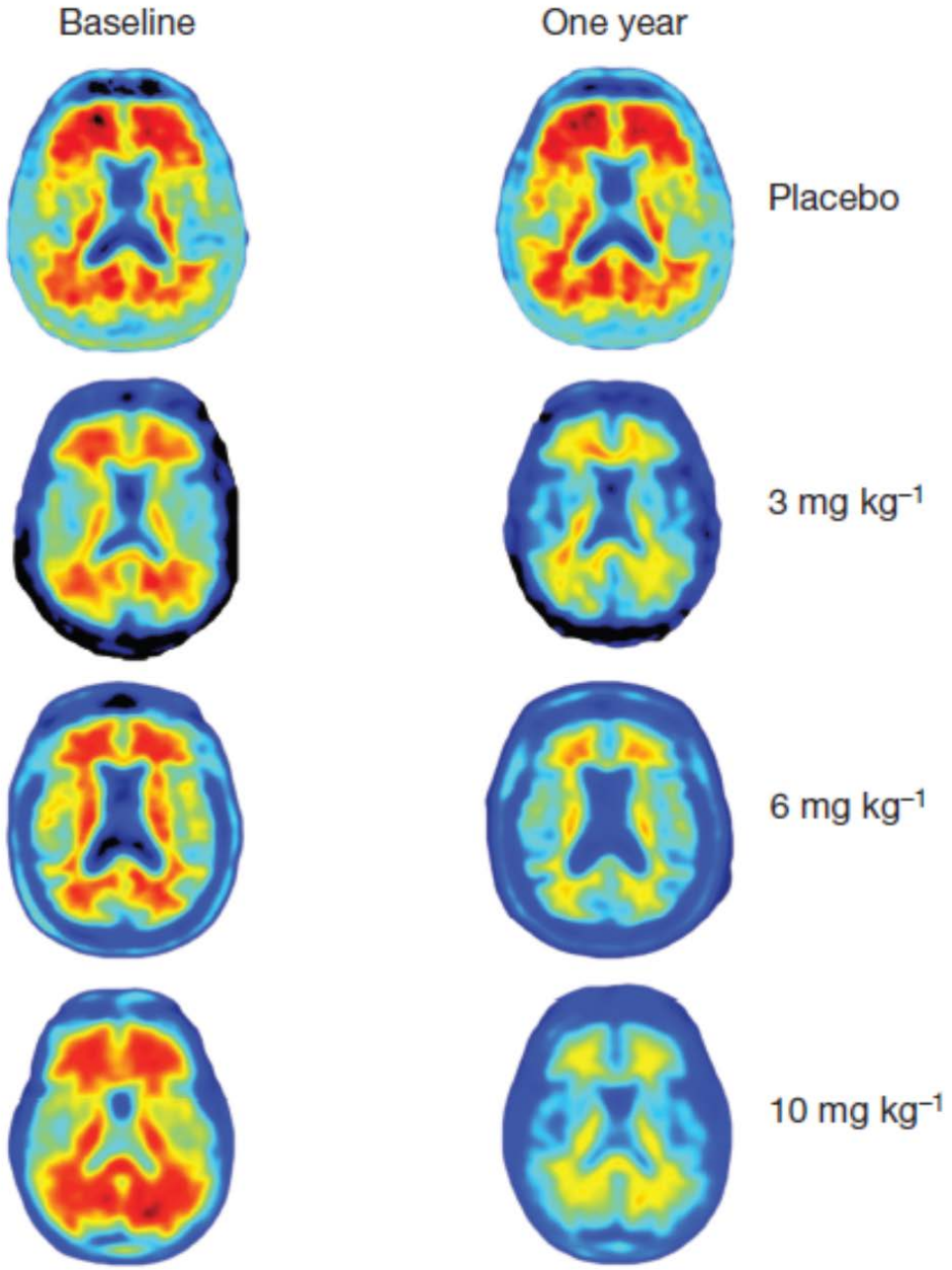
- 67 sites US, Canada, Australia and Japan
- 6762 participants screened (14% minority)
- 4487 amyloid PET acquired
- Amyloid PET eligibility = 29.5%
- Fully enrolled: 1169 participants randomized
- Attrition remains low -13.9% over 4 years
- 531 participants baselined in LEARN

“A-platform” trials: beyond A4

- A5 (another A4) aka EARLY: BACE inhibitor trial (ATRI/Janssen), halted because of hepatotoxicity
- A3 (ante-amyloid Alzheimer’s treatment): identify individuals before amyloid PET is positive, control amyloid dysregulation (eg BACE inhibitor) to slow accumulation; to start early 2019
- A45: Combination trial with BACE inhibitor and amyloid-reducing antibody (in review)

Promising anti-amyloid therapies

Aducanumab amyloid reduction (Phase 1b, early AD)

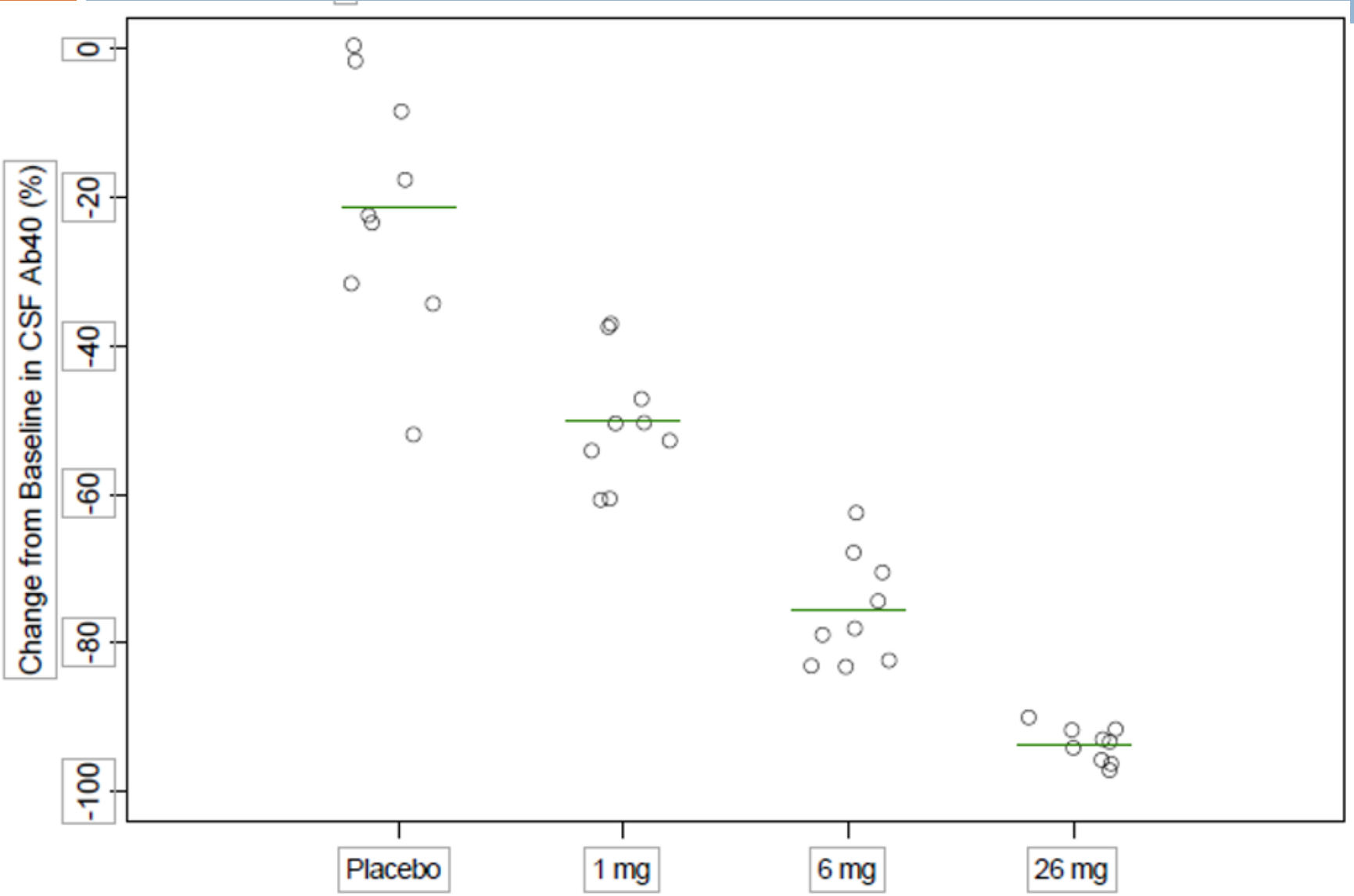


There are now 4 amyloid-reducing antibodies in development

- Aducanumab (Biogen, Eisai): recent failure in symptomatic AD
- BAN-2401(Eisai, Biogen, BioArctic)
- Gantenerumab (Roche)
- N3pG (Lilly)

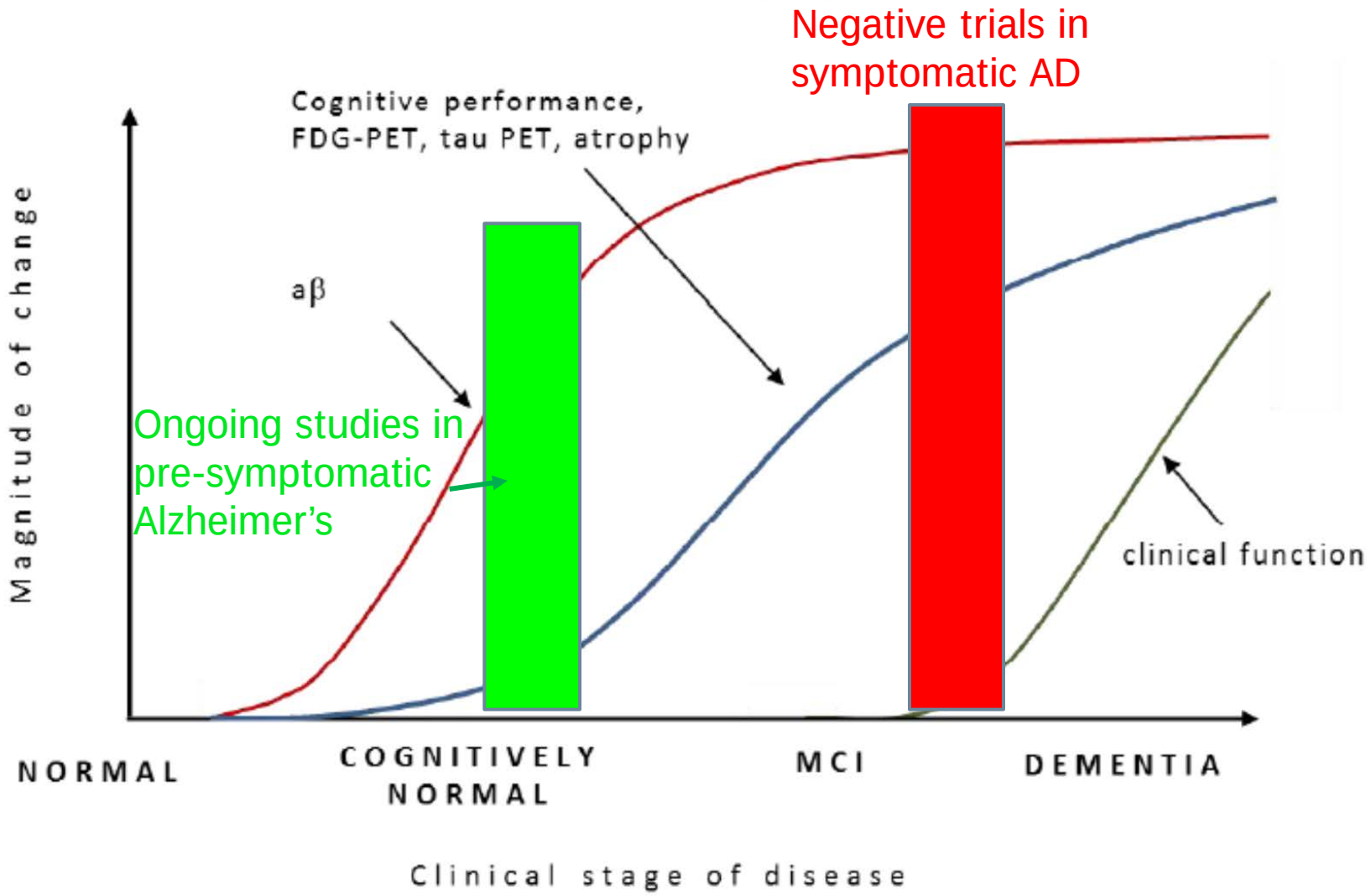
- All show dramatic reduction of brain amyloid, but with accompanying Amyloid-Related Imaging Abnormalities (ARIA)

Beta secretase inhibition: 3 promising drugs in development



We can now remove amyloid from brain and block further amyloid production

Remove amyloid for a cure?



What is the future of AD therapeutics?

- Primary prevention of AD
  - The evidence that amyloid accumulation is the main cause of AD remains highly compelling
  - We can largely eliminate the accumulation of amyloid with BACE inhibitors
  - Therefore, it is likely that we can prevent AD

Comorbidities complicate AD drug development (especially in later stages)

- Vascular disease
- Lewy bodies
- TDP-43
- Etc.

Other therapeutic approaches

- Tau immunotherapies
- Neuroprotection: NGF, BDNF, exercise
- Anti-inflammatories
- APOE-related therapeutics

- Many other strategies are being pursued
- Combinations are also being tested

Key ATRI infrastructure grant awards

- ACTC: a clinical trials consortium (successor to the ADCS)
- TRC-PAD: a new approach to recruitment into early stage trials

ATRI Biorepository

- Just opened in San Diego
- Will house all specimens for A4, LEARN, EARLY, INI, FYN and all future ATRI trials
- Optimization of biofluid assays for amyloid (CSF, plasma)
- Sharing of specimens

Coming ATRI studies

- A3 and A45 will start in 2019
- Several others in the works

- Alzheimer's Primary Prevention Project: early planning phase

Conclusion and timeline

- Major advances may be near
  - Multiple promising anti-amyloid treatment trials in very early stage AD will read out in the next 4-8 years
  - Primary prevention studies will take longer, as we need to validate methods for selecting at-risk individuals, and use of surrogate endpoints

Acknowledgments

- NIA: ACTC, ADNI, TRC-PAD etc.
- Alzheimer's Association, Lilly, Janssen
- Reisa Sperling
- Keith Johnson, Ron Petersen, Jeff Cummings
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- Many, many other colleagues, individuals with (or at risk for) AD and their families