UCSF Weill Institute for Neurosciences

Memory and Aging Center

Pharmacological treatment of Alzheimer's disease

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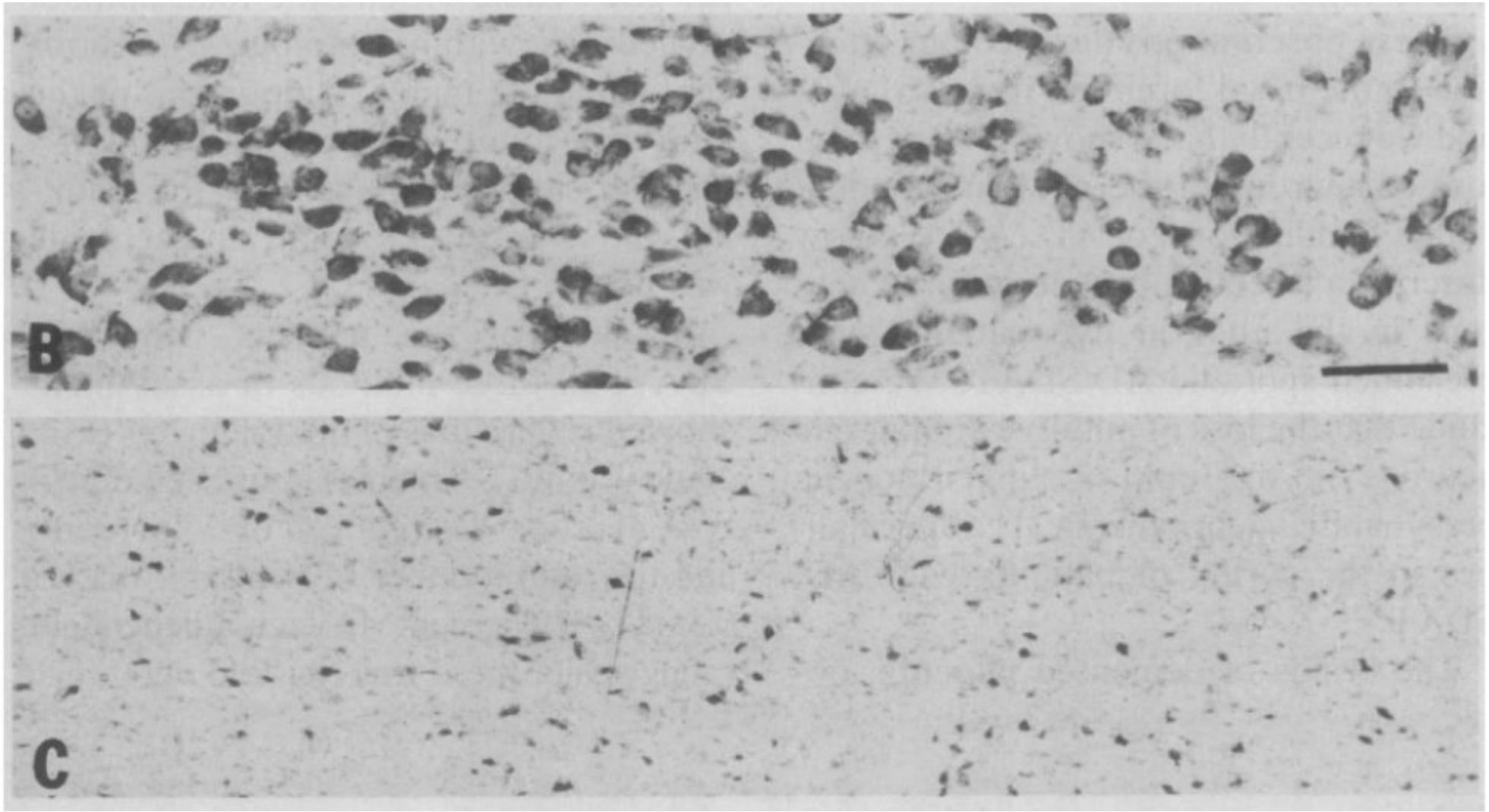
5/13/2019

The mainstay of treatment for Alzheimer's disease is supportive care from family and other caregivers

The nucleus basalis of Meynert shows a profound reduction of cholinergic neurons in Alzheimer's disease

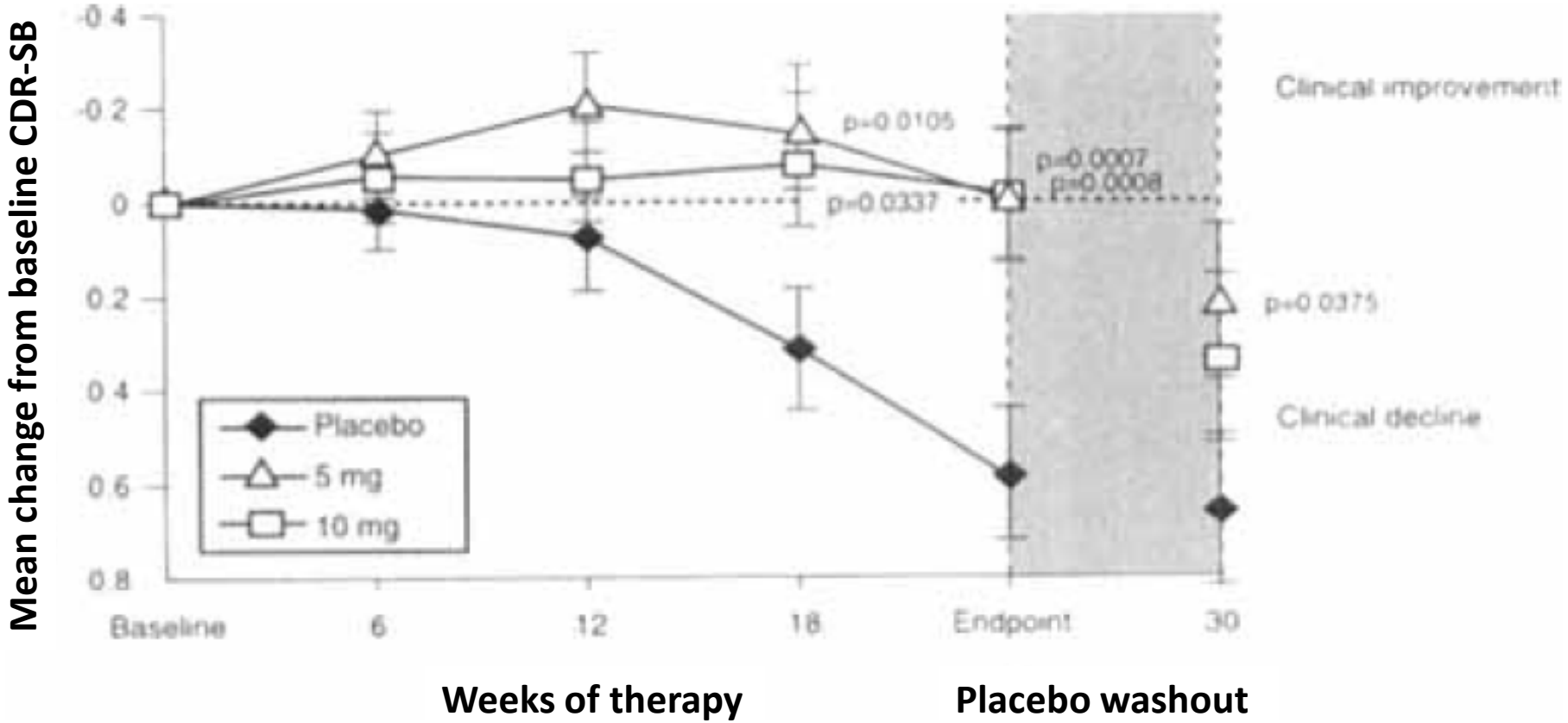


Healthy control

Alzheimer's disease

Whitehouse et al. Science 1982;215:1237

Cholinesterase inhibitors are a symptomatic treatment for Alzheimer's disease



Roger SL, et al. Neurology 1998;50:136-145

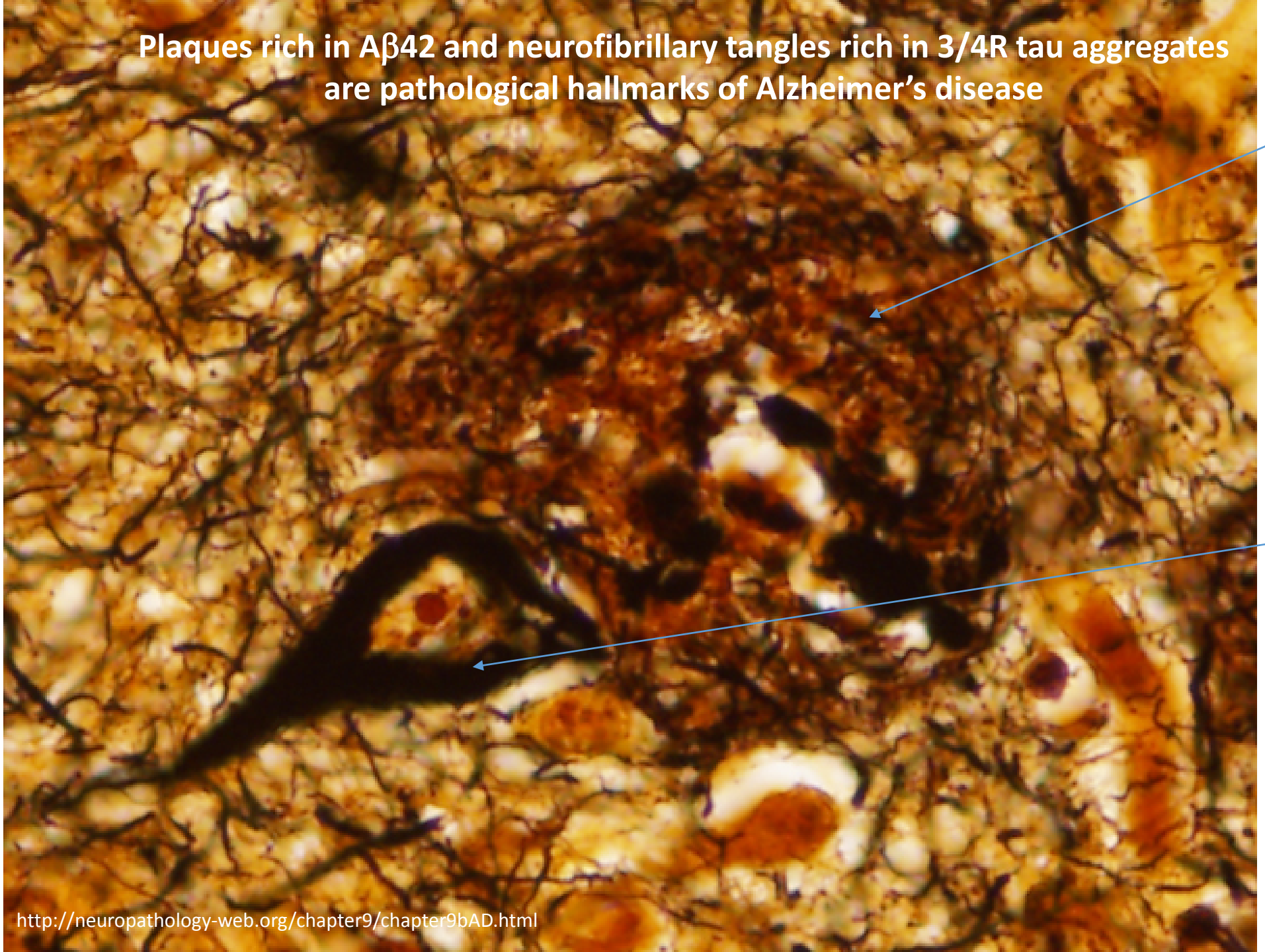
Donepezil
Rivastigmine
Galantamine

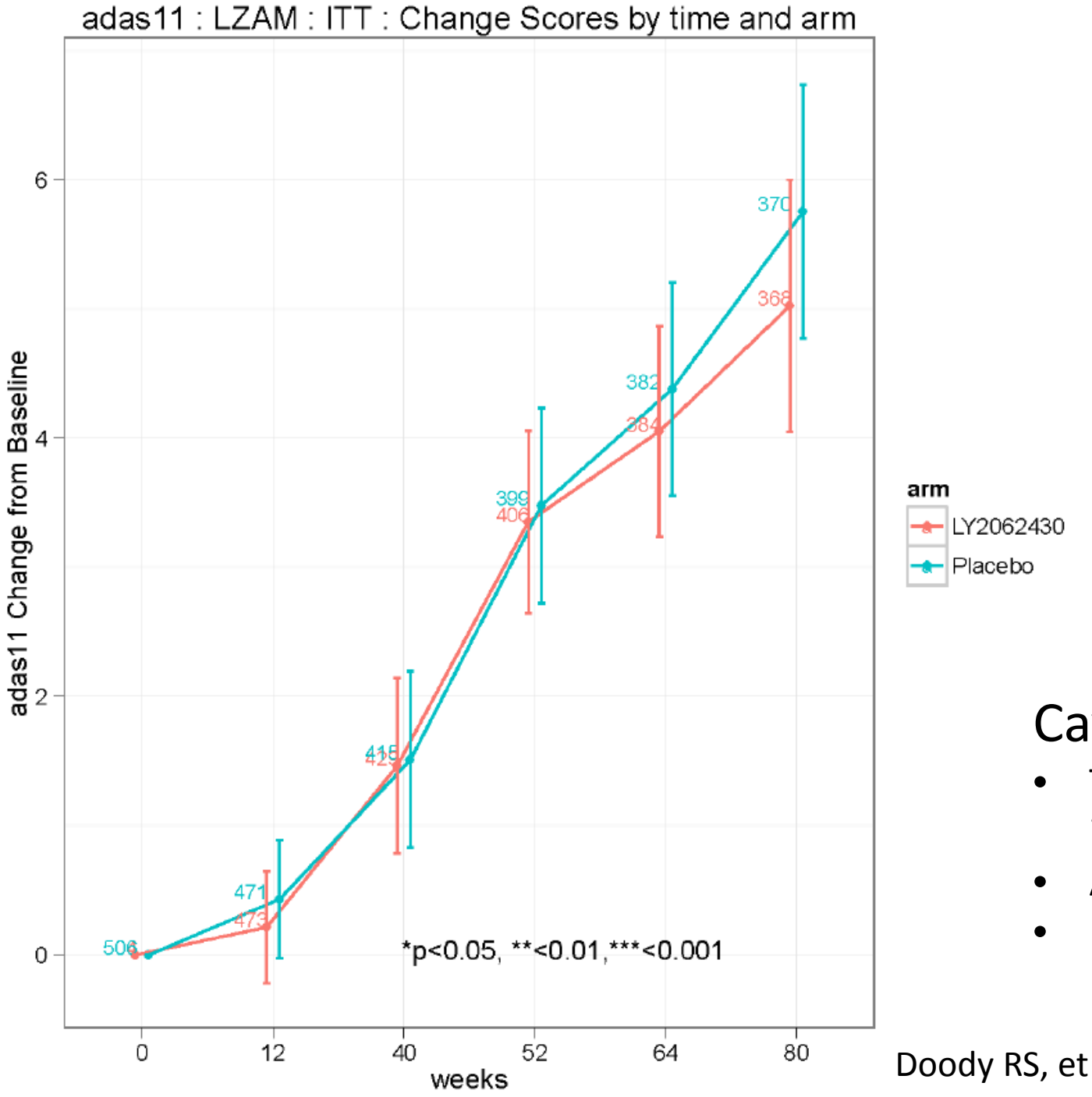
Cholinesterase inhibitors

Memantine

NMDA receptor antagonist

Approved therapies in AD (only used for the treatment of the dementia phase)


Plaques rich in Aβ42 and neurofibrillary tangles rich in 3/4R tau aggregates are pathological hallmarks of Alzheimer's disease
Plaque (Aβ42)
Tangle (Tau)
http://neuropathology-web.org/chapter9/chapter9bAD.html



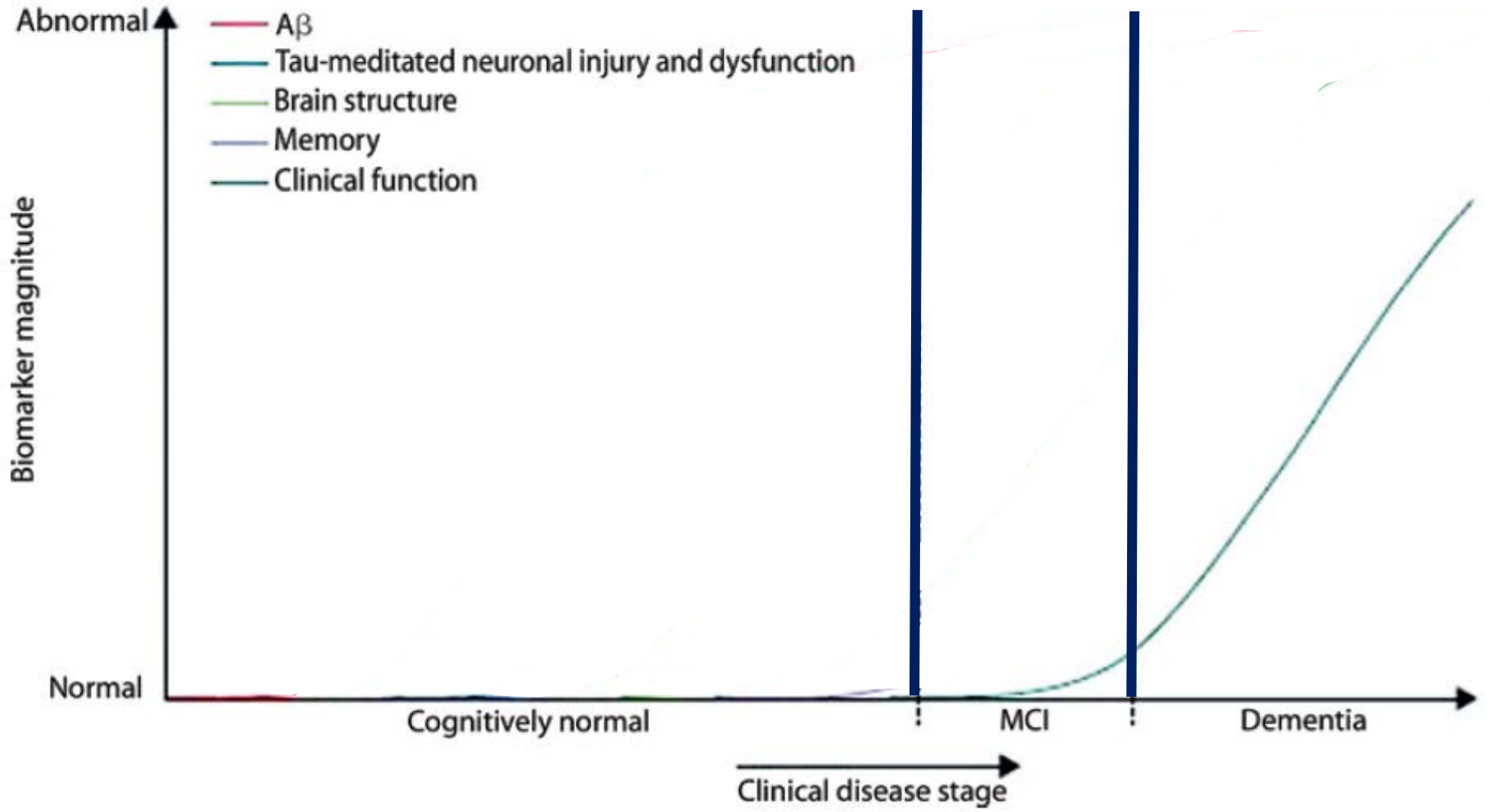
In two phase 3 double-blind trials, anti-amyloid therapy with solanezumab failed to improve cognition or functional ability

Caveats:

- Treatment started too late in the disease course
- AD diagnosis was clinical
- Drug not potent enough?

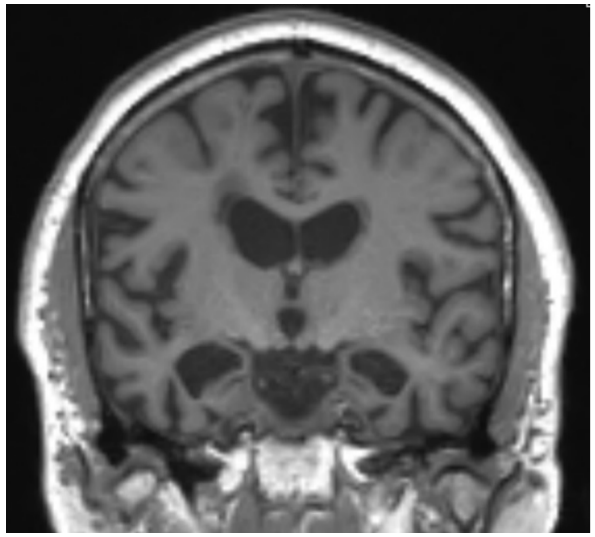
Doody RS, et al. N Engl J Med 2014;370:311-321

An effective treatment for Alzheimer's disease will ideally target the earliest possible detectable abnormality

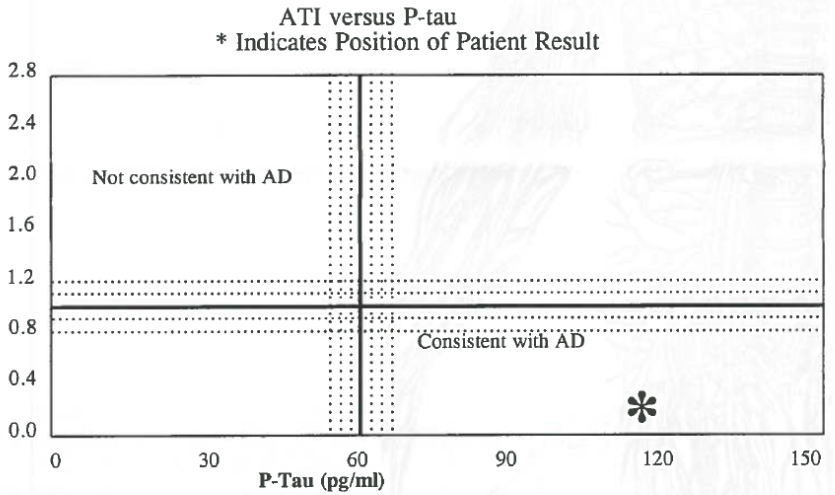


Jack CR Jr, et al. Lancet Neurol 2010;9:119-128

Alzheimer's disease biomarkers aid in patient selection for clinical trials



Brain MRI



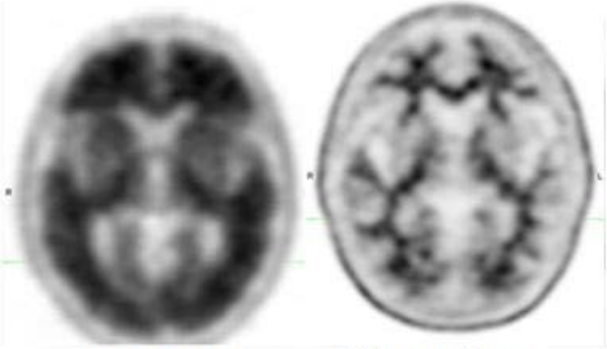
Comments

This analysis detected levels of $A\beta_{(1-42)}$ peptide, total tau and phospho-tau protein in cerebrospinal fluid which are consistent with a diagnosis of Alzheimer's disease (AD) as a cause of his/her neurological symptoms. 1-11

Technical Results

Aß42	230.95 pg/ml
T-Tau	910.5 pg/ml
P-Tau	115.1 pg/ml
ATI	0.18

Aβ42, tau and p-tau in CSF



Brain amyloid PET

	Manufacturer	Epitope	Origin	Isotype	Target	Possible mechanism of action	Outcomes in latest stage trial	Amyloid biomarker inclusion criteria in trials	Trials planned or in progress	Rate of amyloid-related imaging abnormalities
Solanezumab (NCT0760005, NCT01900665)	Eli Lilly	Mid-domain	Humanised	IgG1	Soluble, monomeric, non-fibrillar Aβ	Sequestration of soluble monomeric Aβ	Negative clinical outcomes in two phase 3 trials in mild-to-moderate Alzheimer's disease; possible slowing of cognitive decline in mild disease	None	Phase 3 trials underway in mild, preclinical, and autosomal-dominant Alzheimer's disease	Low
Bapineuzumab (NCT00575055, NCT00574132)	Pfizer/Johnson & Johnson	N-terminus	Humanised	IgG1	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in two phase 3 trials despite significant decrease in amyloid PET and phosphorylated tau concentrations in cerebrospinal fluid	None	..	Related to dose and *APOE* ε4 carrier status
Crenezumab (NCT 01397378, NCT01723826, NCT01998891)	Roche/ Genentech	Mid-domain	Humanised	IgG4	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in phase 2 trials in mild-to-moderate Alzheimer's disease; possible cognitive slowing in mild disease in patients given high doses	None in ABBY trial; amyloid PET in BLAZE trial	Phase 3 trial in autosomal-dominant Alzheimer's disease underway	Low
BAN2401 (NCT01767311)	Eisai/Biogen	N-terminus	Humanised	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	No phase 2 trials yet completed	Amyloid PET	Phase 2 trial underway in mild cognitive impairment	..
Gantenerumab (NCT01224106, NCT02051608)	Roche/ Genentech	N-terminus and mid-domain	Human (phage display library and affinity maturation)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Negative clinical outcomes in phase 3 trial for prodromal Alzheimer's disease	Cerebrospinal fluid Aβ	New phase 3 trial in planning phase	Related to dose and *APOE* ε4 carrier status
Aducanumab (NCT02484547, NCT02477800)	Biogen/ Neurimmune	N-terminus	Human (RTM)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Dose-dependent decrease in amyloid PET and cognitive decline in early Alzheimer's disease (mild cognitive impairment and mild disease) in interim analysis of phase 1b trial	Amyloid PET	Phase 1 trial in prodromal or mild Alzheimer's disease and phase 3 trial of early disease underway	Related to dose and *APOE* ε4 carrier status

Aβ=amyloid β. ..=not applicable. RTM=reverse translational medicine.

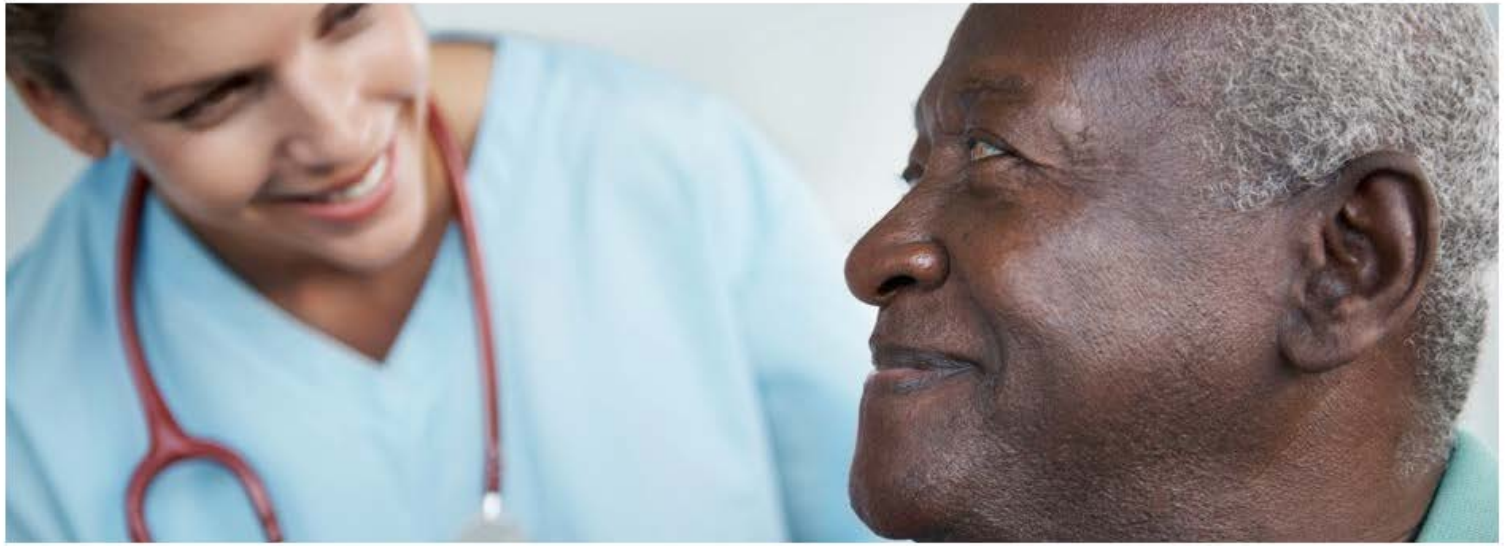
Scheltens P, et al. Lancet 2016;388:505-517

***Table*: Anti-amyloid monoclonal antibodies in clinical development**

A number of anti-amyloid therapies have failed to show benefits in clinical trials

The A4 Study
NOW IS THE TIME

ABOUT | SITE LOCATIONS | NEWS & NEWSLETTERS » | A4 STUDY TEAM | SPANISH



What is the A4 Study?

The purpose of the Anti-Amyloid Treatment in Asymptomatic Alzheimer's study (the "A4 Study" for short) is to test whether a new investigational treatment, called an anti-amyloid antibody, can slow memory loss caused by Alzheimer's disease. Amyloid is a protein normally produced in the brain that can build up in older people, forming amyloid plaque deposits. Scientists believe this buildup of deposits may play a key role in the eventual development of Alzheimer's disease-related memory loss. The overall goal of the A4 Study is to test whether decreasing amyloid with an antibody investigational treatment can help slow the memory loss associated with amyloid buildup in some people.

The A4 Study invited older individuals (ages 65-85) who have normal thinking and memory function but who may be at risk for memory loss due to Alzheimer's disease, but have no outward signs of the disease to participate in the study. We enrolled 1,169 adults who have an "elevated" level of amyloid plaque in their brain. Physicians and researchers used an imaging test called a PET scan to determine whether a potential participant has evidence of this plaque buildup. People who do not show evidence of elevated amyloid in their brains were not able to participate, but some were asked to participate in a separate study. This group will not receive the investigational drug or placebo (i.e., an inactive substance designed to mimic the

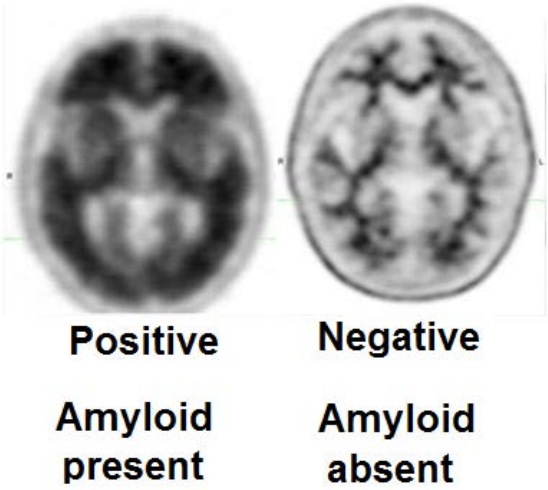
Anti-amyloid treatments are focusing on reducing brain amyloid before AD symptoms begin

https://a4study.org/

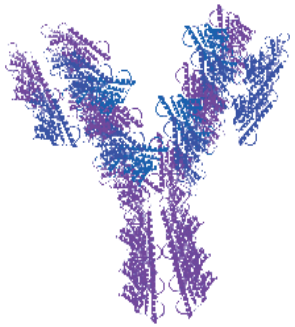
Emerging anti-amyloid trials: press release May 10, 2019

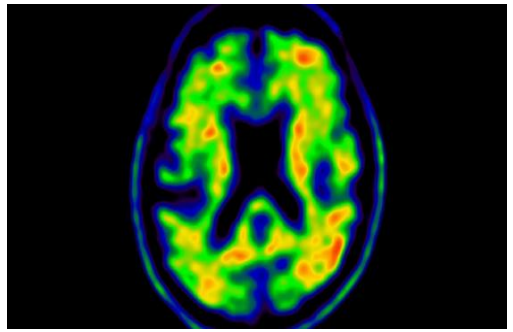
- **A45** (pre-symptomatic AD)
  - Cognitively normal individuals with positive amyloid PET
  - BAN2401 (anti-amyloid monoclonal antibody) followed by elenbecestat (BACE inhibitor)
- **A3** (primary prevention)
  - Cognitively normal individuals with *negative* amyloid PET at risk of amyloid accumulation
  - Elenbecestat (BACE inhibitor) vs. placebo
- **Enrollment to begin in early 2020**

https://www.a3a45.org/

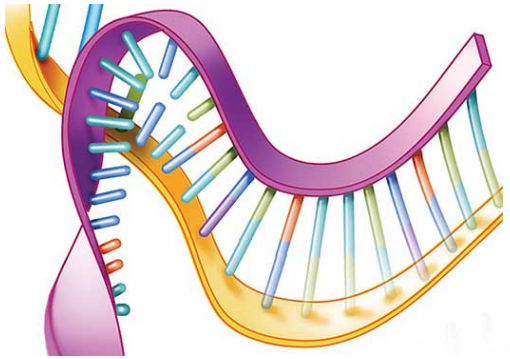


Treatment of Alzheimer's disease: thinking out of the box

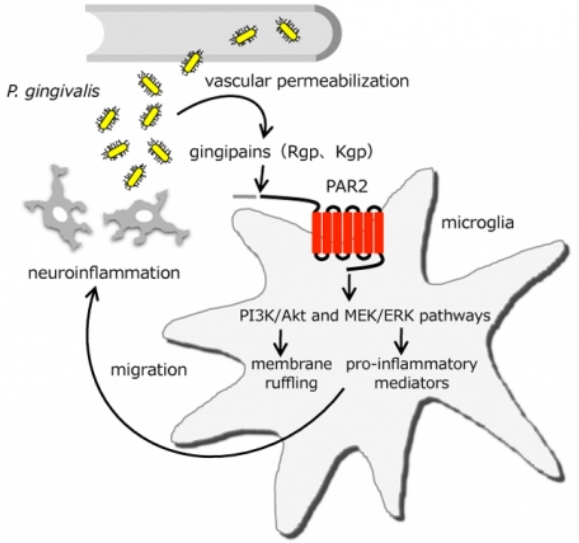


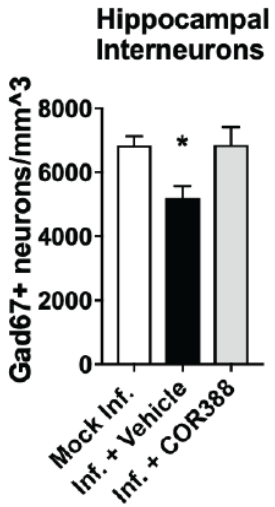


Anti-tau monoclonal antibodies



Anti-sense oligonucleotides





COR388: anti-gingipain protease inhibitor

BLOOD PRESSURE
2018, VOL. 27, NO. 5, 247–248
https://doi.org/10.1080/08037051.2018.1507621

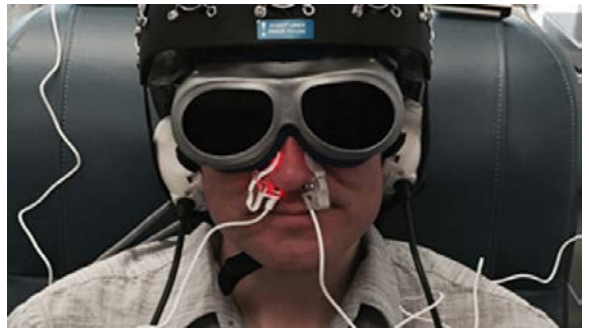
Taylor & Francis
Taylor & Francis Group

EDITORIAL

Check for updates

Intensive blood pressure lowering prevents mild cognitive impairment and possible dementia and slows development of white matter lesions in brain: the SPRINT Memory and Cognition IN Decreased Hypertension (SPRINT MIND) study

Intensive blood pressure control



Transcranial photobiomodulation

West T, et al. J Prev Alzheimers Dis 2017;4:236-241
https://www.alzforum.org/therapeutics/biib080
Kaba S, et al. Clinical Trials on Alzheimer's Disease October, 24-27,2018
Kjldsen SE, et al. Blood Press 2018; 27:247-248
Chao LL. Photobiomodul Photomed Laser Surg 2019;37:133-141

Conclusion

- Therapy development in Alzheimer’s disease is challenging, but it is an active field of research
- Current approaches pursue early intervention
- Novel emerging strategies will likely accompany anti-amyloid and anti-tau approaches in the future