Advances in Immunological treatments of Alzheimer's Disease

Alireza Faridar, MD.

09/21/2022

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Alzheimer's Disease- Epidemiology

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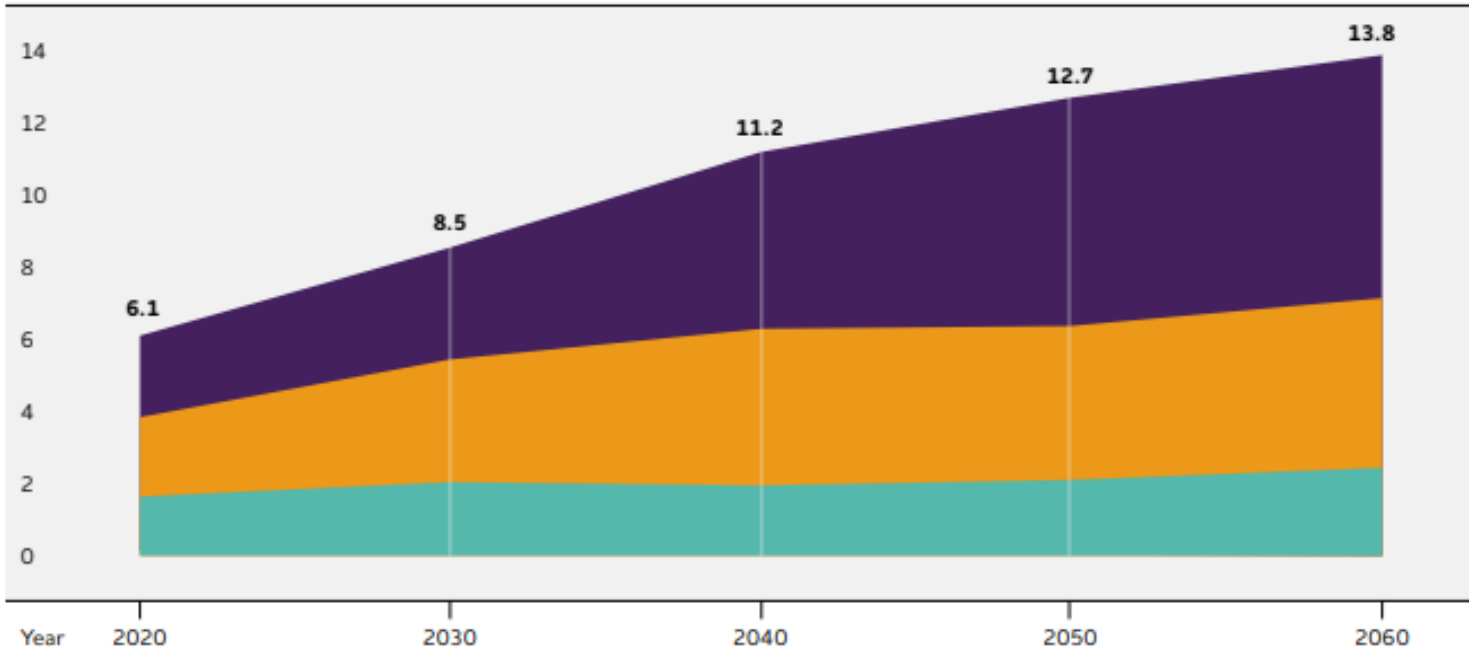
Projected Number of People in the U.S. Population with Alzheimer's Dementia



Created from data from Rajan et al.[A6,224]

2022 Alzheimer's Disease Facts and Figures

Neuropathologic alteration in AD

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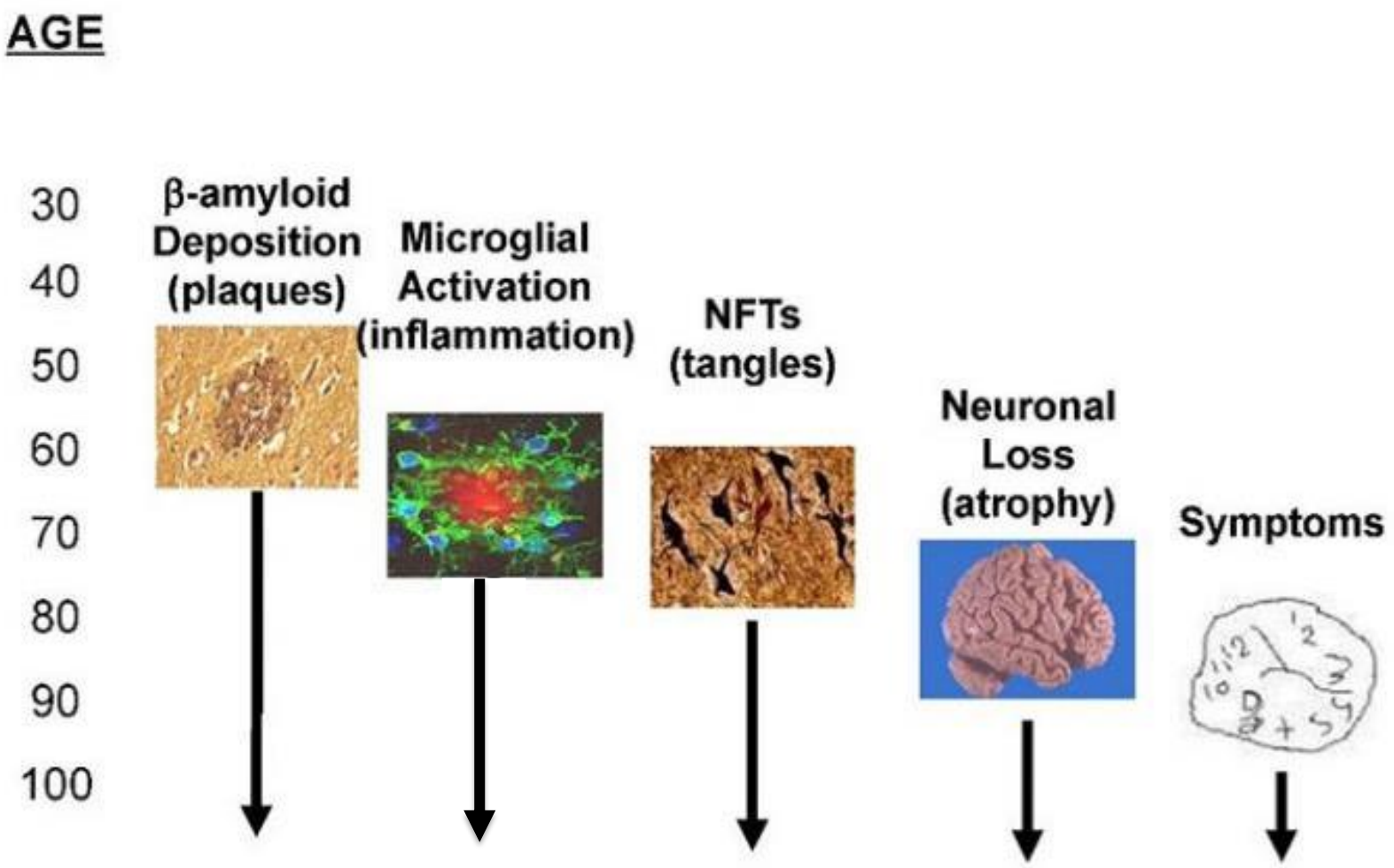

FDA-approved treatments

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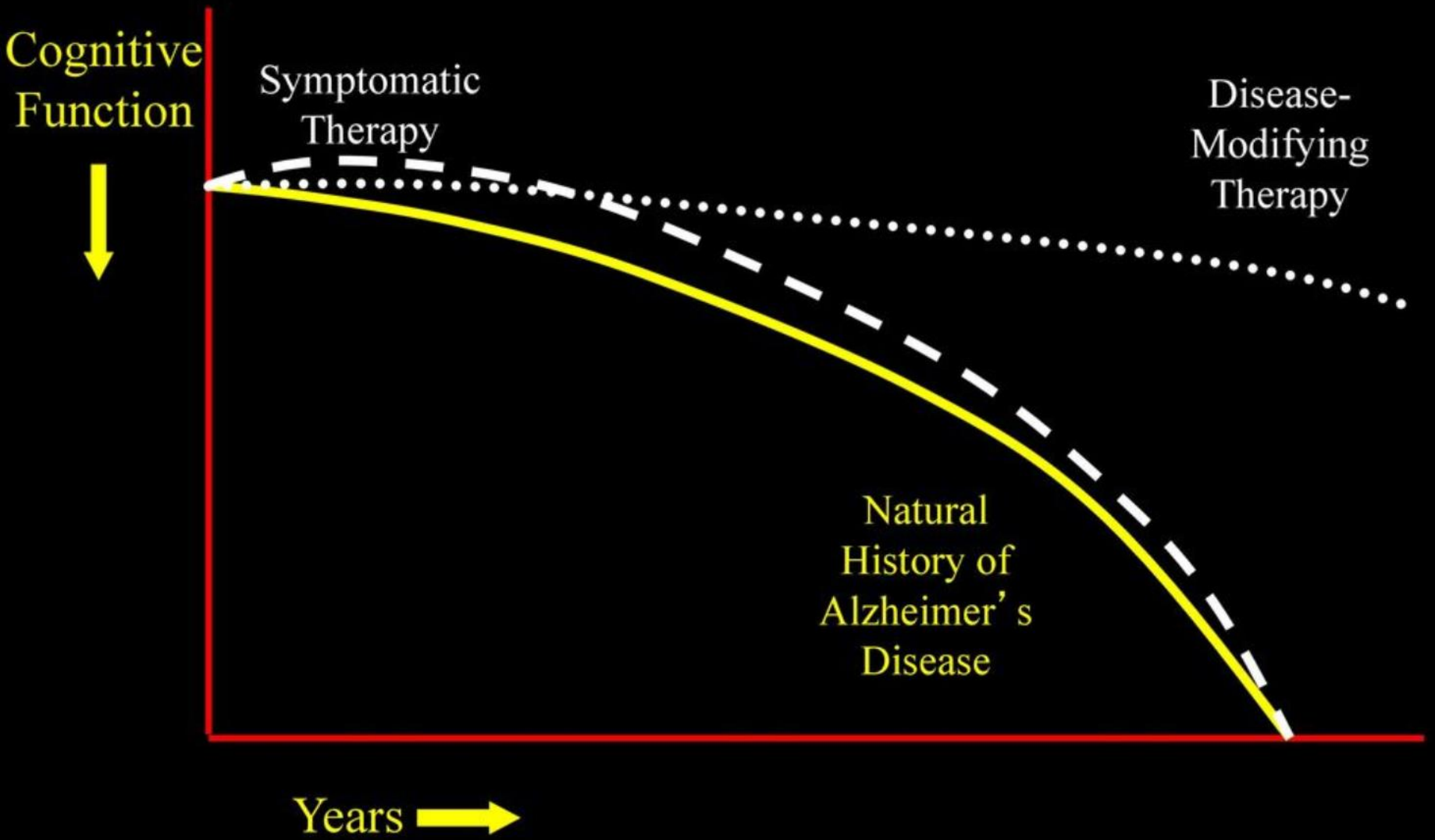

AD Drug Development Pipeline 2022

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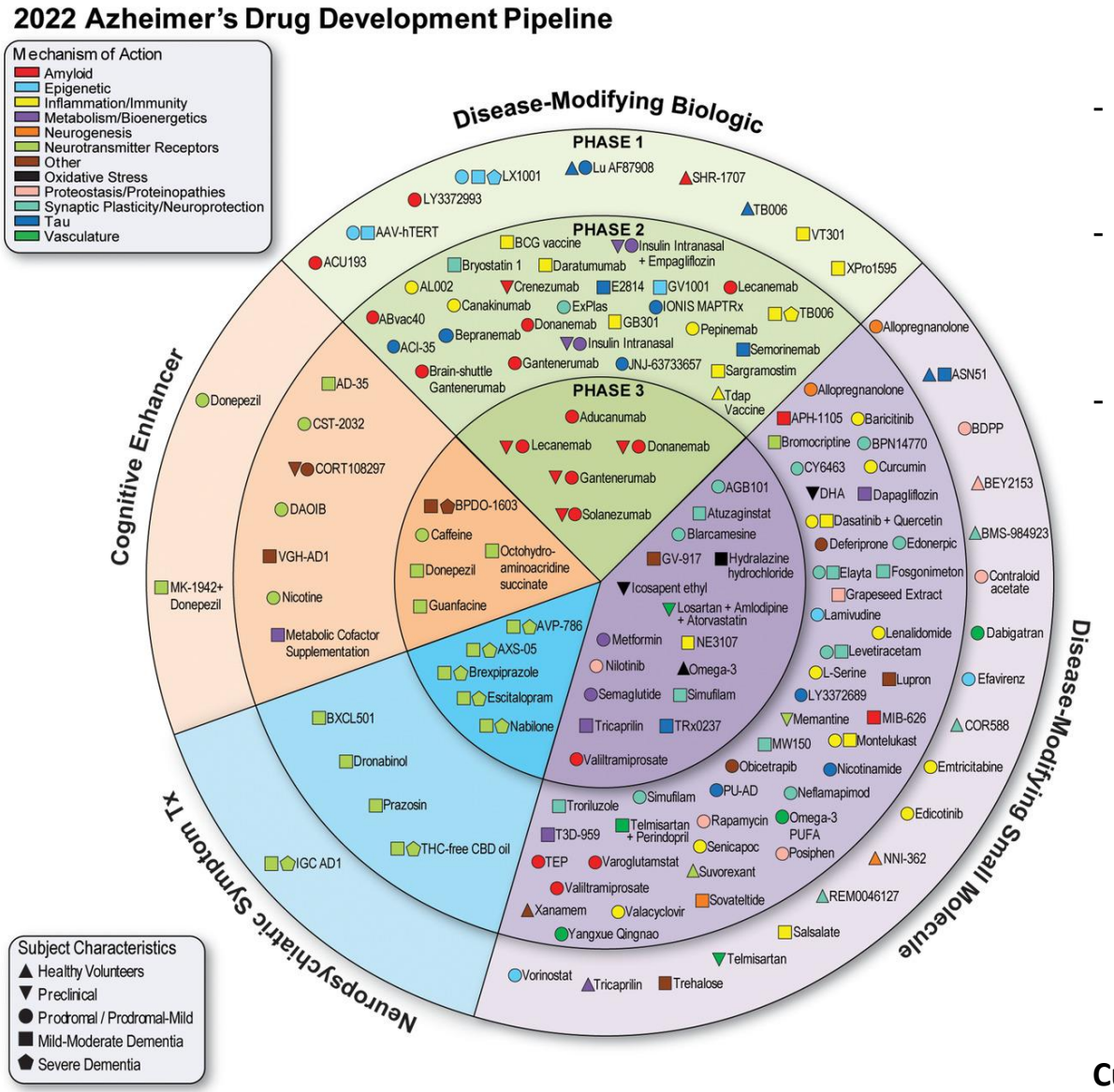

- **147 agents are in clinical trials for AD**
- **Disease-modifying therapies represent 83% of the candidate treatments**
- **31 agents advanced to phase 3 trials**

Cummings et al, Alzheimers dement 2022.

Mechanisms of action of disease modifying agents in all phases of clinical trials

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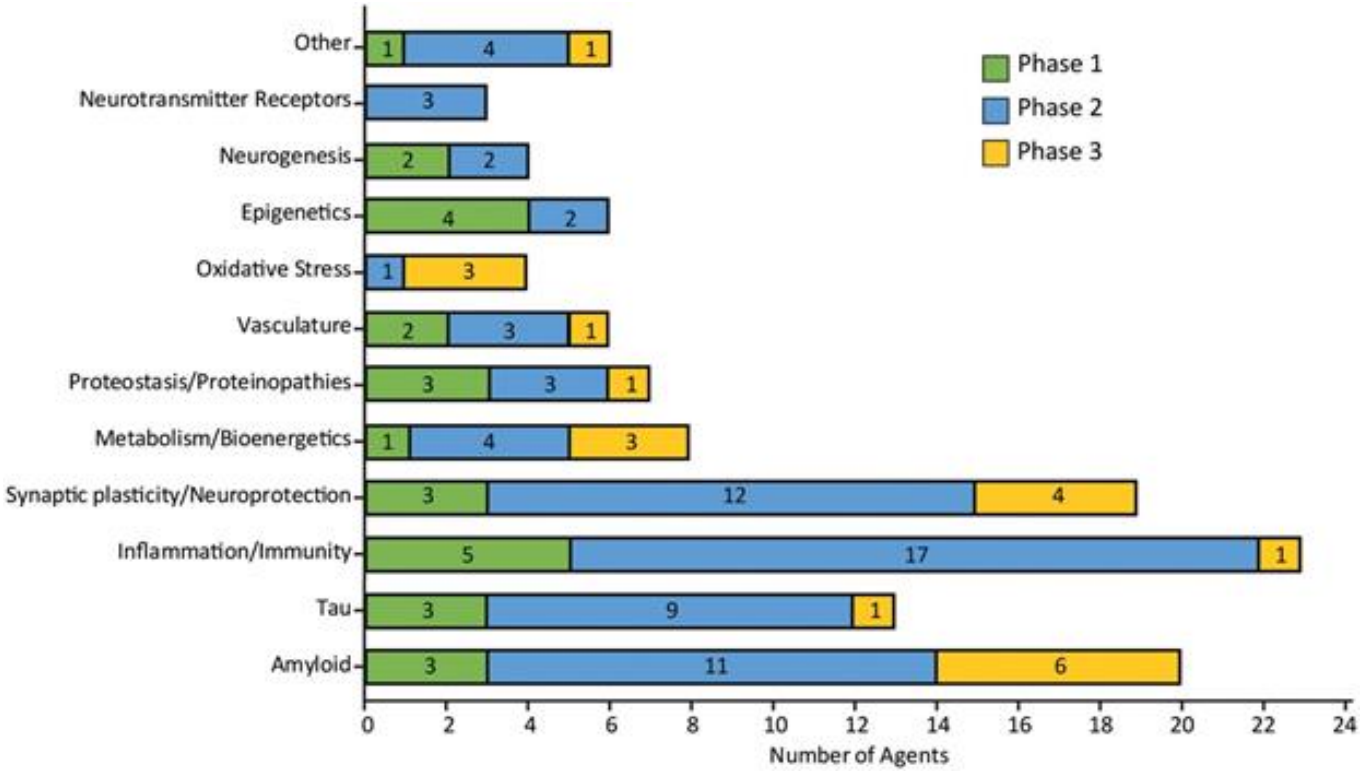
- **Twenty agents target amyloid, 13 target tau and 23 target inflammation**



Cummings et al, Alzheimers dement 2022.

Amyloid Hypothesis in Trials

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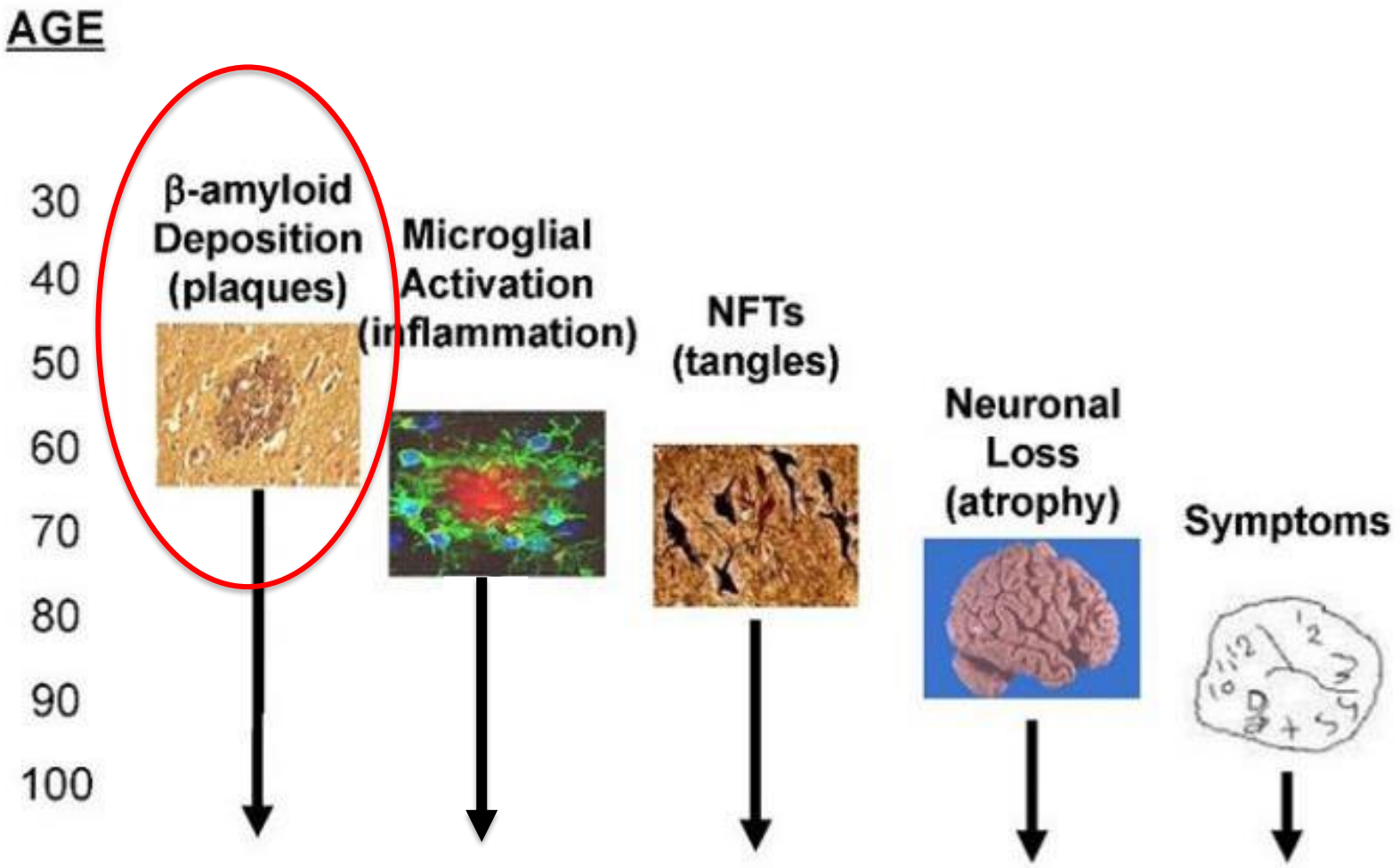

Aducanumab Phase 3 studies: Engage and Emerge

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Studies	Two identical,18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ sample size	3285 patients at 348 sites in 20 countries
Population	▪ Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia) • MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, with confirmed amyloid pathology
Doses	▪ Two dosing regimens (low and high) and placebo; randomized 1:1:1
Primary endpoint	▪ CDR-SB at 18 months
Other endpoints	▪ Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI ▪ Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers

Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

Emerge: Longitudinal change from baseline in amyloid PET SUVR

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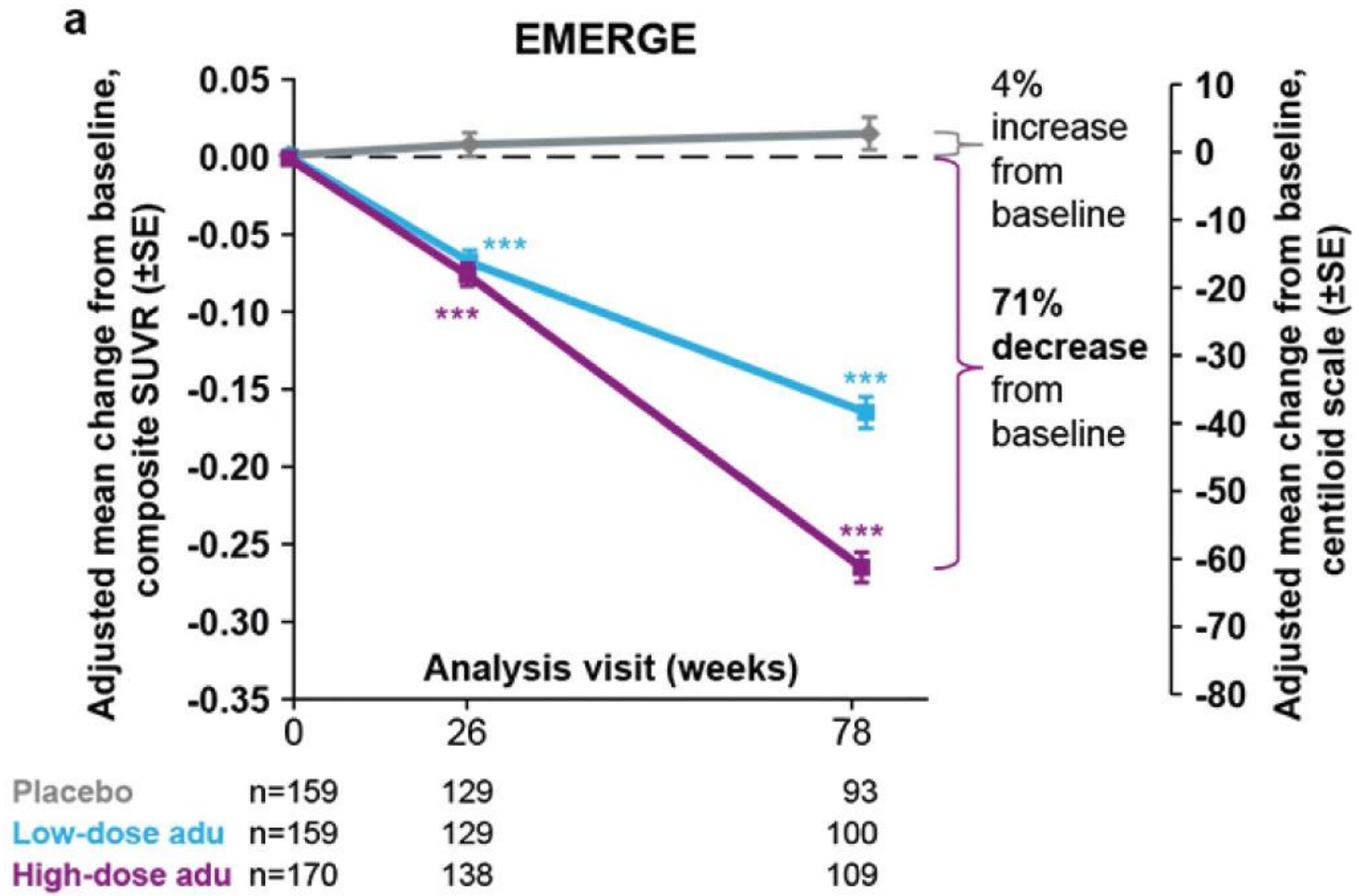

Haeberlein et al. 2022

Emerge: CSF biomarker of tau pathology and neurodegeneration

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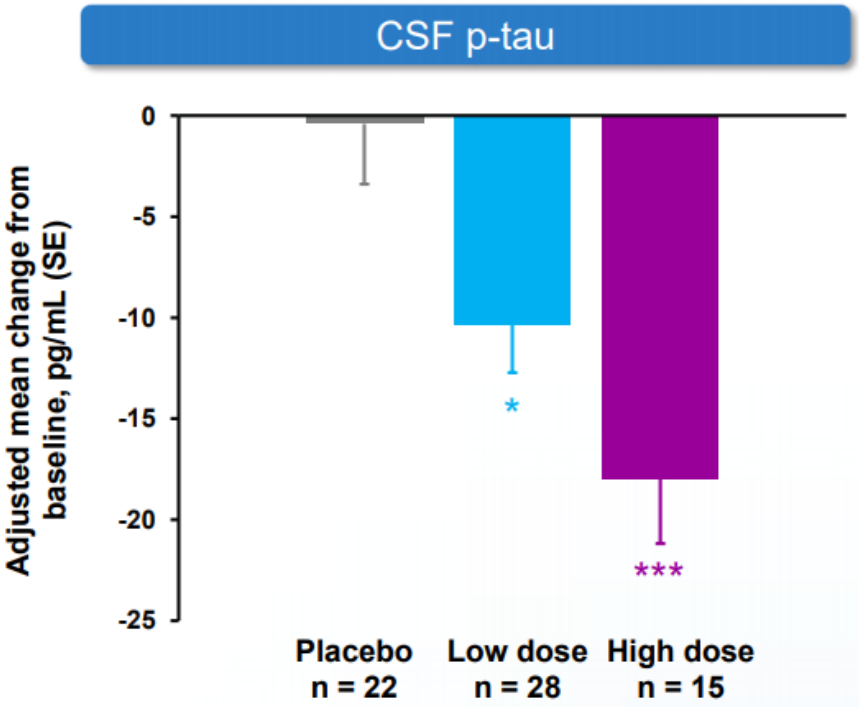

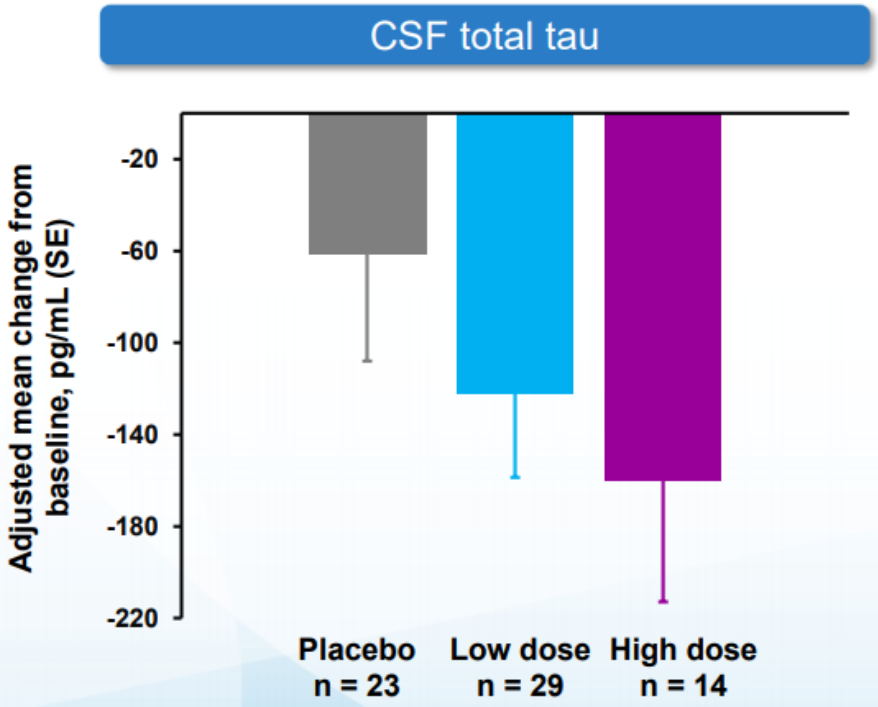

Haeberlein et al. 2022

EMERGE study met primary and secondary endpoints

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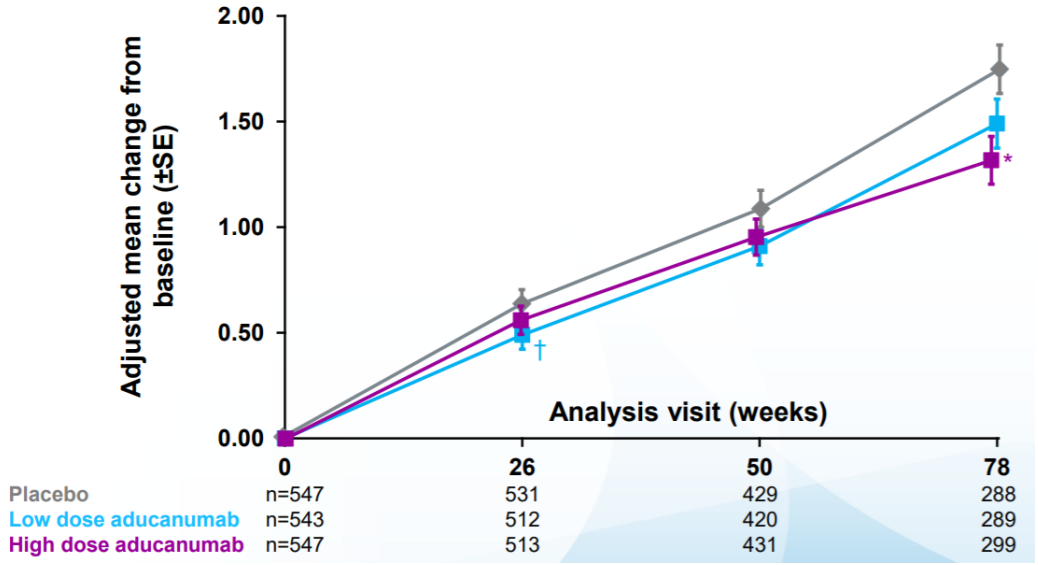
	Placebo decline (n=548)	Difference vs. placebo (%)[a] p-value	
		Low dose (n=543)	High dose (n=547)
CDR-SB	1.74	**-0.26** (-15%) 0.0901	**-0.39** (-22%) 0.0120
MMSE	-3.3	**-0.1** (3%) 0.7578	**0.6** (-18%) 0.0493
ADAS-Cog 13	5.162	**-0.701** (-14%) 0.1962	**-1.400** (-27%) 0.0097
ADCS-ADL-MCI	-4.3	**0.7** (-16%) 0.1515	**1.7** (-40%) 0.0006



Haeberlein et al. 2022

ENGAGE study did not meet primary endpoints

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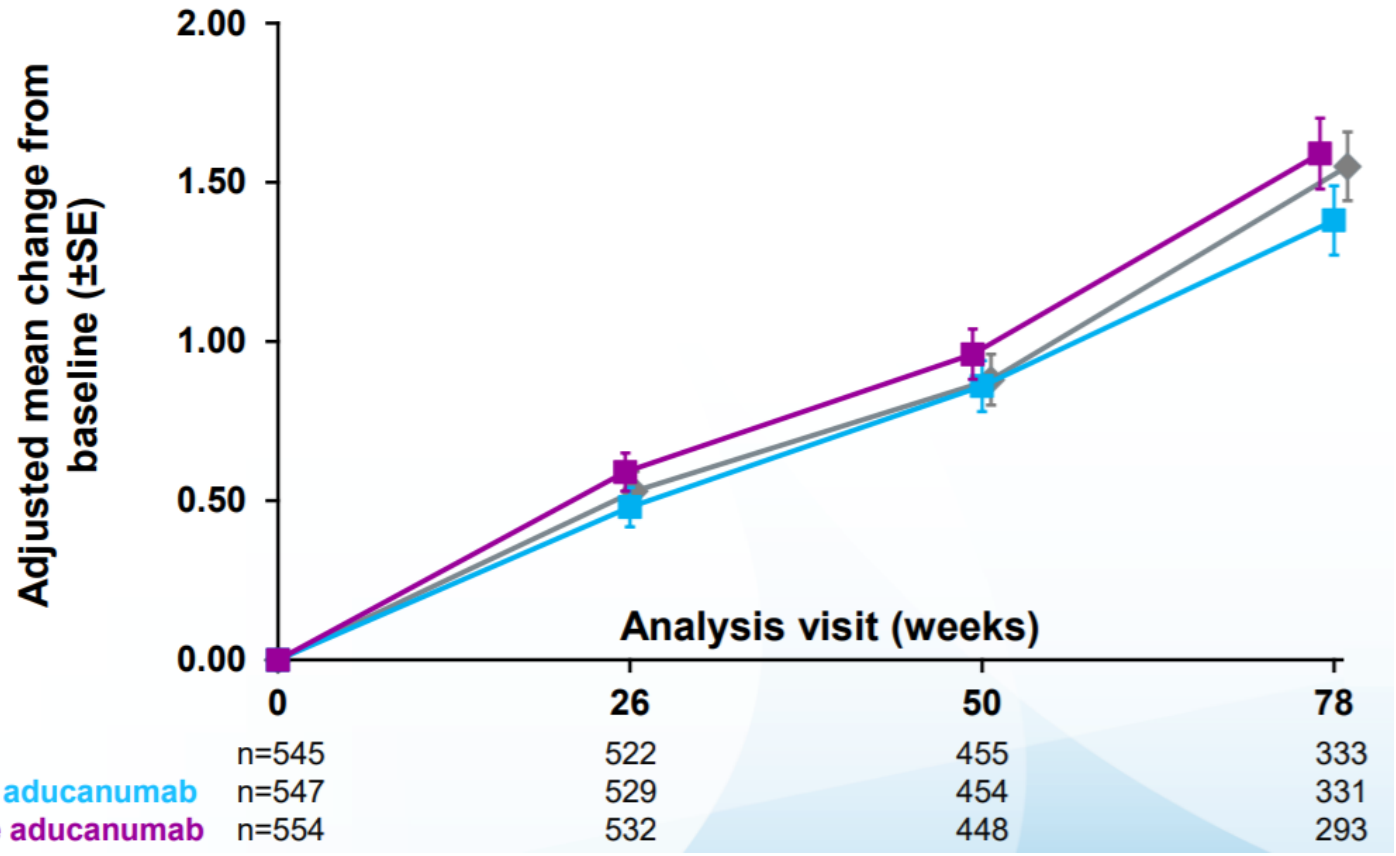

Haeberlein et al. 2022

ENGAGE study did not meet primary endpoints

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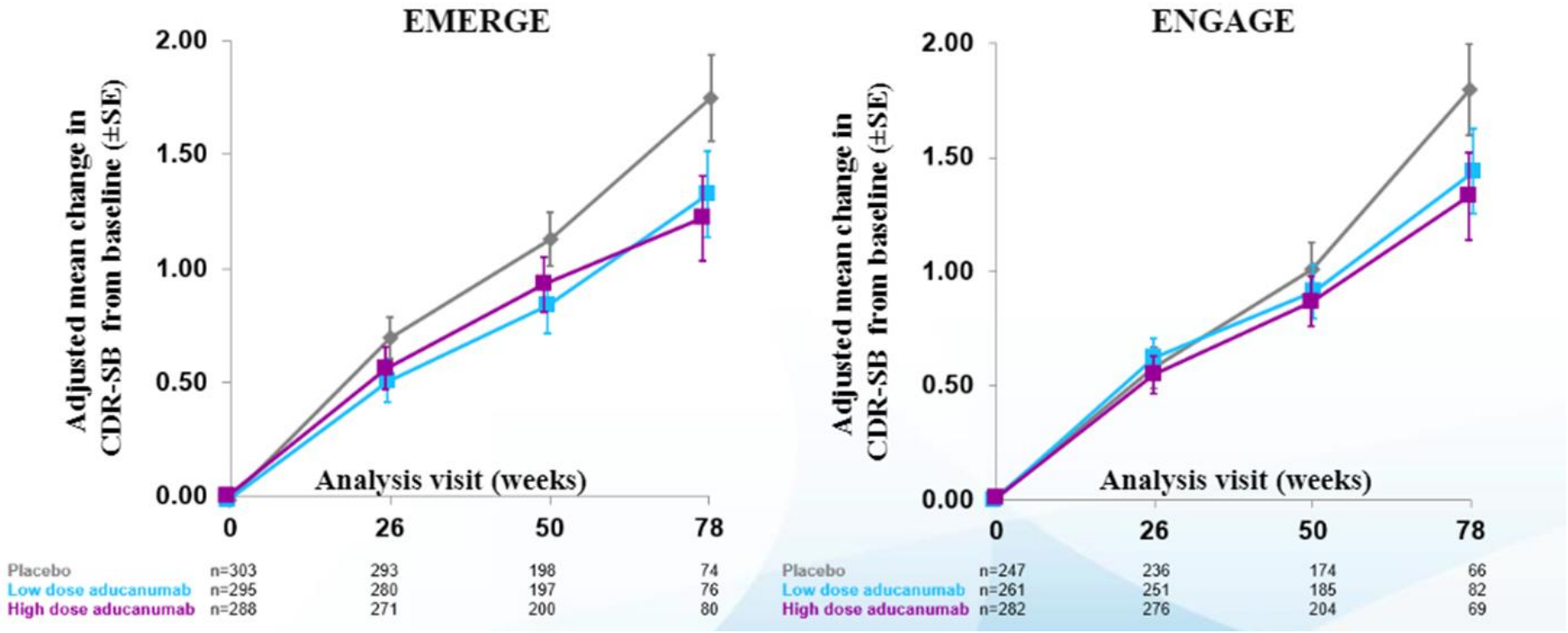

Haeberlein et al. 2022

Aducanumab, the first disease-modifying therapy (DMT) were approved for AD

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CMS Released Final Decision On Aduhelm in April 2022:

The drug will only be covered when a person with Mild Cognitive Impairment or mild dementia is enrolled in a randomized controlled trial

Reconsideration of amyloid hypothesis

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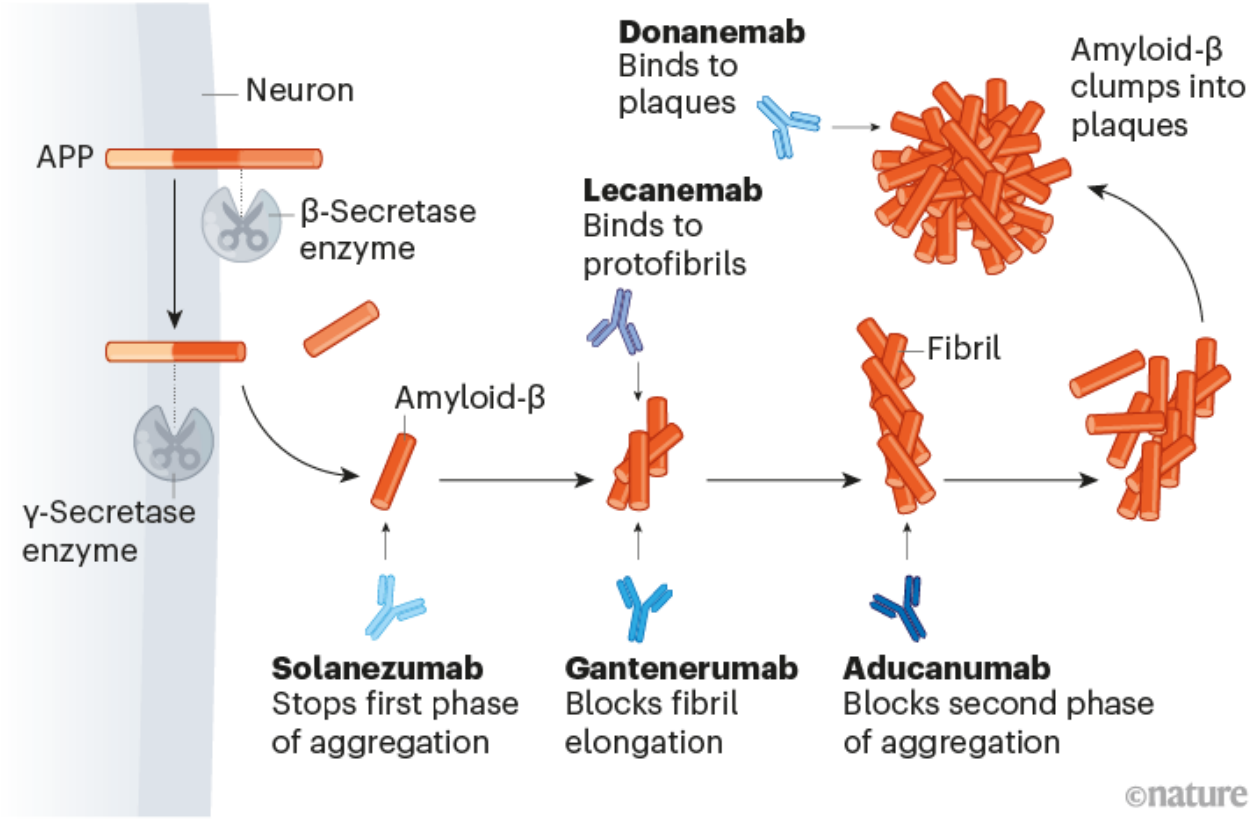
- Two other anti-amyloid antibodies, donanemab and lecanemab were accepted recently for priority review under the FDA accelerated approval pathway
- Roche's Phase 3 studies of gantenerumab will read out this fall.
- This means that three more anti-amyloid antibodies could be approved next year



Asymptomatic Alzheimer's Disease Anti-Amyloid Trials

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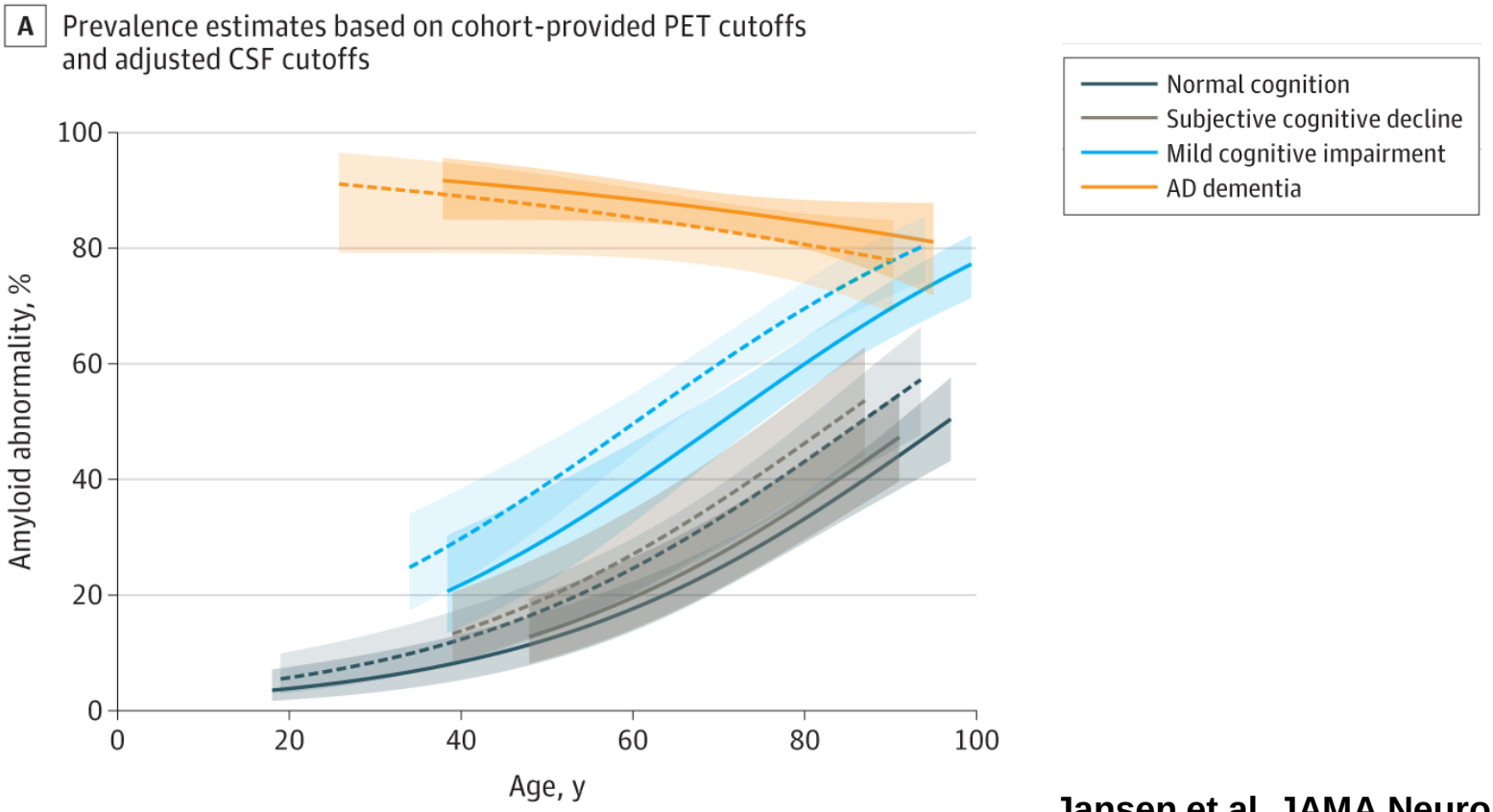
- A third of cognitively normal people >70 have amyloid building up in their brains
- 85% of them develop AD symptoms within 10 years



Jansen et al. JAMA Neurol 2022

Targeting Tau protein in AD

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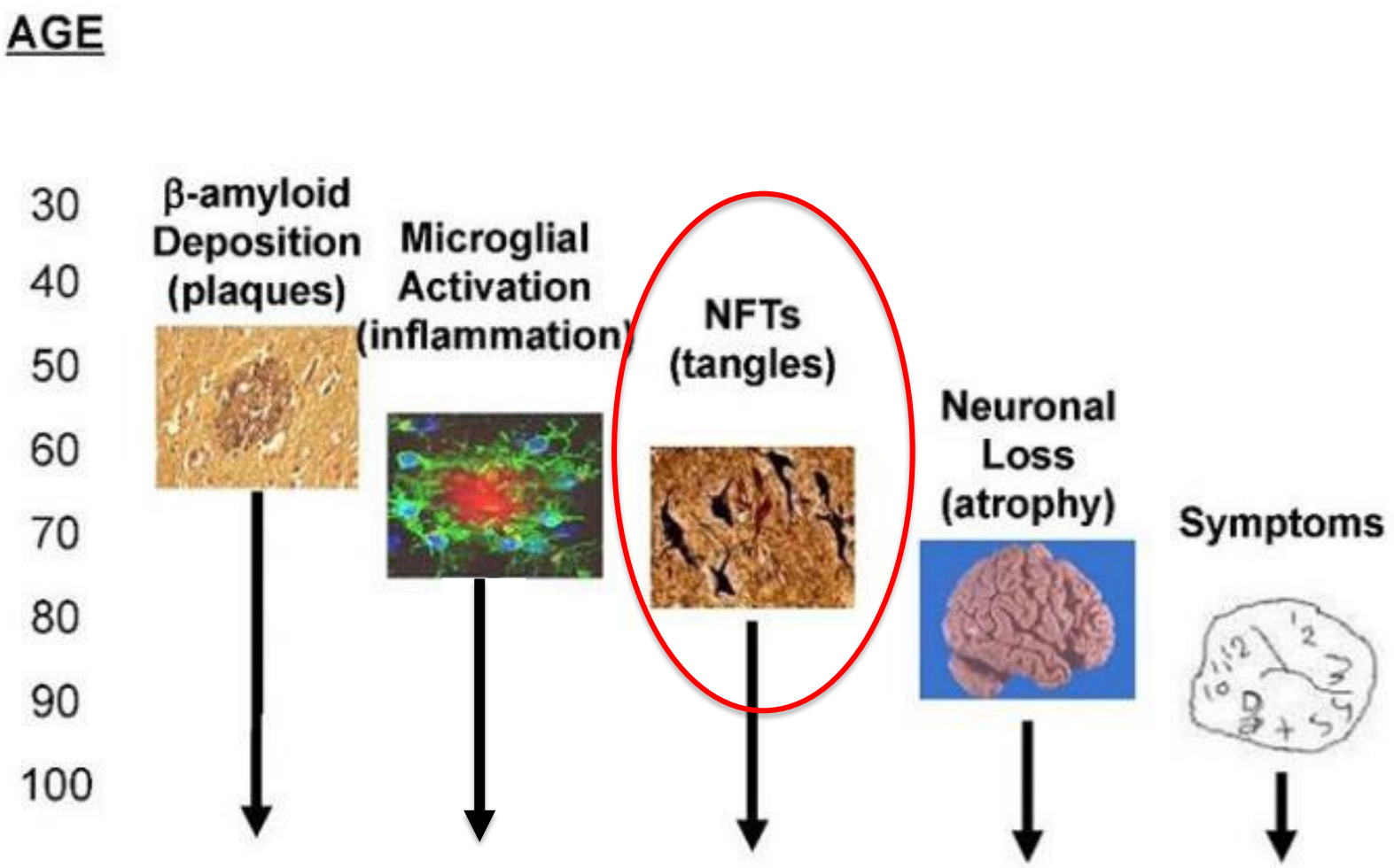

Tau hyperphosphorylation and aggregation in AD

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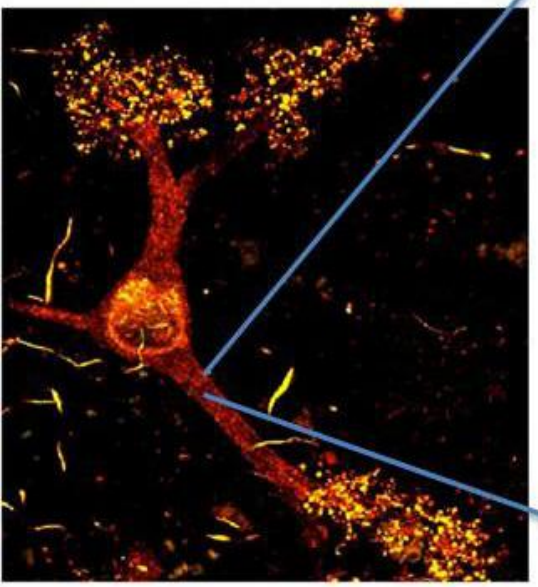
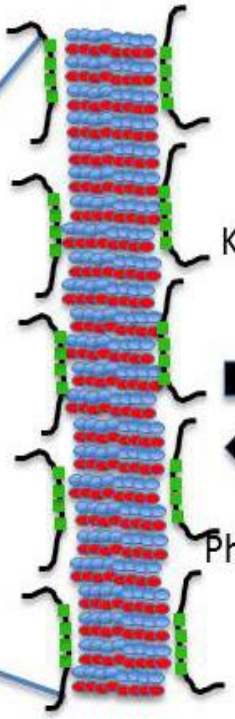


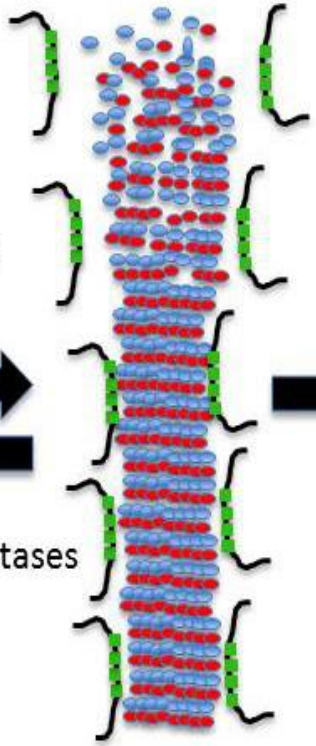
Prolongation neuronal
Axon and dendrites



Tau stabilizes
microtubule

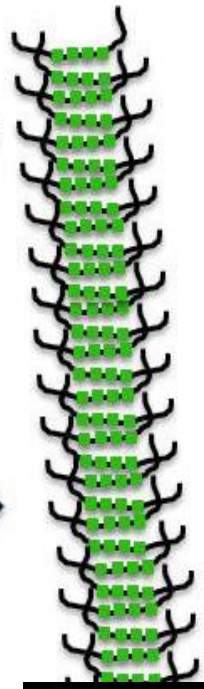
Kinases

Phosphatases

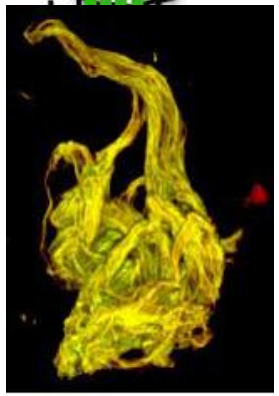


Tau phosphorylation
Microtubule despolymerization

Hyperphosphorylation
and truncation



PHF



Tangle

Stereotypical pattern of Tau accumulation in AD

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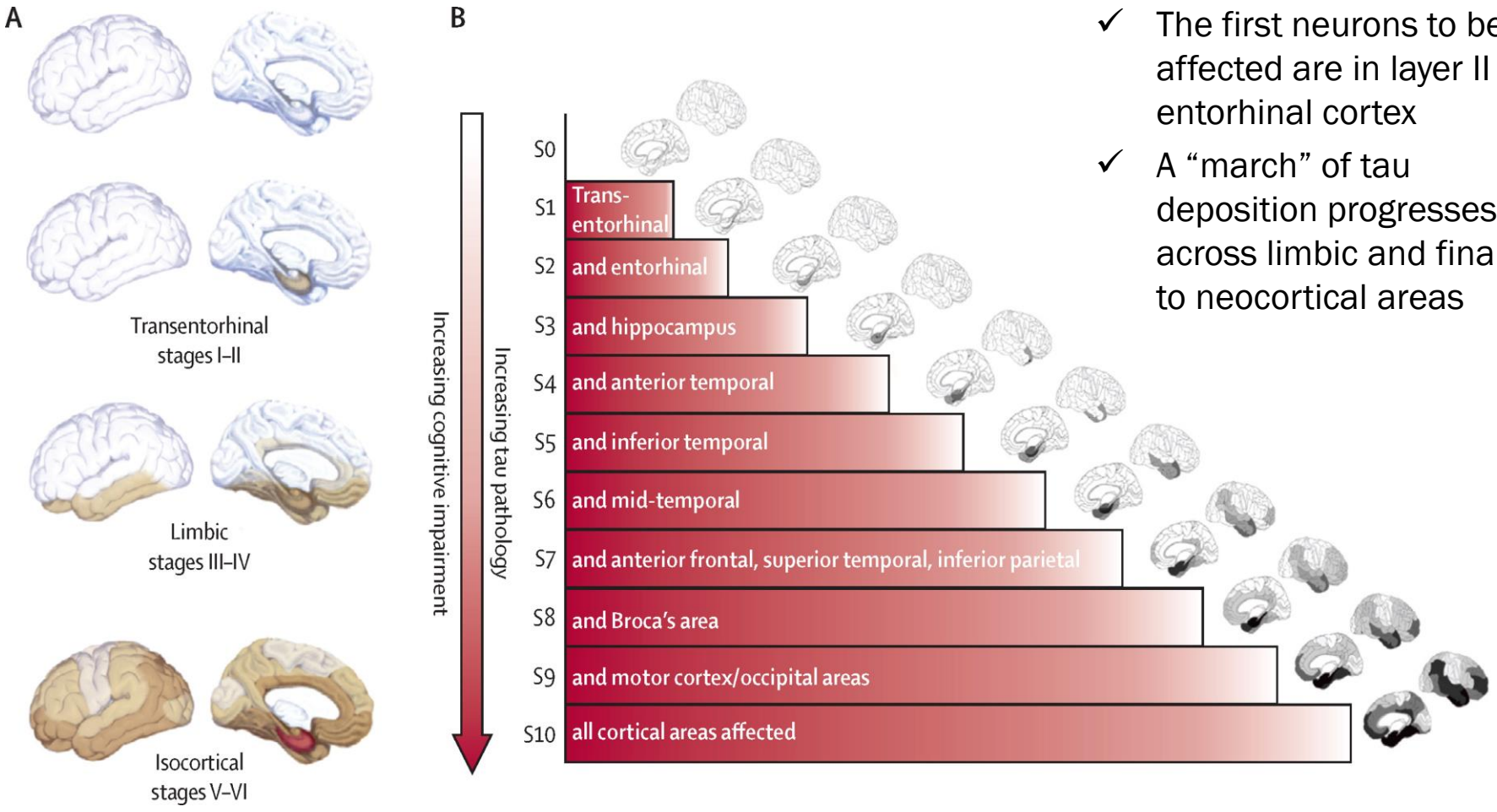

- ✓ Stereotypal pattern
- ✓ The first neurons to be affected are in layer II of entorhinal cortex
- ✓ A "march" of tau deposition progresses across limbic and finally to neocortical areas

Tau propagation hypothesis

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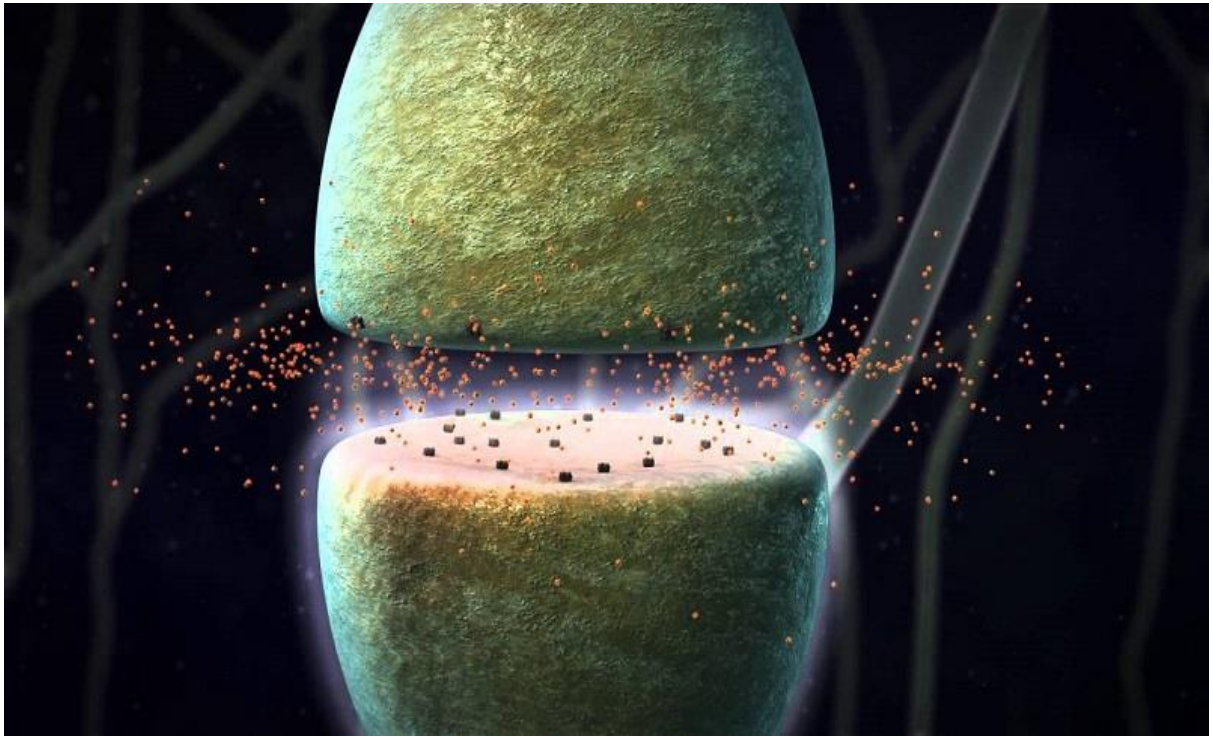
- Pathologic Tau protein is released from neurons and then transduced to recipient neurons to mediate tau propagation



Current Tau-targeting therapies in AD

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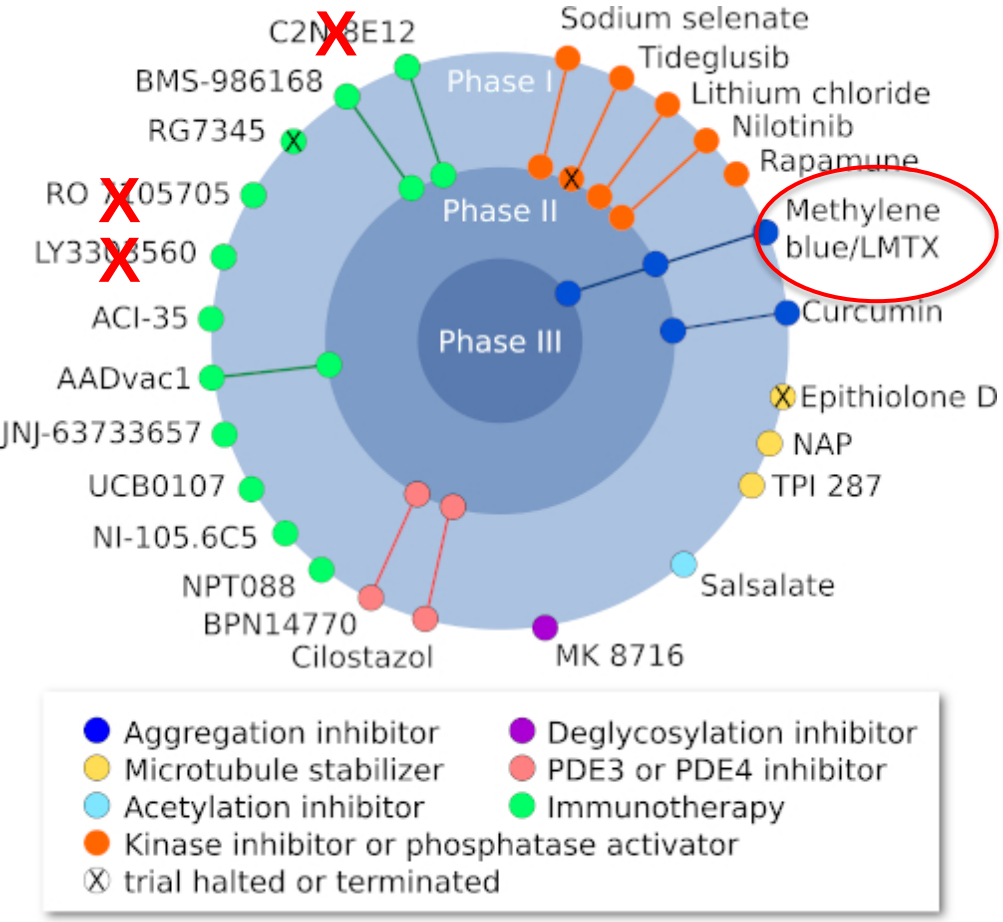

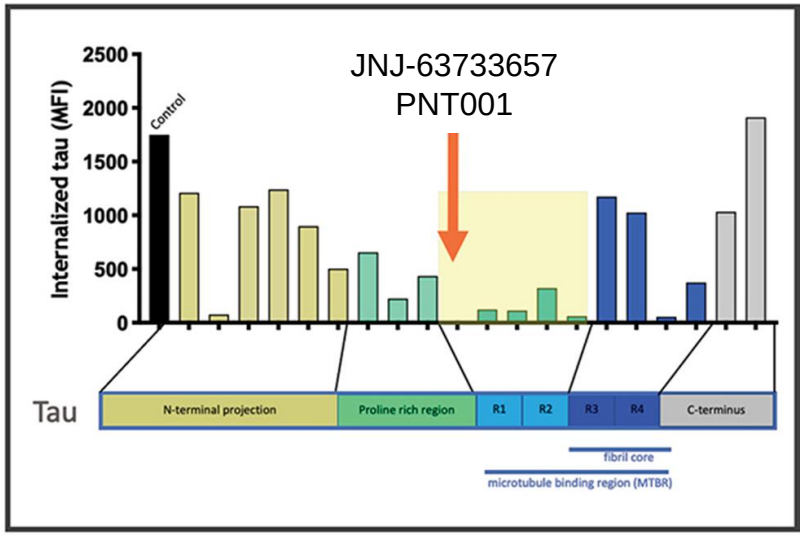

Congdon& Sigurdsson, Nature review Neurology

Courtesy of Prothena

The future of Tau immunotherapy

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- It's still early days for tau immunotherapies
- There are many variable to explore with Anti-tau immunotherapies
- Right immunological tools
- Best region of tau protein to target by antibody
- The appropriate dose
- Optimum stage of the disease

Inflammation as a third core feature of AD pathology

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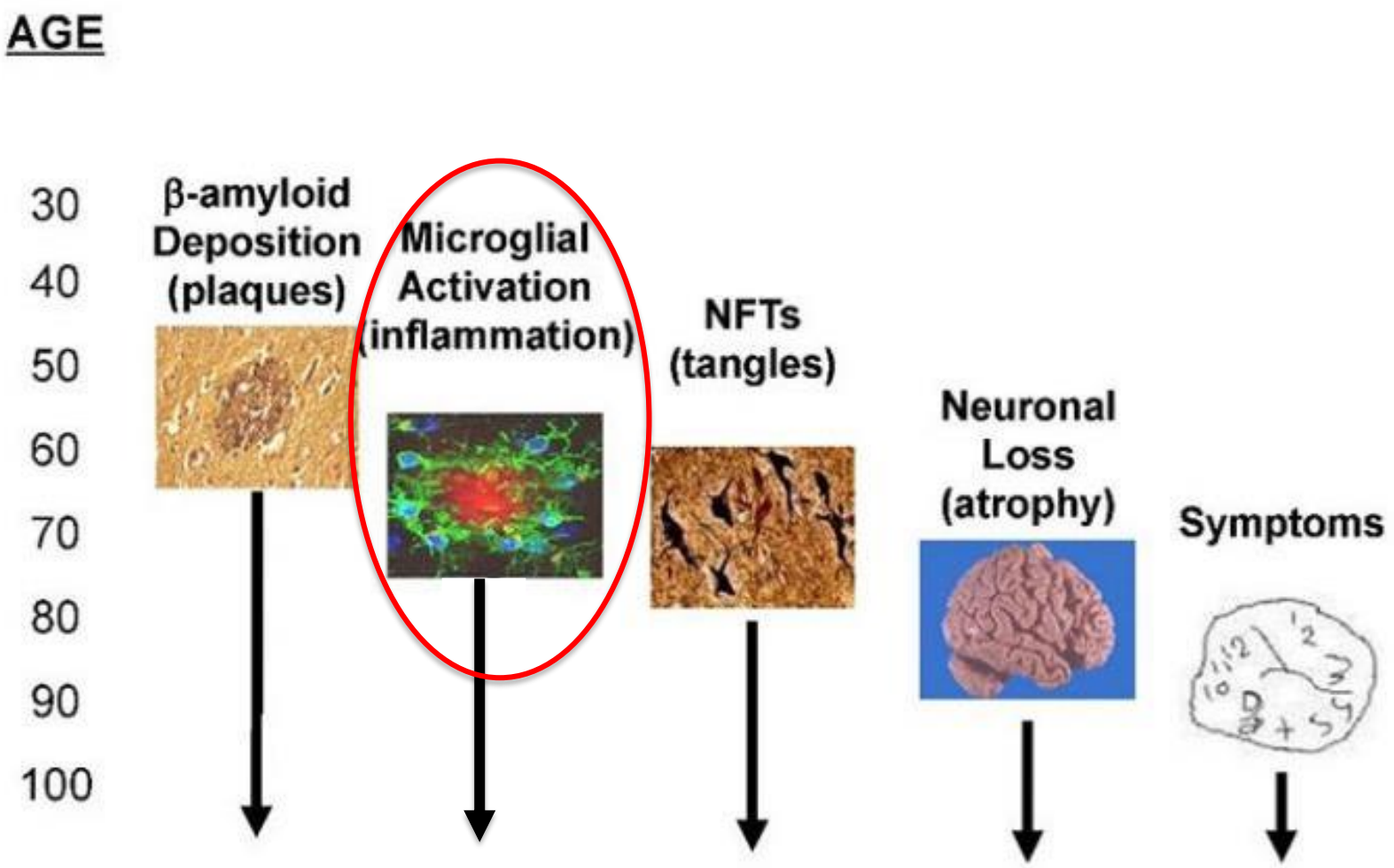

Genetics ignite focus on microglial inflammation in Alzheimer's disease

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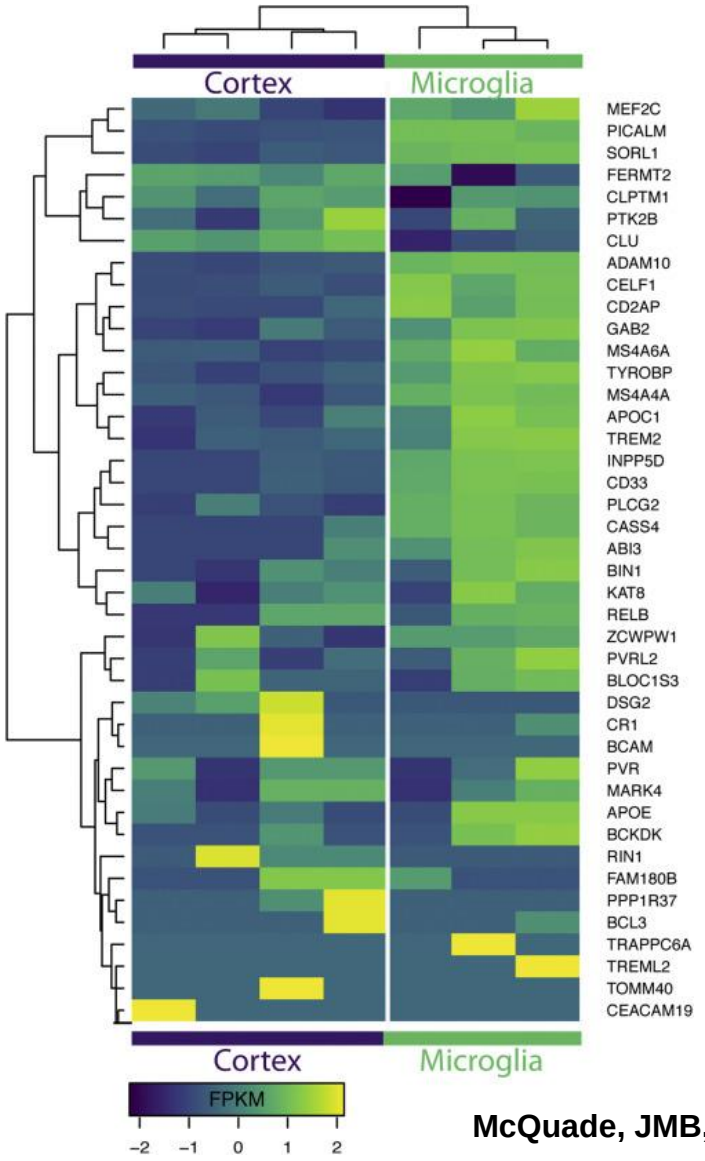
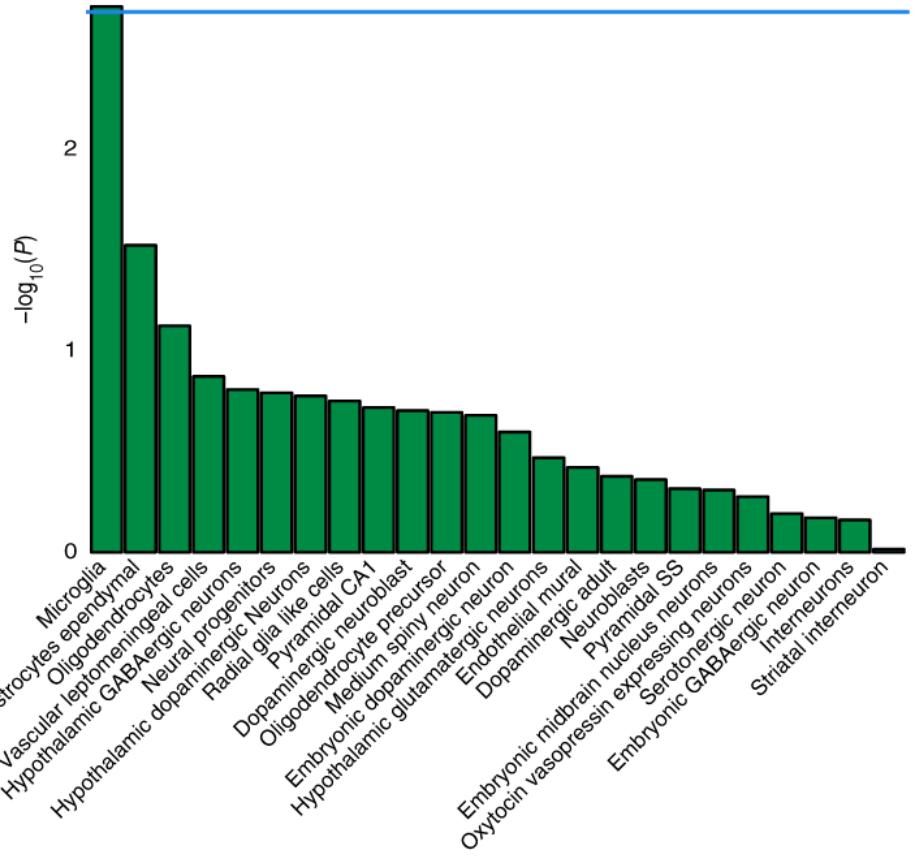


60.4 of Alzheimer risk genes are most highly expressed by microglia



McQuade, JMB, 2019

Hansen nature genetic 2019

Resilient (mismatch) brains

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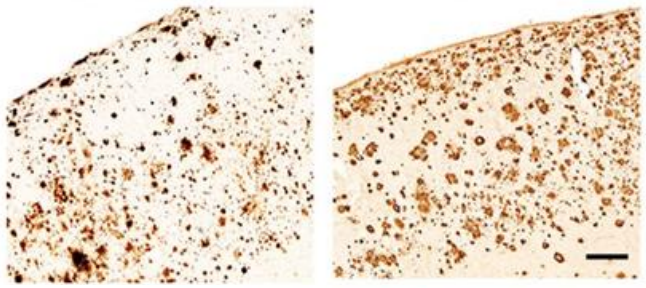
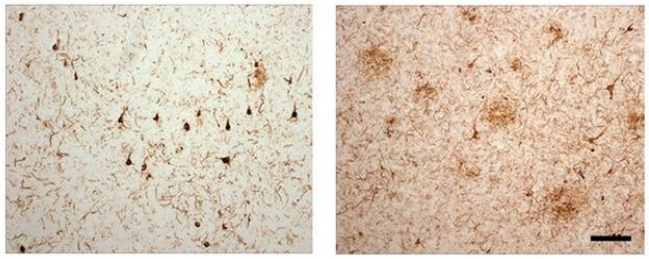
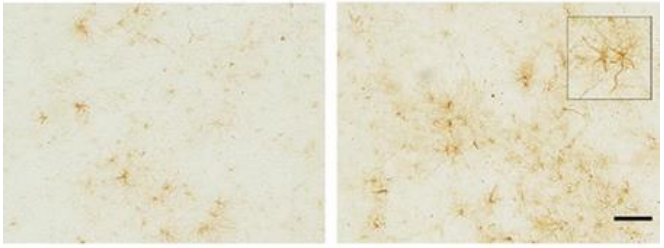
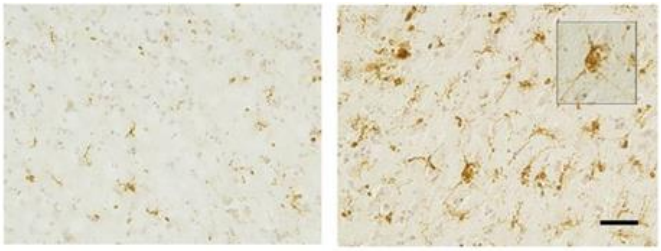
	Non-demented Resilient brain	Alzheimer's disease
Amyloid-β plaque		
Neurofibrillary tangles		
GFAP positive astrocytes		
CD68-positive microglia		

Same number of plaques and tangles, but no neuronal loss or dementia in the absence of neuroinflammatory microglia

Perez-Nievas et al, Brain 2013

Association between NSAID exposure and reduced risk of AD

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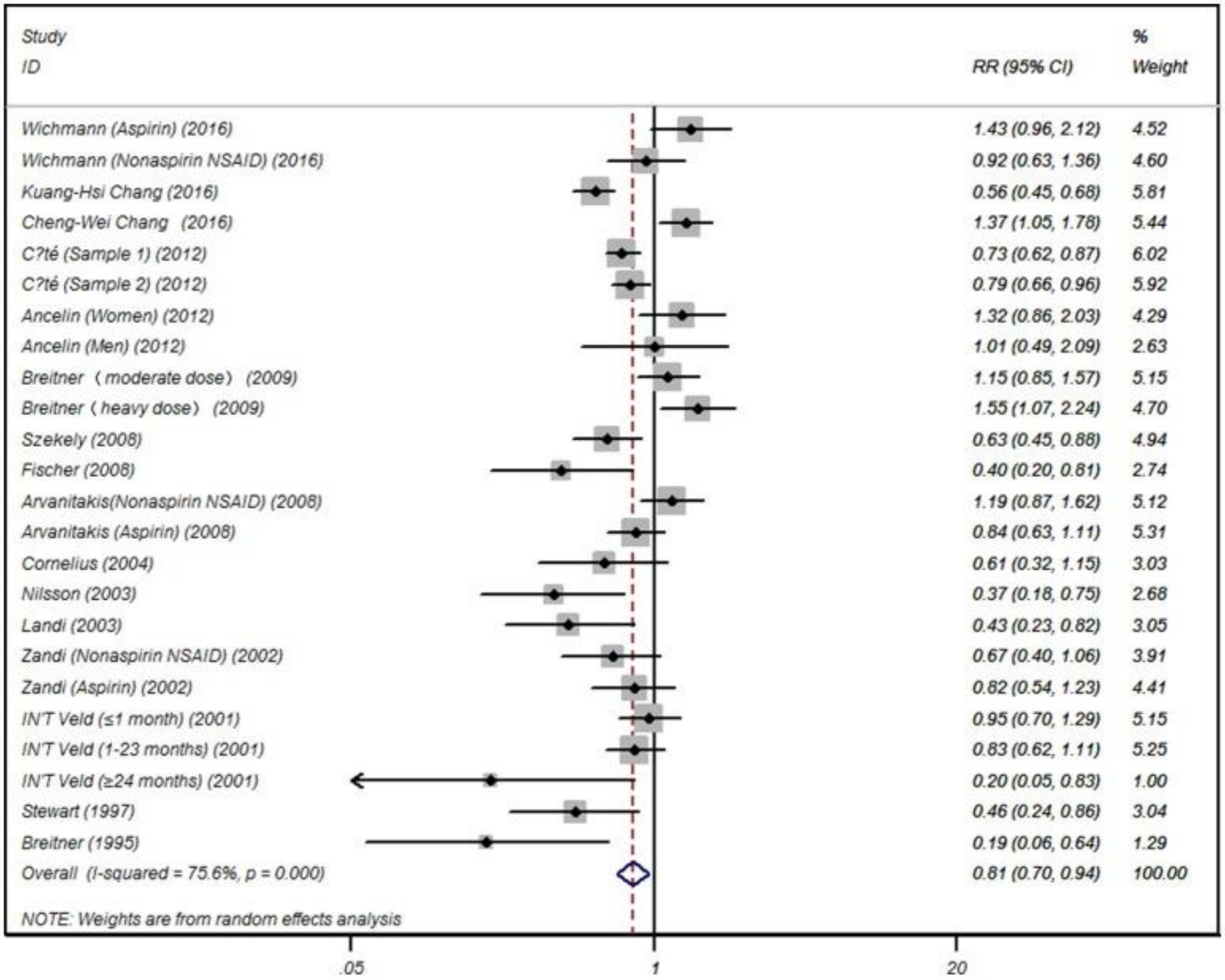

Zhang, Front Aging Neurosci. 2018

INTREPAD: A randomized trial of naproxen to slow progress of presymptomatic AD

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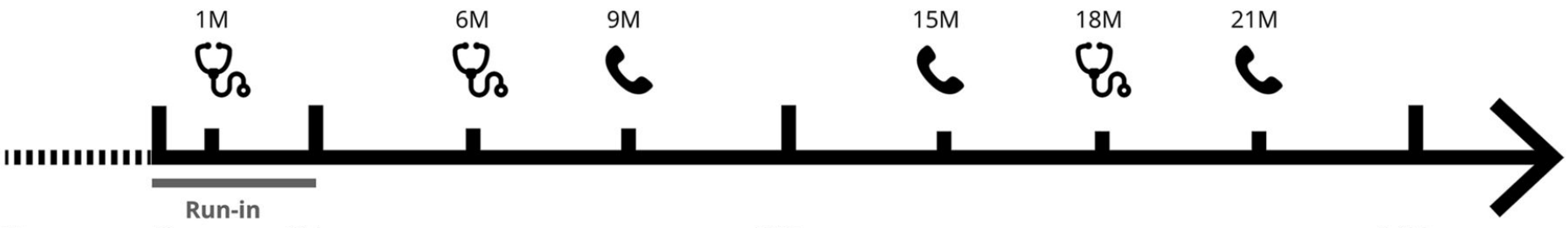
- Asymptomatic people in their 60s at high risk of Alzheimer's disease took daily naproxen for two years
- Neuropsychological performance were monitored for 48 months



Closing the book on NSAIDs for Alzheimer's Prevention

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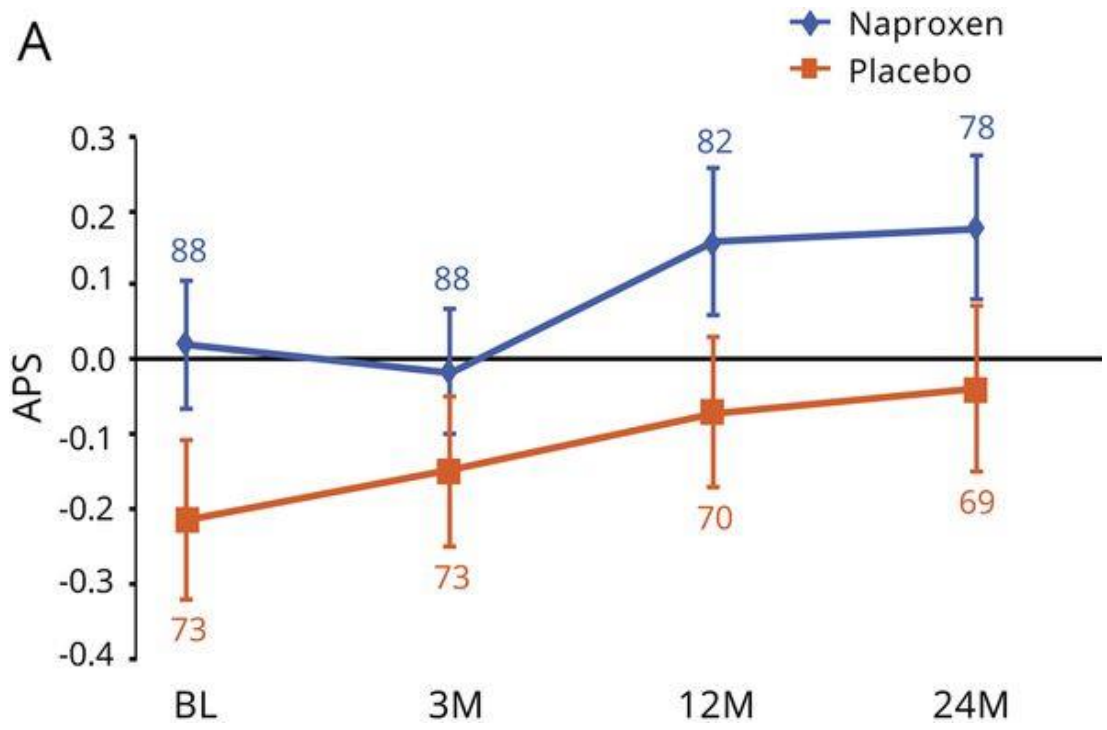
Naproxen Treatment has no effects on Alzheimer Progression Score (APS)



Pierre-François Meyer et al. Neurology 2019

Microglia mediates the balance between neuroprotection and cytotoxicity

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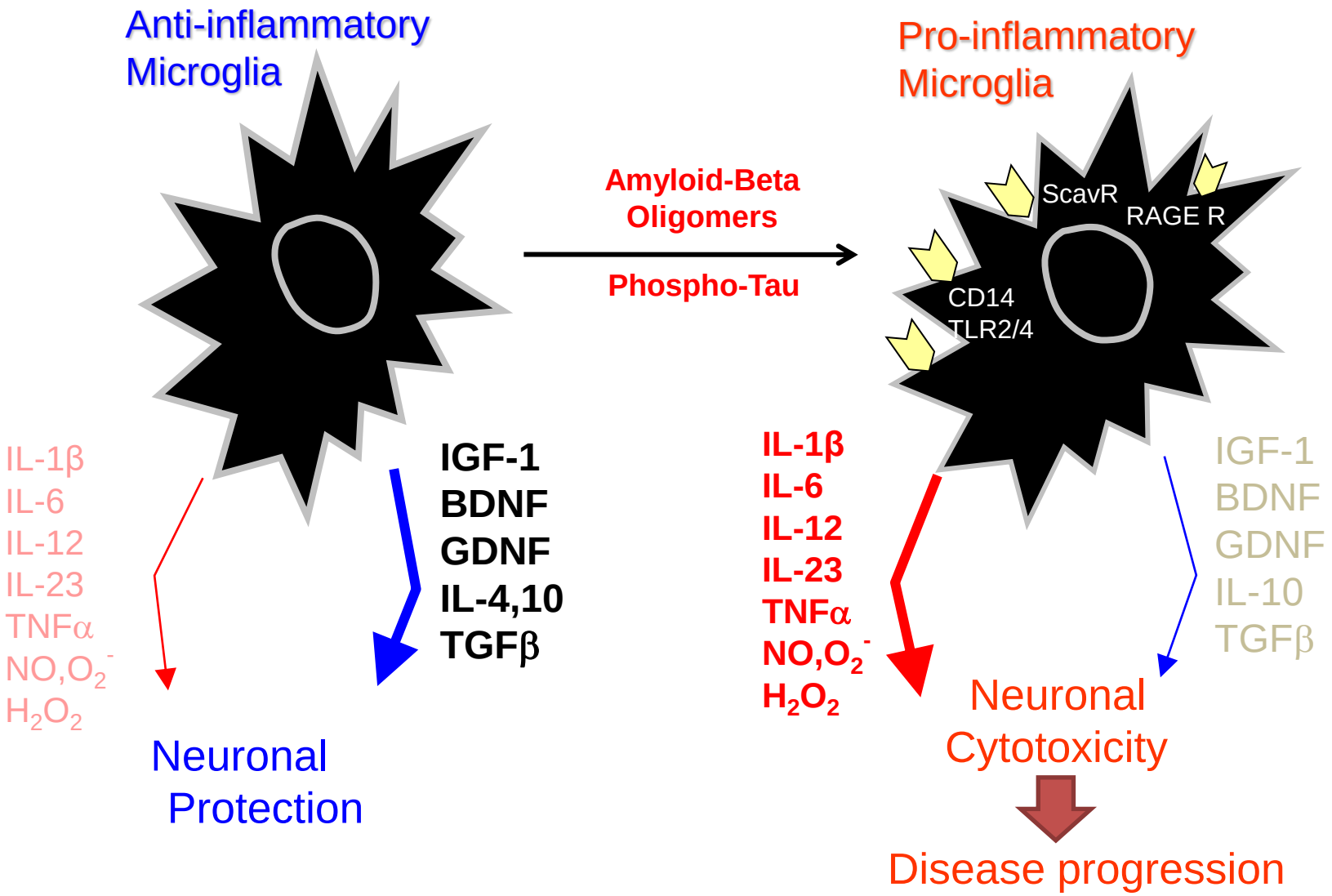

An early and late peak in microglial activation in Alzheimer's disease

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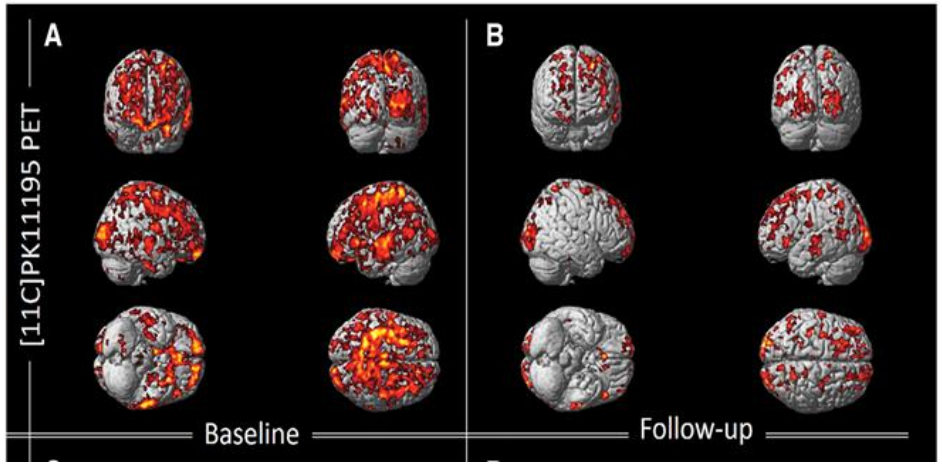
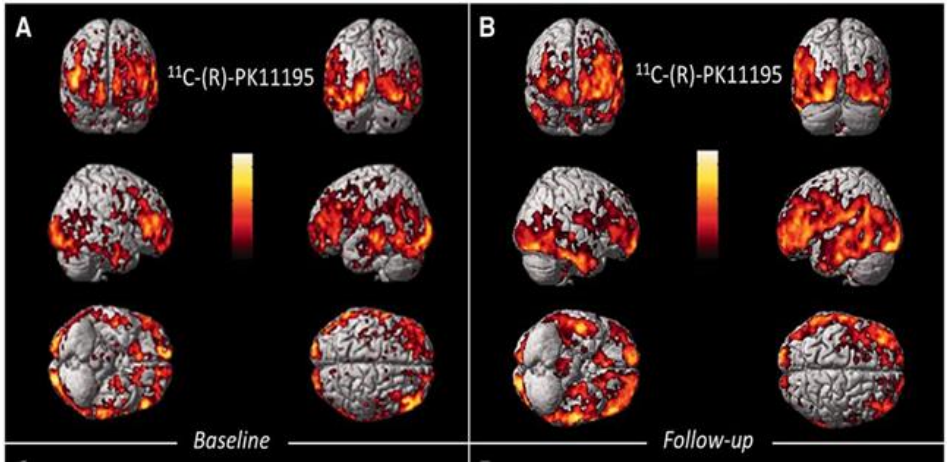
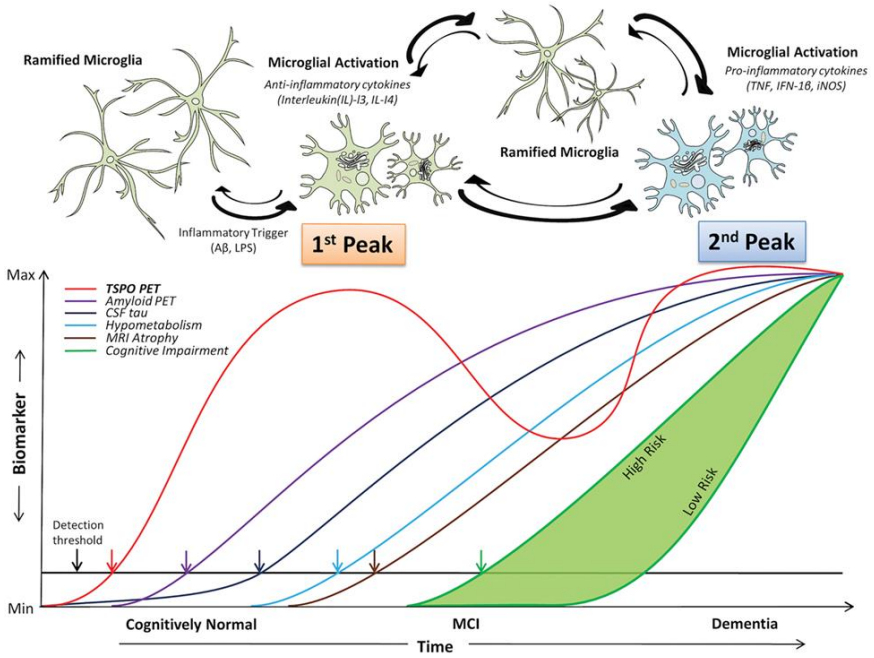
MCI



Alzheimer Dementia





Fan, Brain 2017

Pro-inflammatory Microglia as a potential therapeutic target

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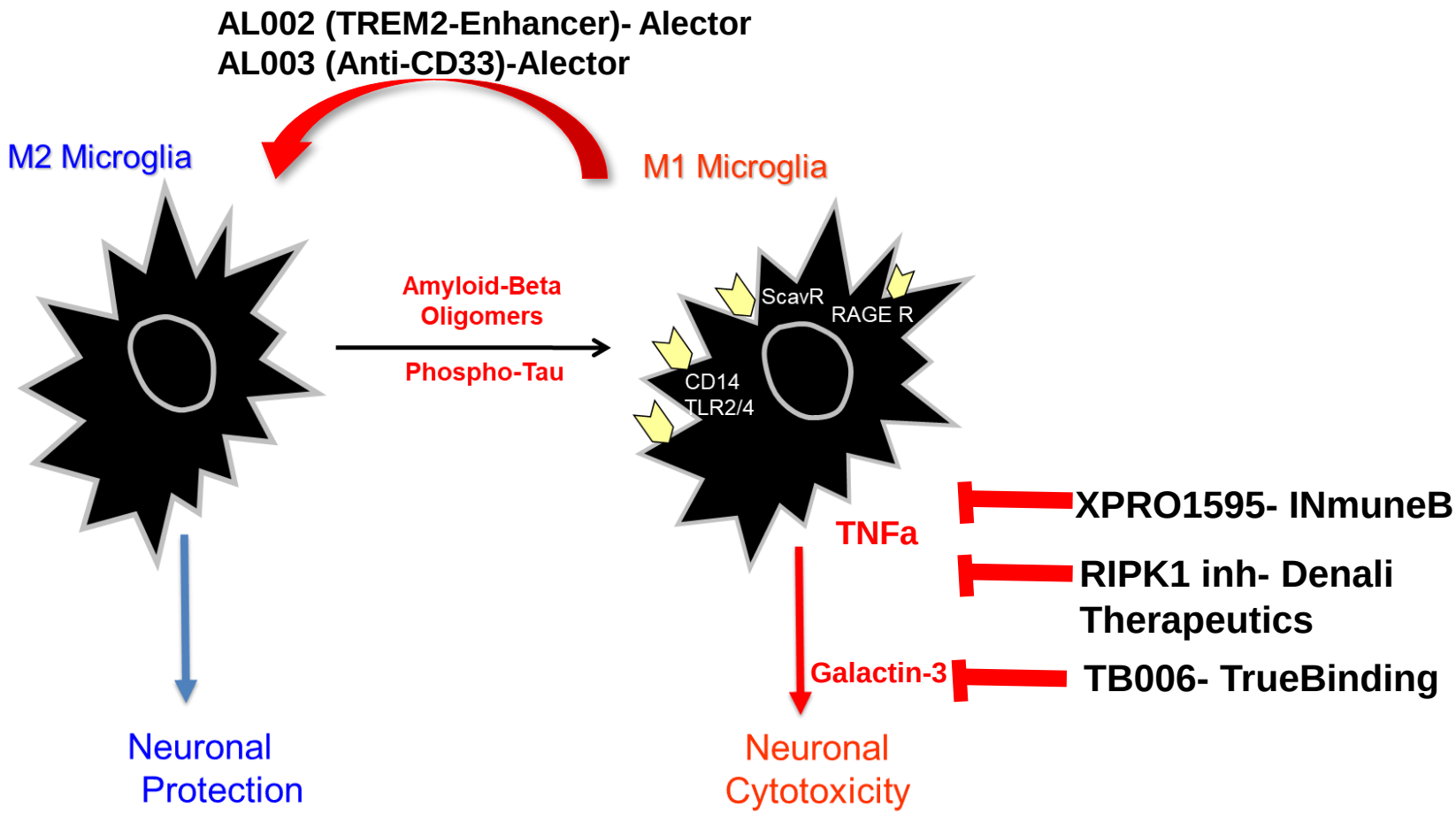

Pathogen theory in Alzheimer's disease

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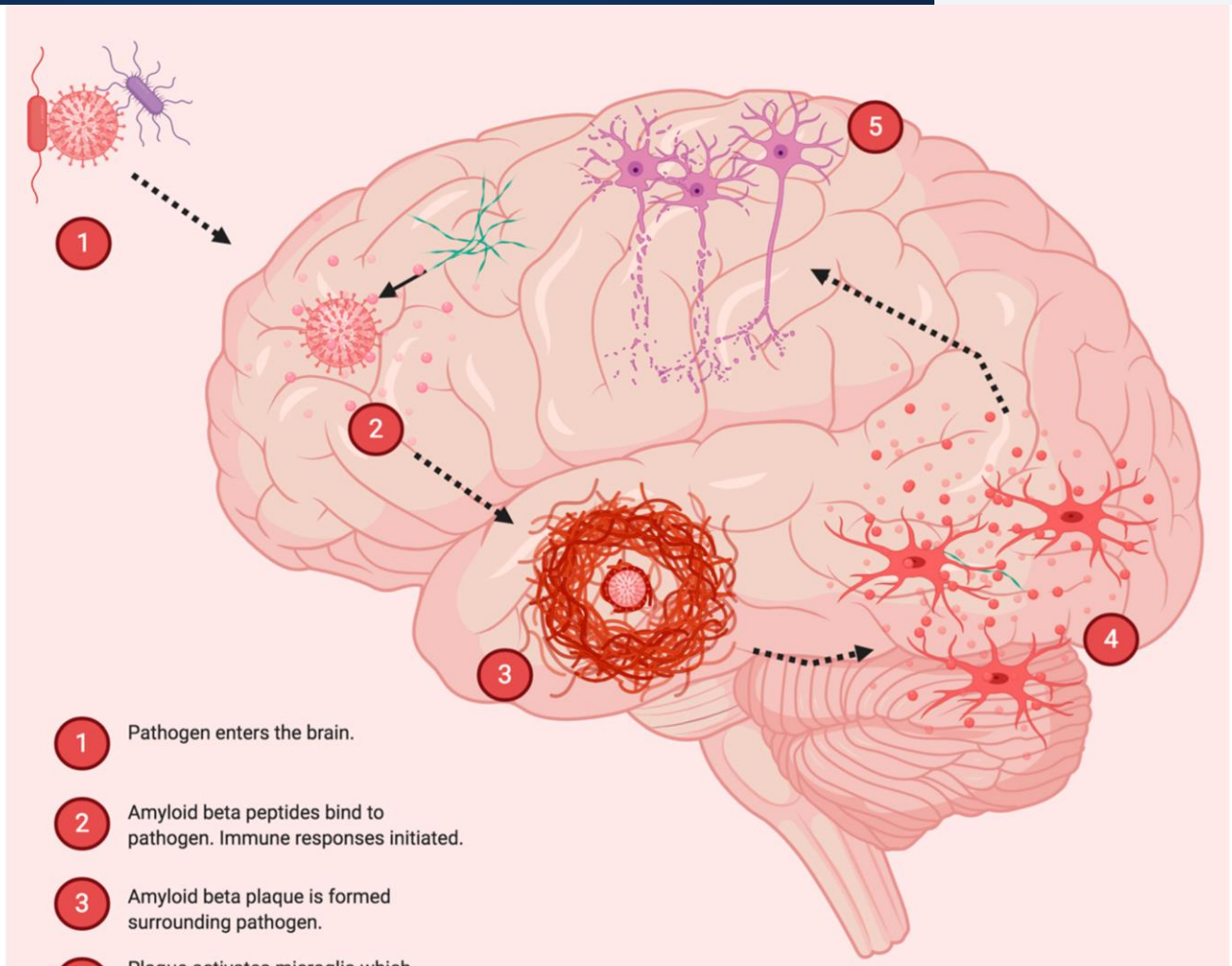

Naughton, J. Pers. Med. 2020

Targeting Viruses in clinical trials

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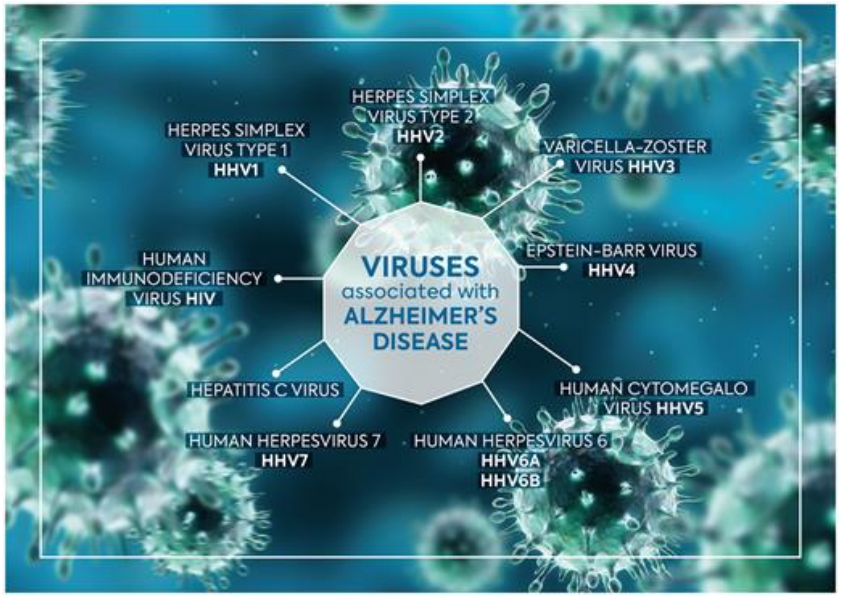
Several studies detected viruses particularly herpesviruses inside amyloid plaques

Wozniac, J Path 2009.

Anti-viral drug of Valacyclovir have targeted this virus in a trial of mild to moderate Alzheimer patients (VALAD Trial).



Panza, Brain 2019.
Cummings et al, Alzheimers dement 2020.

Targeting Microbiata in AD

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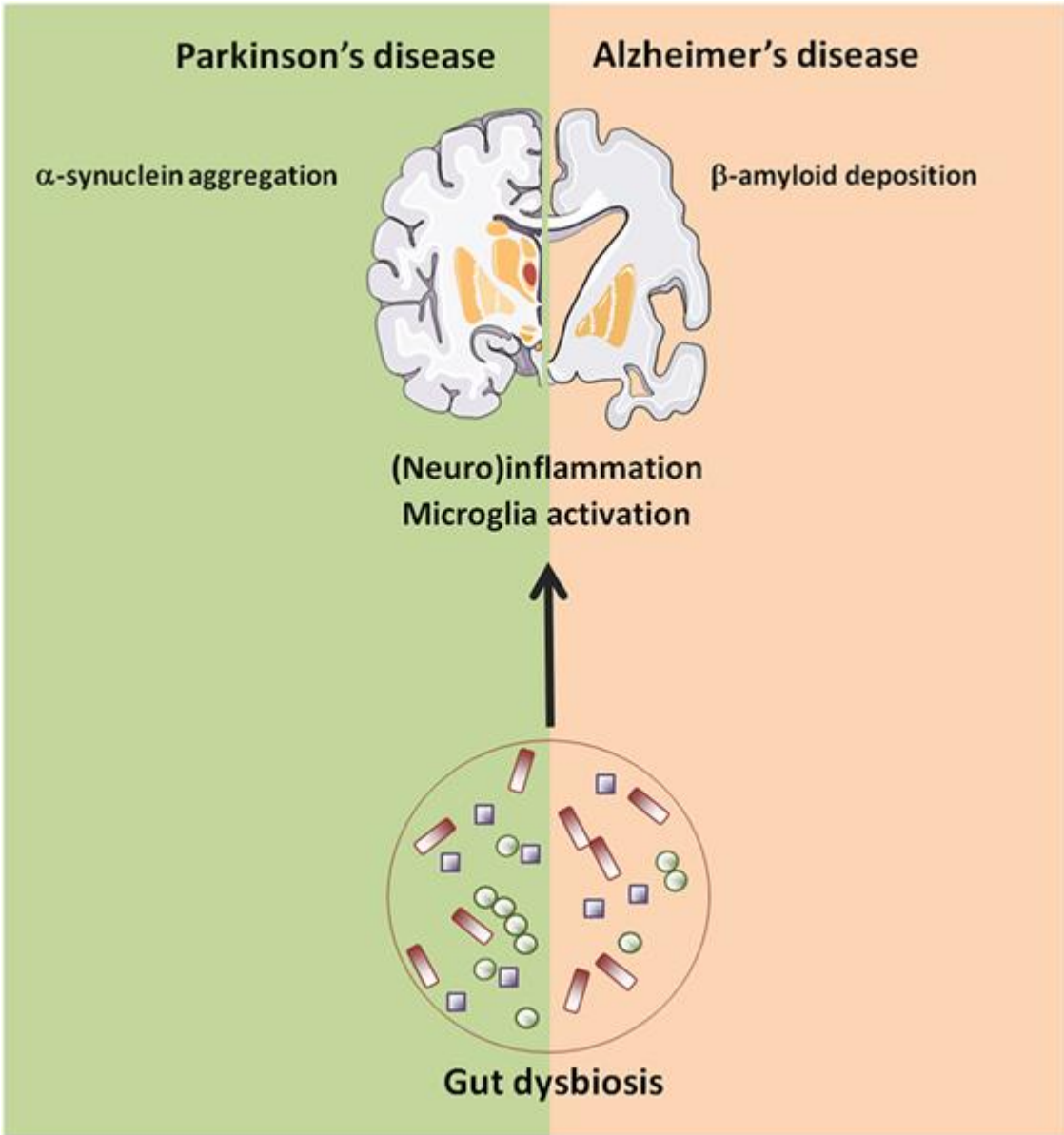
- Cor 388 is in phase 3 study and targets oral microbiom.
- GV-971 (oligomannate) targets gut microbiome
- GV-971 was already approved in China for improvement of cognition in patients with mild-to-moderate AD
- The global Phase 3 trial was terminated early due to financing problems and complications of the COVID pandemic in China



Tregs immunomodulatory status in AD

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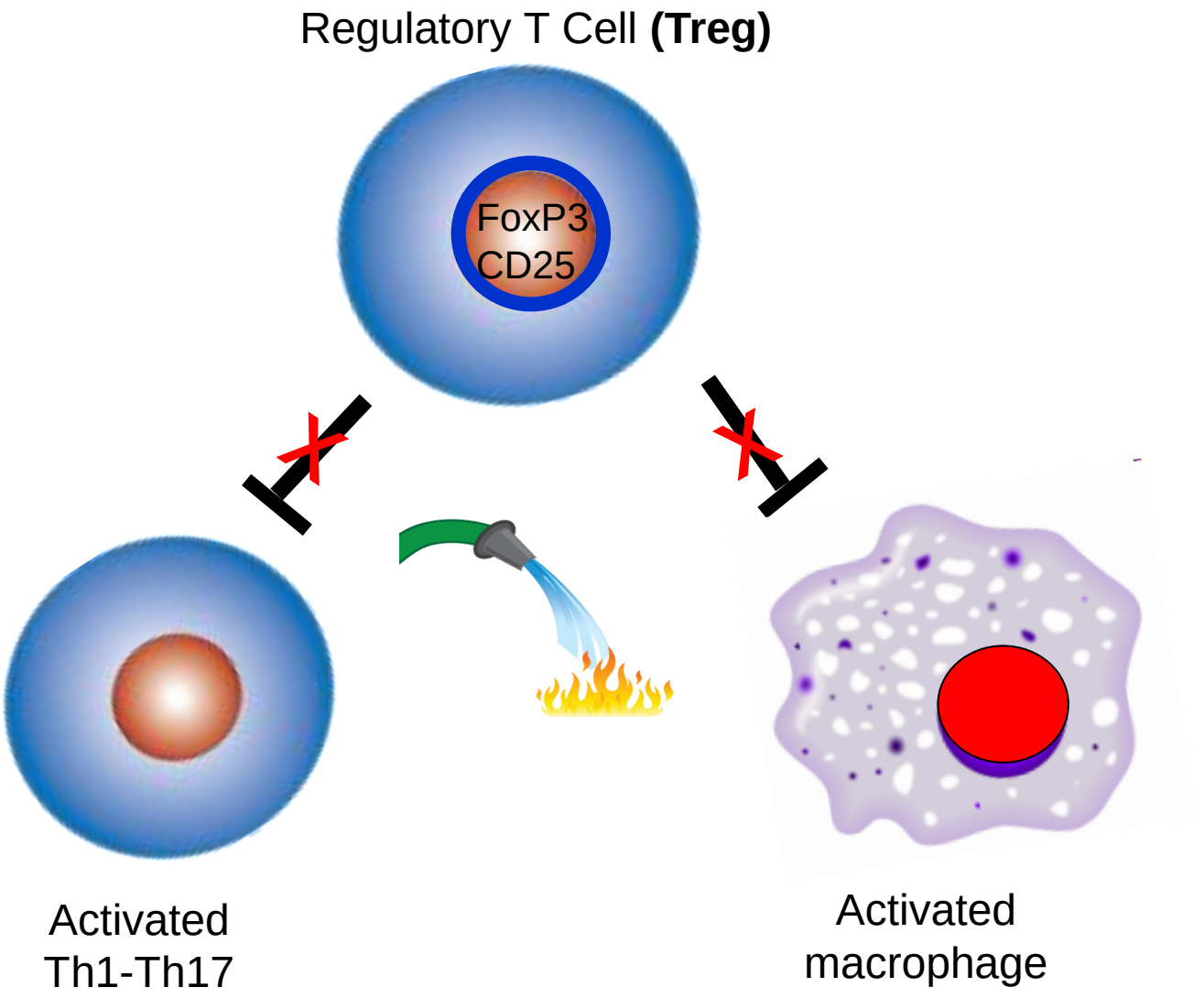

Peripheral immune status in AD individuals

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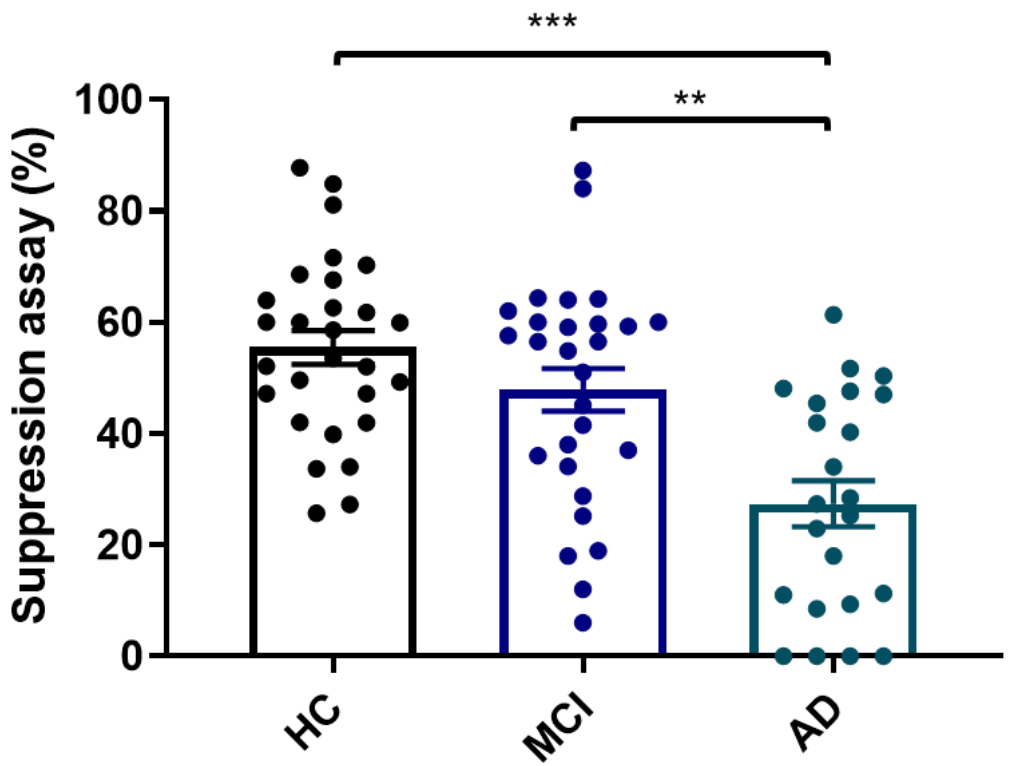
Compromised suppressive function of Tregs in Alzheimer's individuals



Faridar A et al, Brain communication

The contribution of peripheral immune status in neuroinflammation in AD

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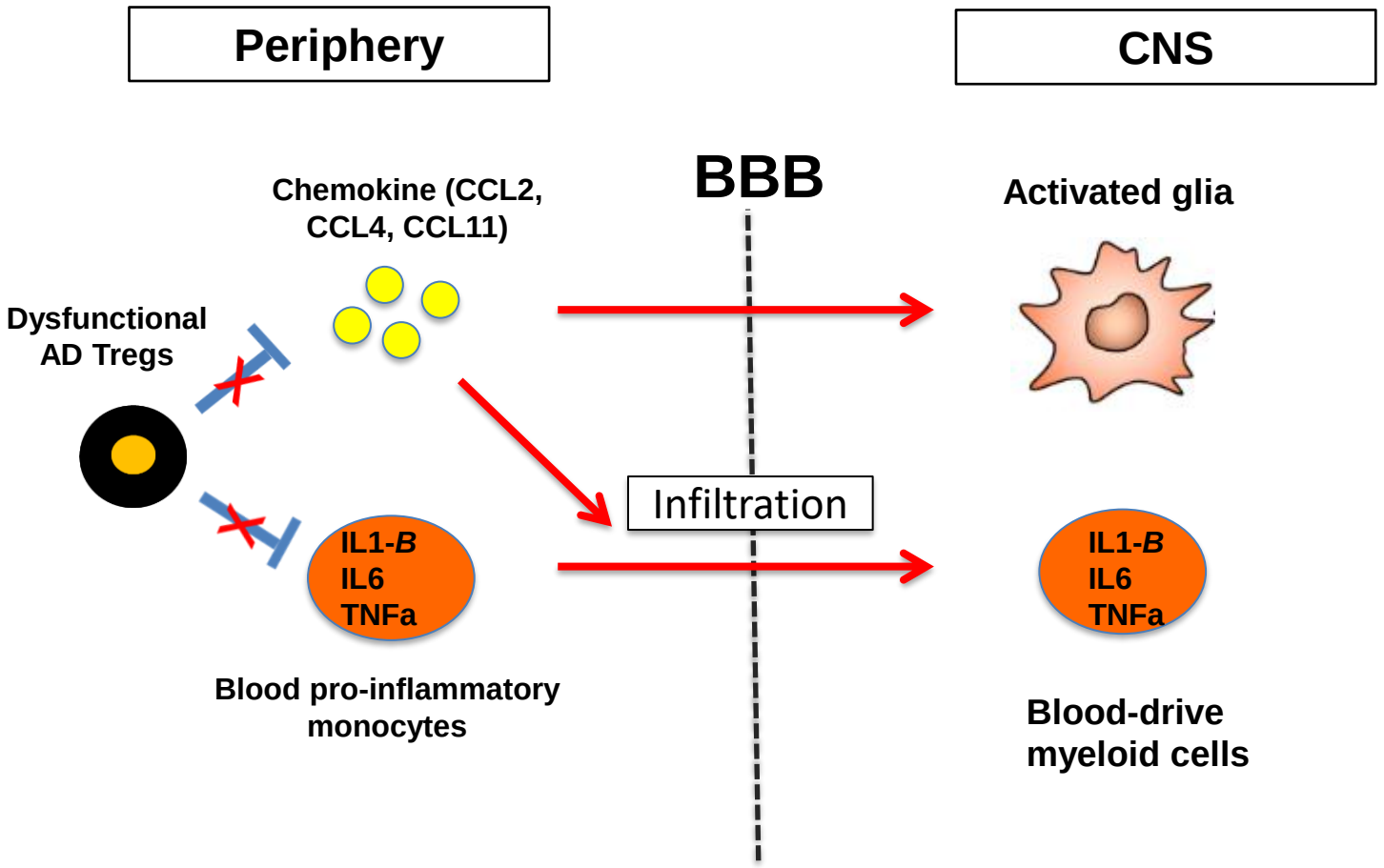

In vitro expansion of AD patients' Tregs in the presence of IL-2

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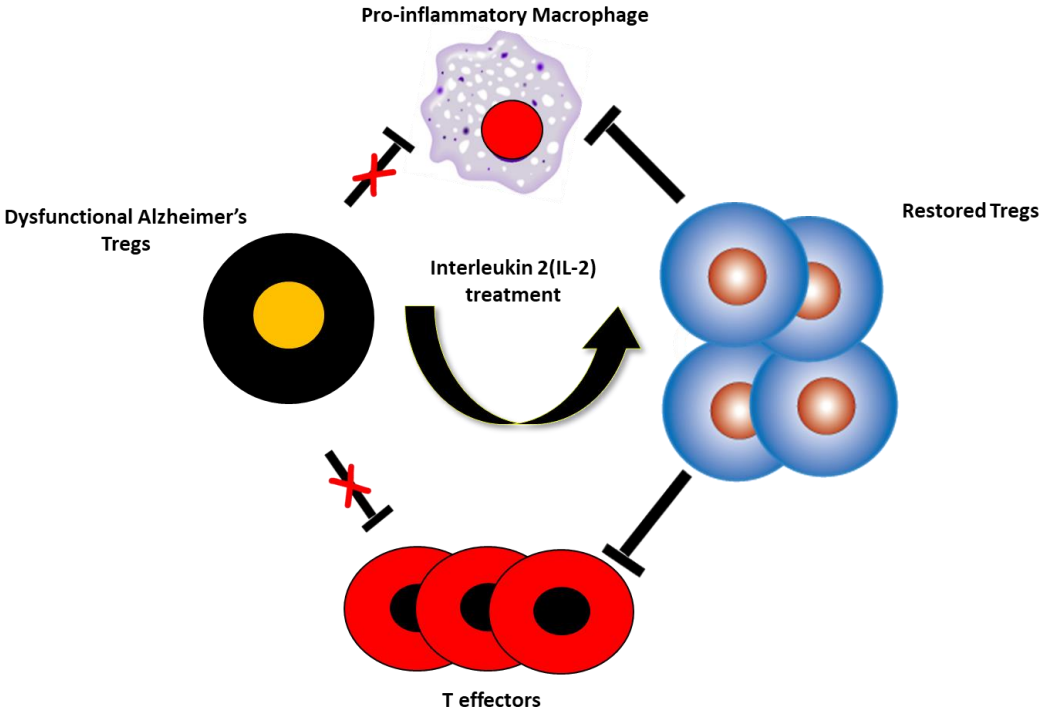

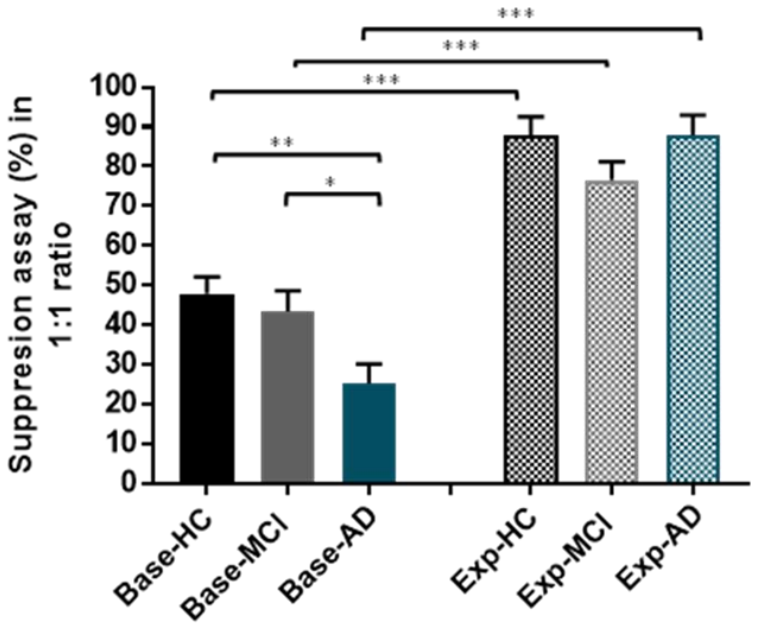

Faridar A et al, 2020

Treg Administration to AD mice ameliorated AD pathology

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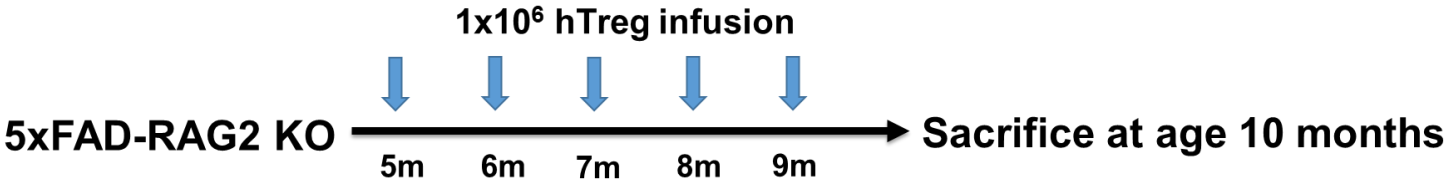

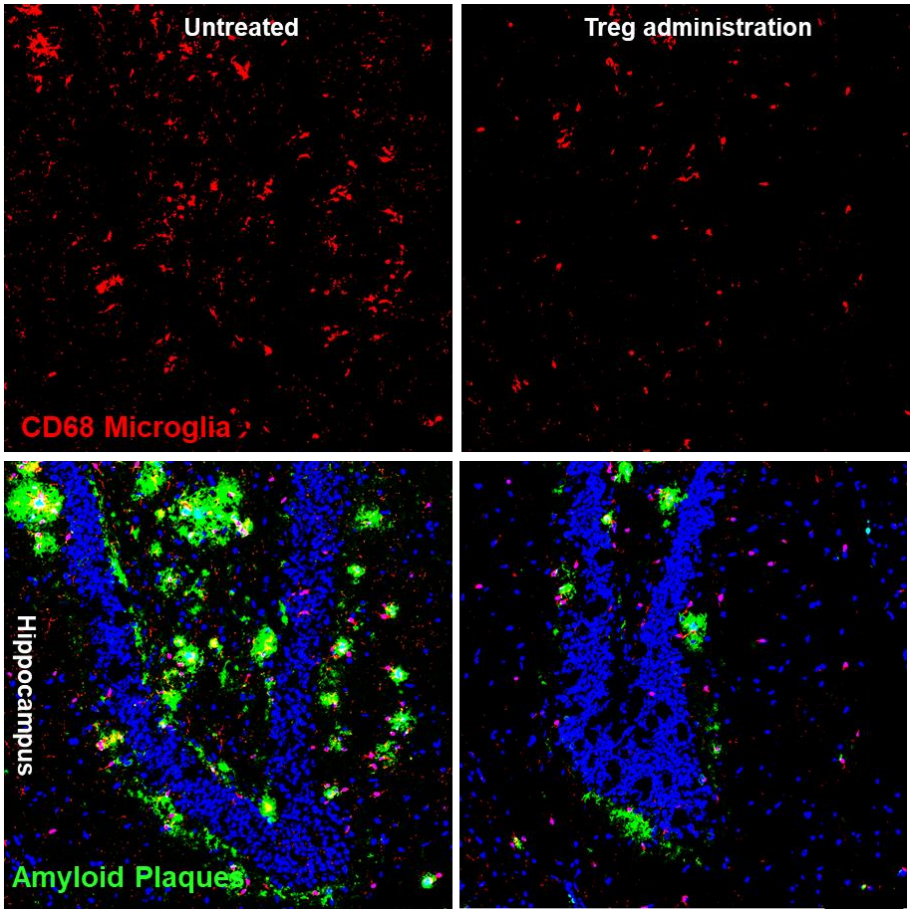

Faridar et al. Acta Neuropathologica comms 2022

In vivo expansion of Tregs in the clinical setting of AD

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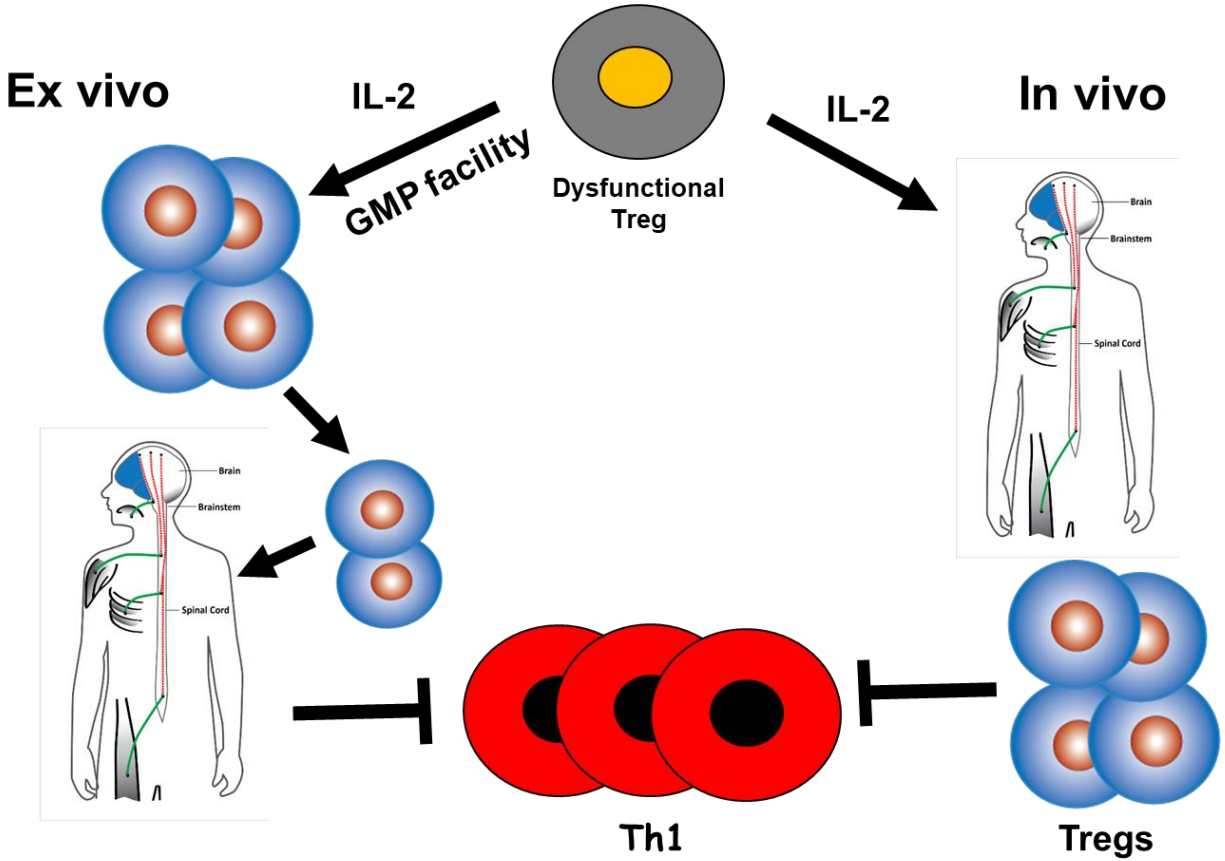

Eight mild to moderate Alzheimer's individuals were enrolled

In vivo Treg expansion strategy were applied for a total of 4 months

Changes in Tregs and also cognitive function of patients were monitored

Our treatment strategy selectively restored Treg population

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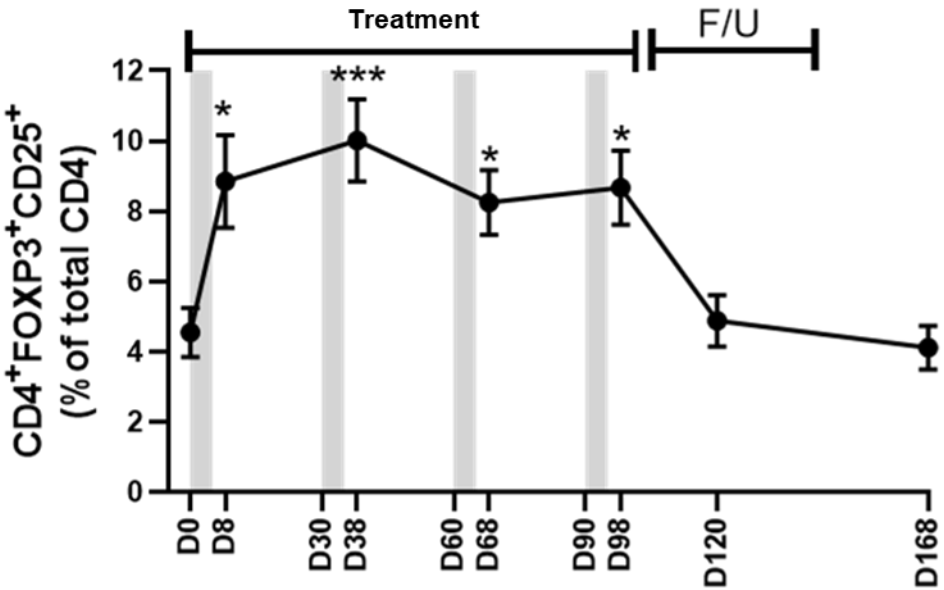

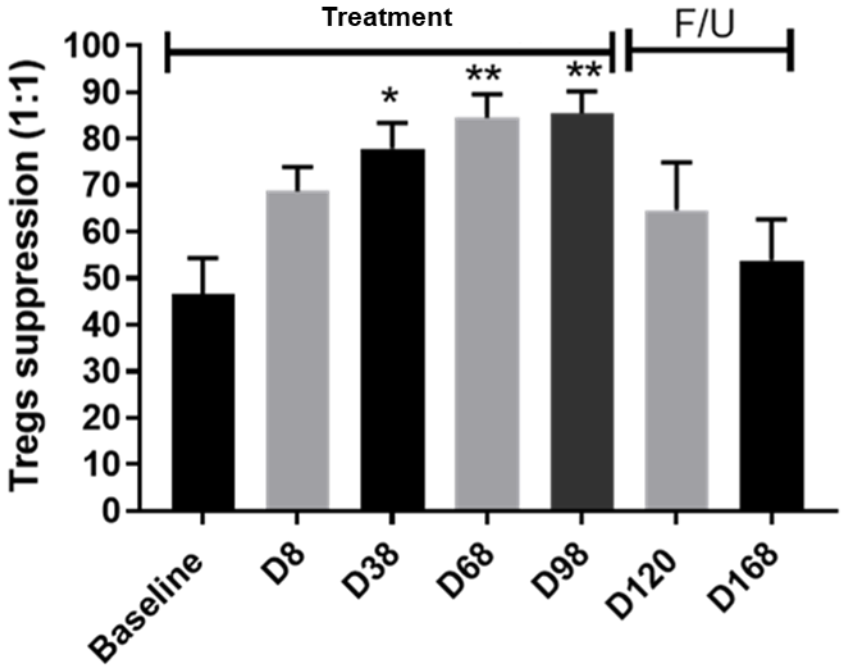

In vivo Treg expansion suppressed pro-inflammatory cytokines and chemokines

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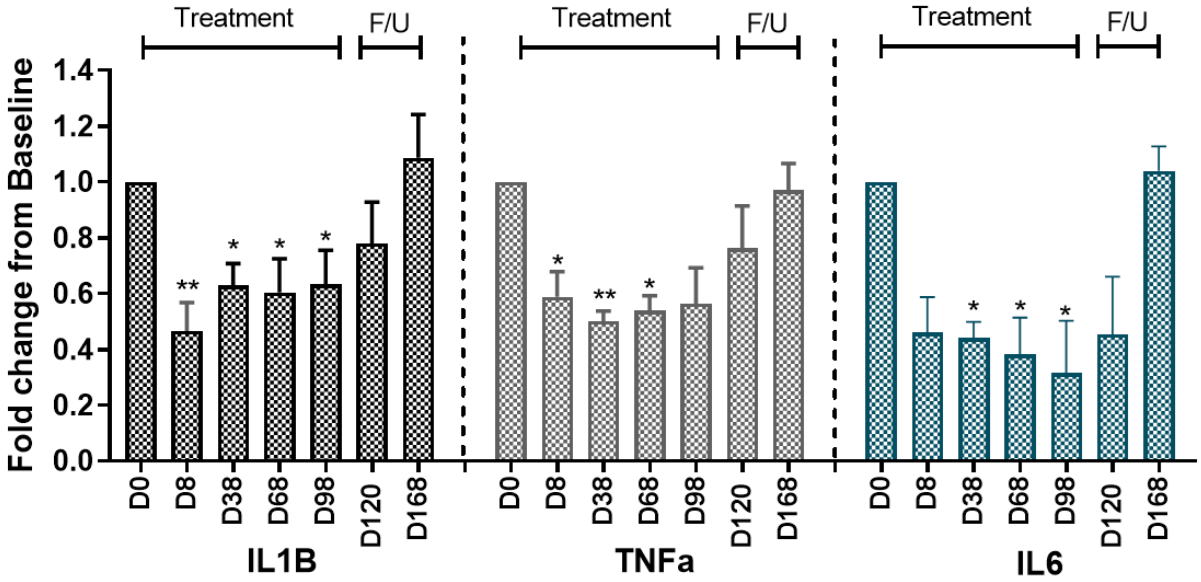

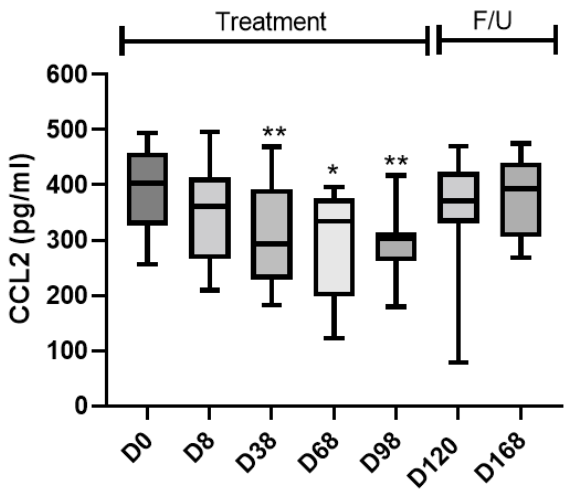

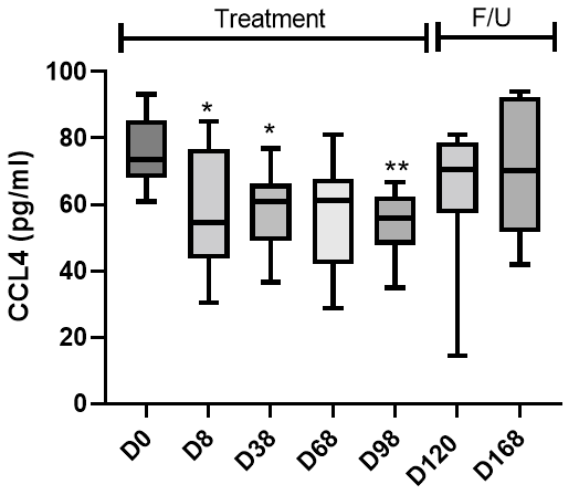

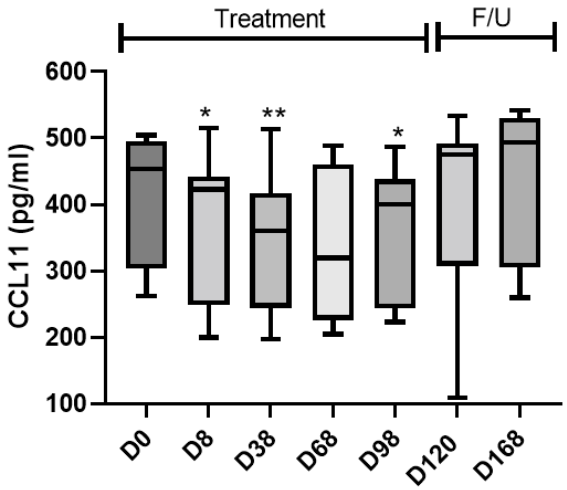

Proposed Mechanism

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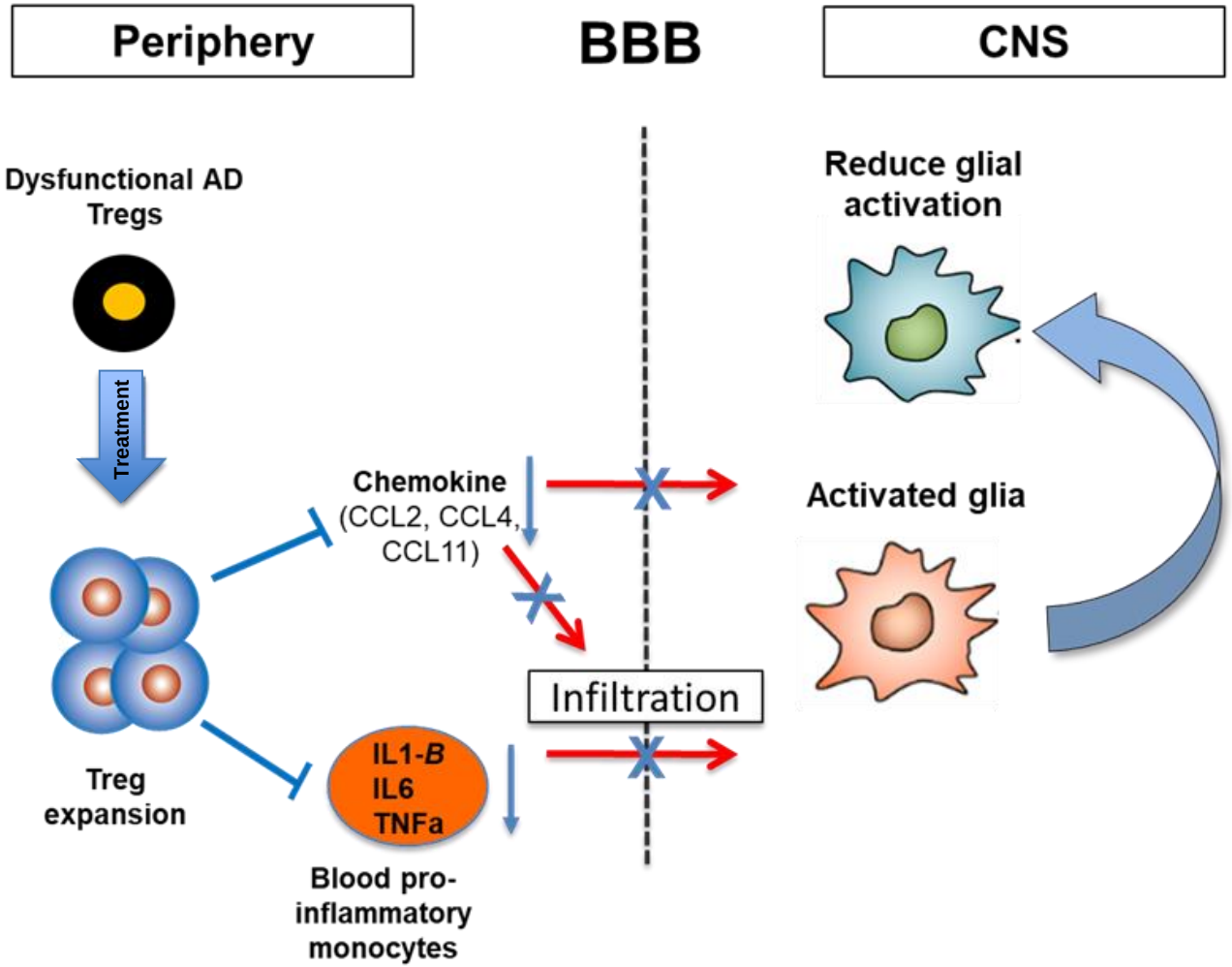

Glial activation modulation following treatment

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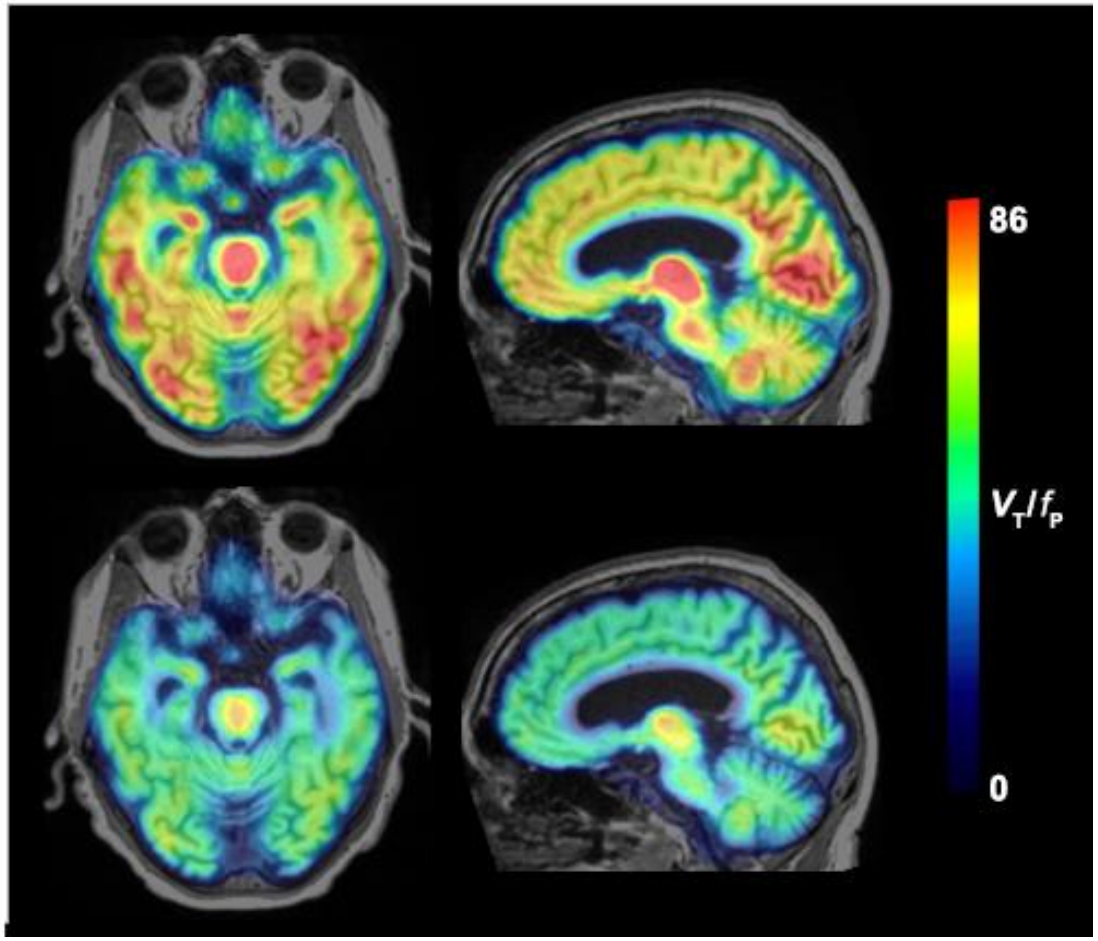
Alzheimer Disease Patient 70y/o

CDR 1

[11C] ER176
Baseline

[11C] ER176
After Treatment



Courtesy to Dr. Pascual

Monitoring cognitive status through Treatment phase

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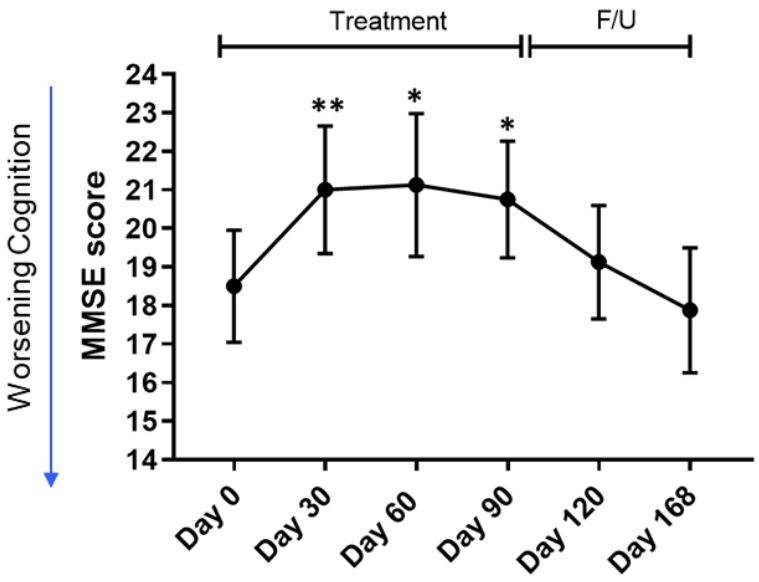
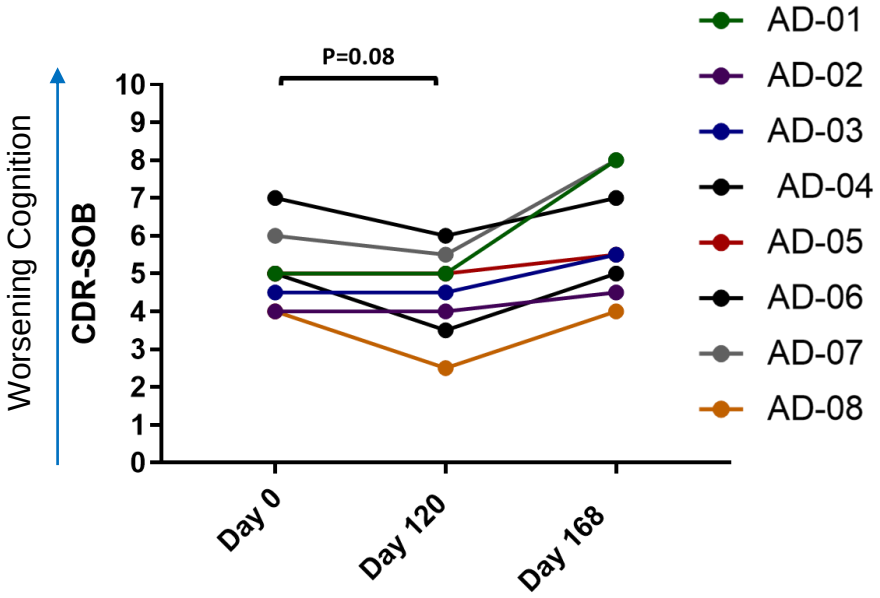
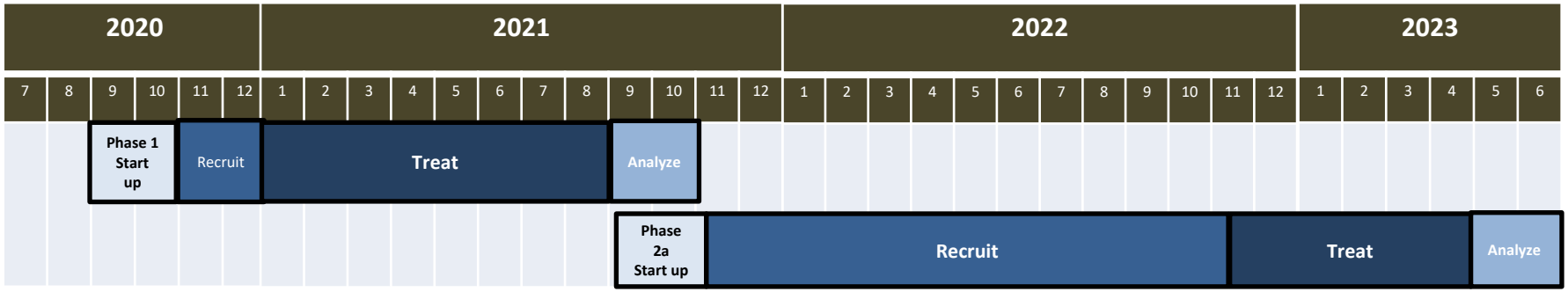




Advancing in vivo Treg expansion strategy to the phase 2a proof-of-concept study



Phase 2a: DB placebo-controlled trial in 40 patients

- **Safety & Tolerability**
- **The impact on AD CSF core biomarkers**
- **The impact on Cognitive decline**

In vivo Treg expansion in clinical trial

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- In vivo Treg expansion strategy was safe and well-tolerated
- It selectively expanded and restored dysfunctional Tregs in Alzheimer's patients
- Enhancing Tregs was associated with improvement in cognitive function of Alzheimer's patients
- The finding will be confirmed in a larger phase 2 study

Summary and next step:

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- FDA approved Anti-Aβ Antibody (aducanumab) as a first disease modifying therapy in Alzheimer's disease
- While anti-amyloid antibodies are signaling some success, researchers agree that these biologic drugs can form only part of the arsenal needed to fight the disease
- Approval for Anti-Amyloid-B monoclonal Antibody is not likely to be the final treatment for AD, but it could open doors for combination therapy

Next Step- Diversify targets and optimize trial design

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- To diversify the therapeutic pipeline with a greater variety of targets
- Combining several DMTs with synergistic mechanisms of action
- To optimize and re-engineener Alzheimer clinical trial design
- Applying platform style clinical trial
- Using machine learning/artificial intelligence to facilitate trials (e. g. Digital twin, Integrated biomarkers)

Next Step- Prevention strategies

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- Presymptomatic stage might be the best opportunity to bend the curve toward normal aging
- To identify asymptomatic, at-risk individuals and advancing preventive approaches
- To place more emphasis on lifestyle interventions which could reduce the incidence of Alzheimer's disease up to 33%

Our team:

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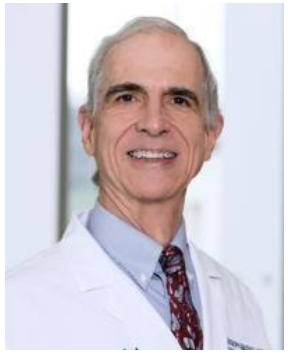
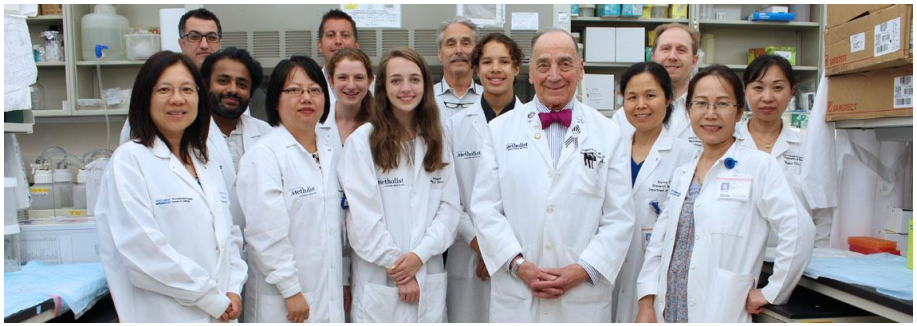
Stanley H. Appel, MD,



Joseph C. Masdeu, MD, PhD,

Alireza Faridar, MD,



Appel's molecular immunology lab

Nantz National Alzheimer's Center

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