The Science of Alzheimer's Disease: Are there opportunities for Intervention? Why is it taking so long?

Bill Frazier 6-4-2017

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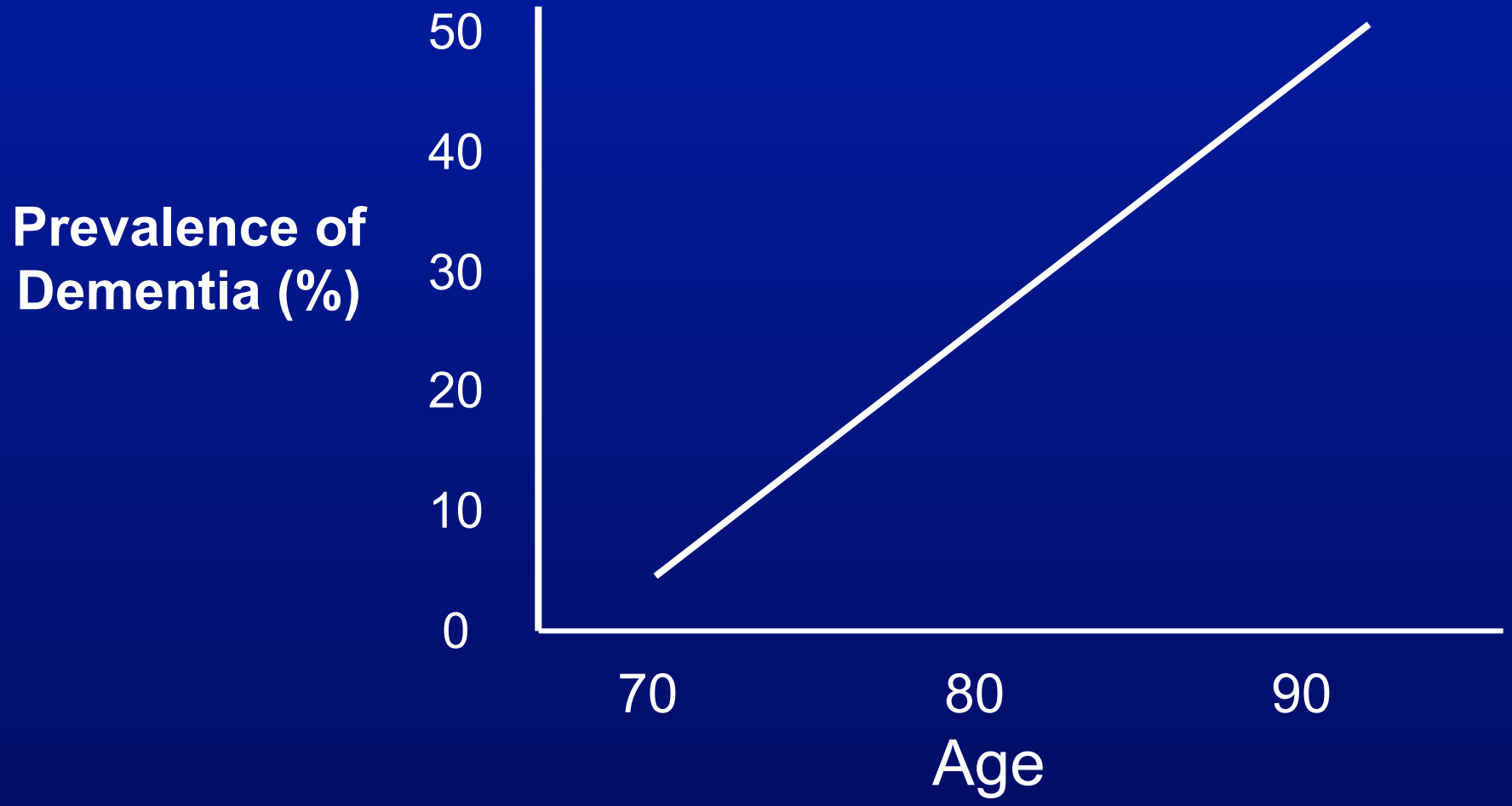
Dementia: Decline in memory and other cognitive abilities sufficient to impair social and occupational functioning



Dementia is very common with increasing age and Alzheimer's disease (AD) contributes to ~70-75% of cases of dementia.

Current estimated cost in US of medical and other care for AD is >$200 billion per year.

Clinical Features of AD

- **Gradual onset and progression**
- **Memory deficits (recent memory)**
- **Other cognitive dysfunction**
  executive dysfunction: problem solving, attention
  language, praxis, visual-spatial dysfunction
- **Behavioral dysfunction**
  personality change, depression, delusions, hallucinations, apathy, sleep disruption

Types of AD and risk

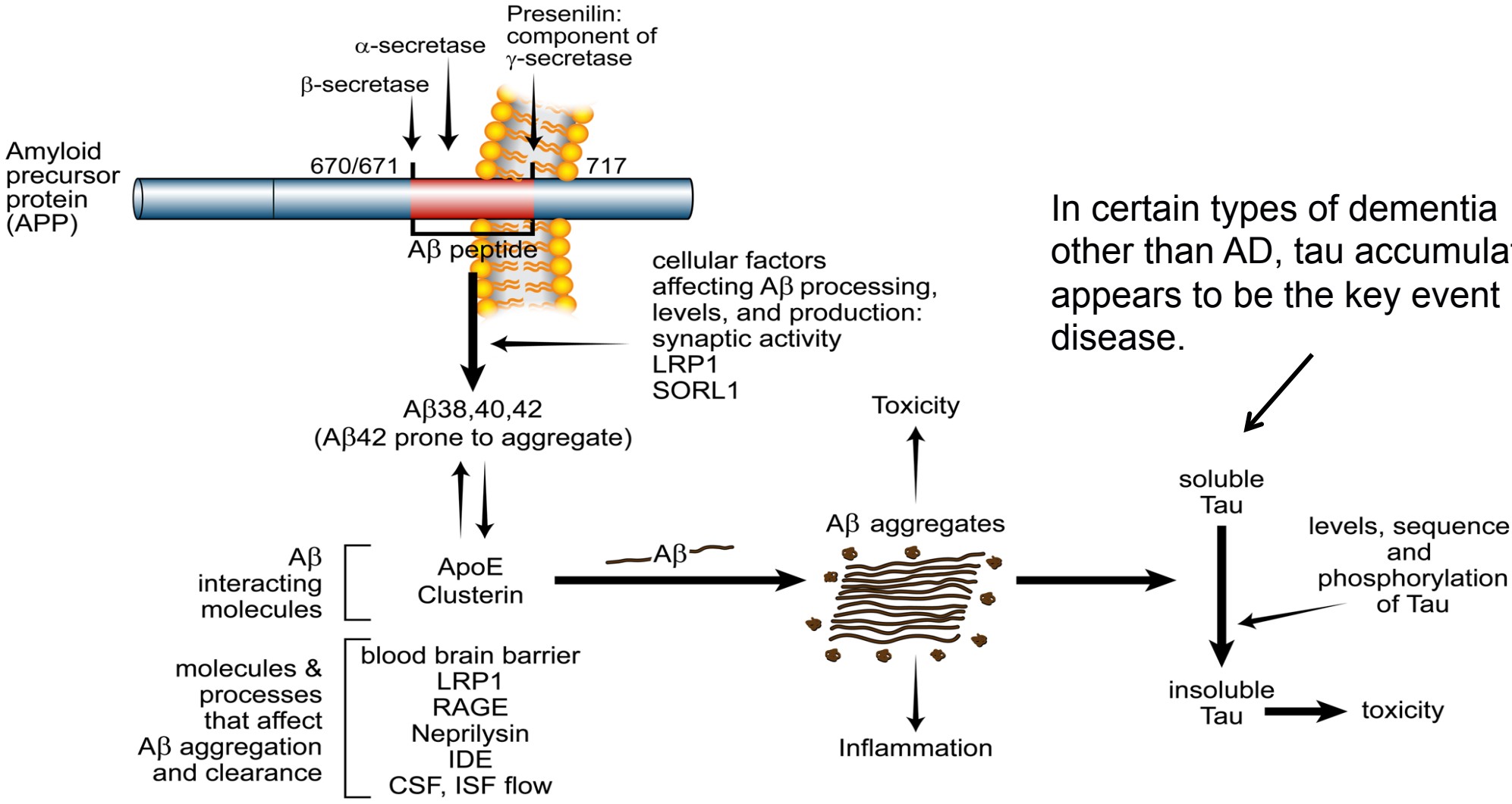
- Two major types of AD:

  1) early onset familial AD (<1% of cases) e.g., the families in Columbia

  2) late onset AD (age > 60, >99% of cases) or "sporadic" AD…influenced by many genes.

- Two strongest risk factors for AD are age and family history (genetics).

Role of Amyloid-β, apoE, and tau metabolism in pathogenesis of Alzheimer's disease and tauopathies



In certain types of dementia other than AD, tau accumulation appears to be the key event in disease.

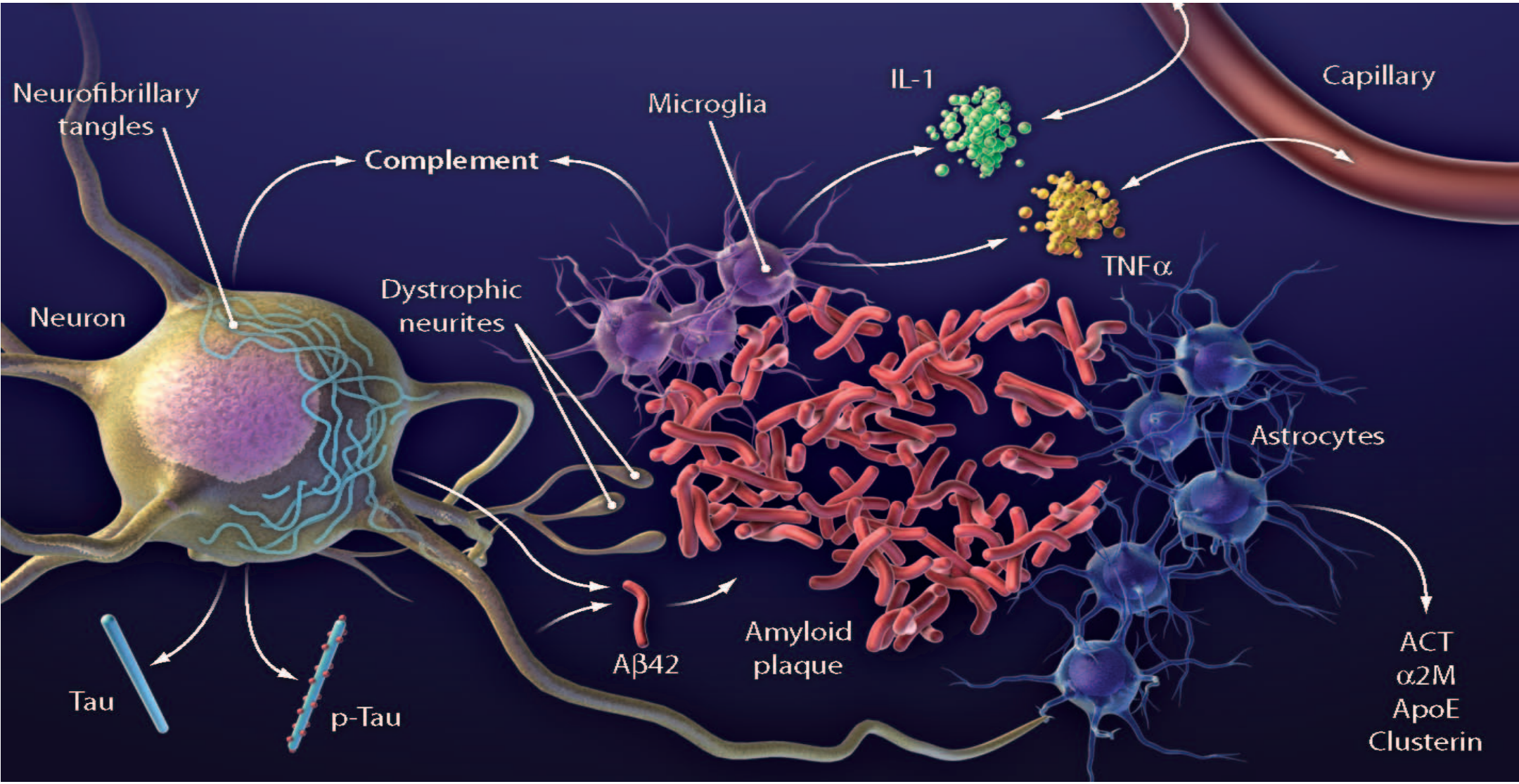
ApoE alleles and AD

- There are 4 alleles/versions of the Apolipoprotein E gene differing by one amino acid each.

- ApoE4 increases risk, E2 decreases risk.
  One copy of E4 increases risk 3X, two copies 12X.

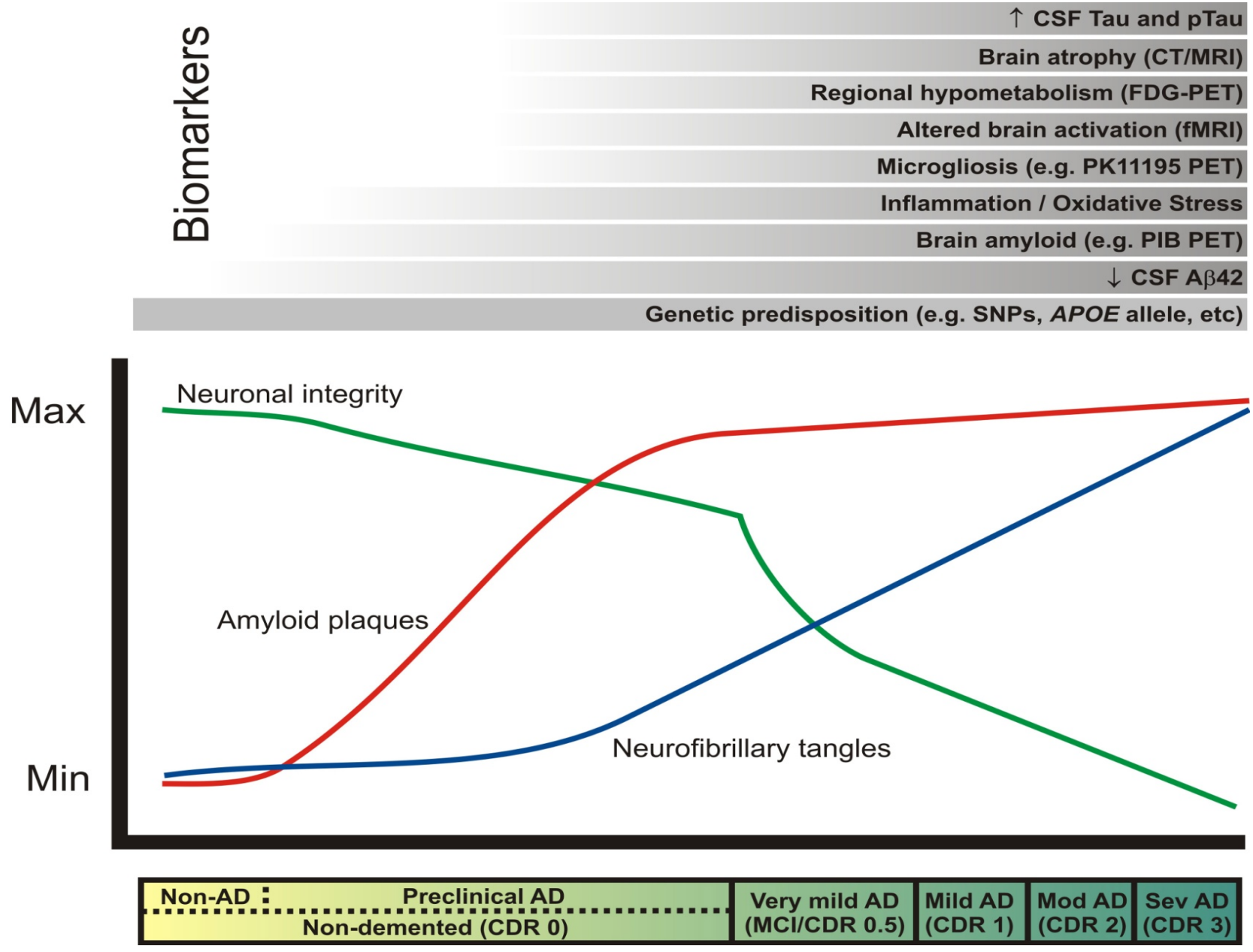
- ApoE is a cholesterol AND Aβ binding protein produced in the brain. It is thought that ApoE2 binds and helps to "dispose" Aβ while E4 does not, allowing it to accumulate.

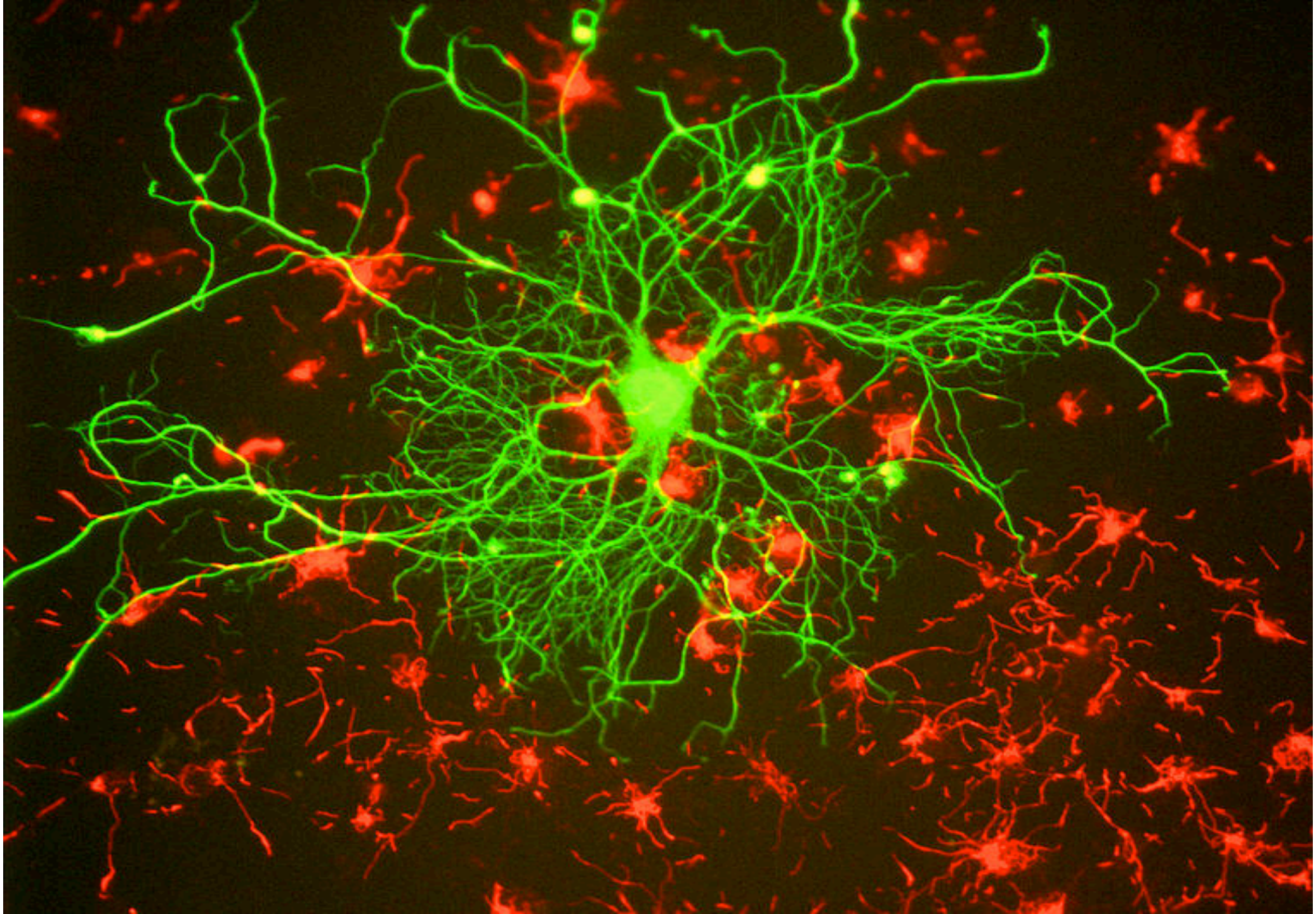
Model of Alzheimer's brain pathology



Holtzman DM, Morris JC, Goate AM (2011) Science Translational Medicine Vol 3, Issue 77

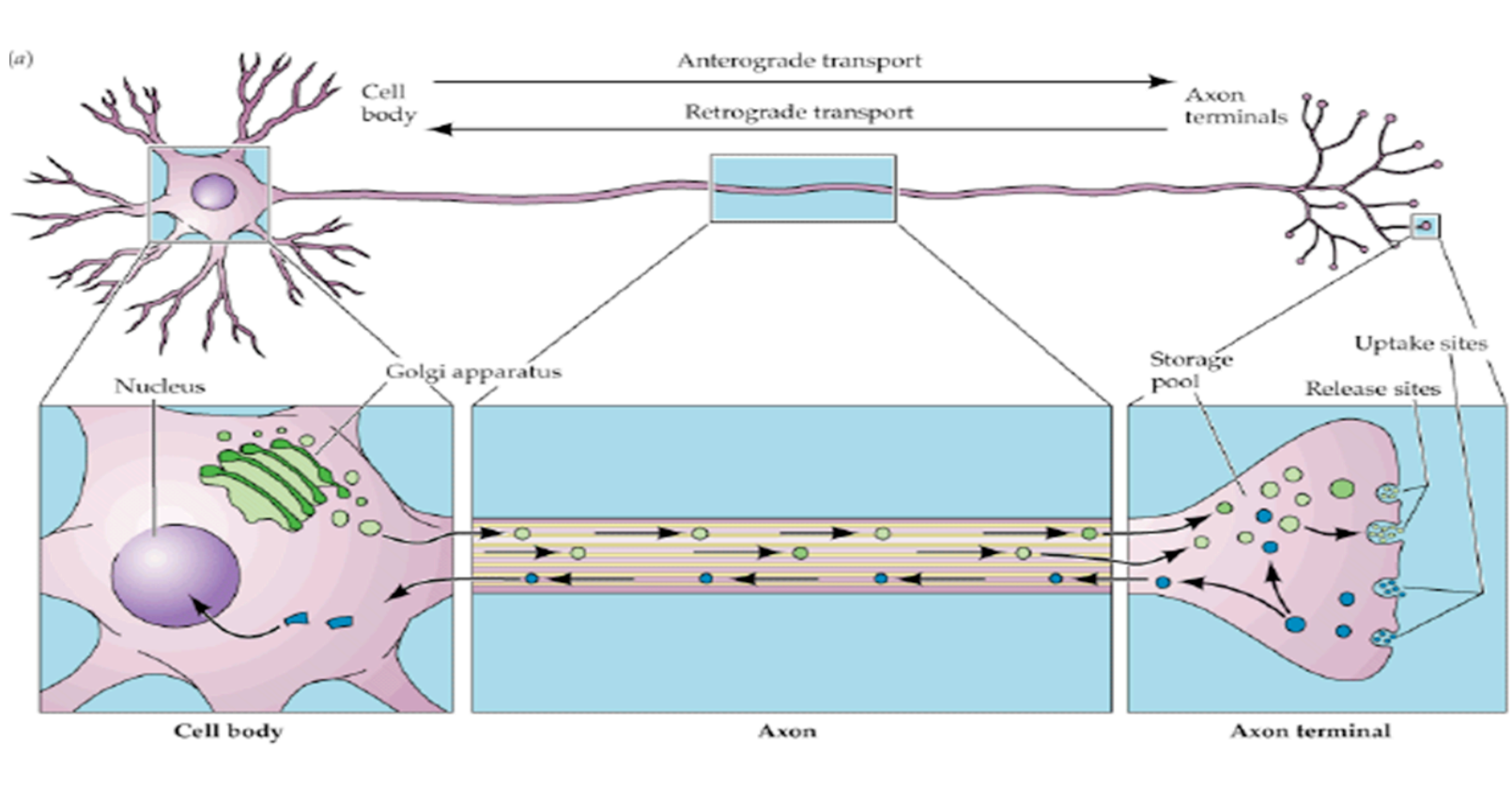
Probable time course of biomarkers of AD-related pathological changes in relation to clinical manifestations





Why is tau pathology important in AD?

All the components needed to keep synapses functional and repair them are made in the cell body of neurons. They must be transported down the axon on microtubules to the terminal. Tau associates with microtubules and has a role in this critical transport process. When tau is "tangled" the process fails and synapses fail, neurons die.



No significant effects of Bapineuzumab or Solanezumab on primary endpoints in Phase III trials of mild to moderate AD

ORIGINAL ARTICLE

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

Stephen Salloway, M.D., Reisa Sperling, M.D., Nick C. Fox, M.D., Kaj Blennow, M.D., William Klunk, M.D., Murray Raskind, M.D., Marwan Sabbagh, M.D., Lawrence S. Honig, M.D., Ph.D., Anton P. Porsteinsson, M.D., Steven Ferris, Ph.D., Marcel Reichert, M.D., Nzeera Ketter, M.D., Bijan Nejadnik, M.D., Volkmar Guenzler, M.D., Maja Miloslavsky, Ph.D., Daniel Wang, Ph.D., Yuan Lu, M.S., Julia Lull, M.A., Iulia Cristina Tudor, Ph.D., Enchi Liu, Ph.D., Michael Grundman, M.D., M.P.H., Eric Yuen, M.D., Ronald Black, M.D., and H. Robert Brashear, M.D., for the Bapineuzumab 301 and 302 Clinical Trial Investigators*

NEJM 2014 370(4):322-33.

Pfizer

ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Ronald G. Thomas, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Rema Raman, Ph.D., Xiaoying Sun, M.S., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Hong Liu-Seifert, Ph.D., and Richard Mohs, Ph.D., for the Solanezumab Study Group

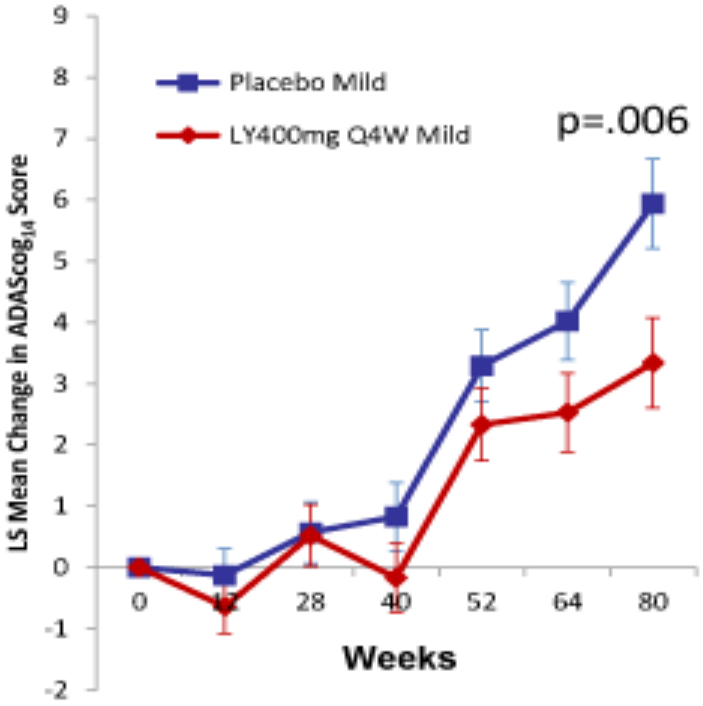
NEJM 2014 370(4):311-21

Lilly

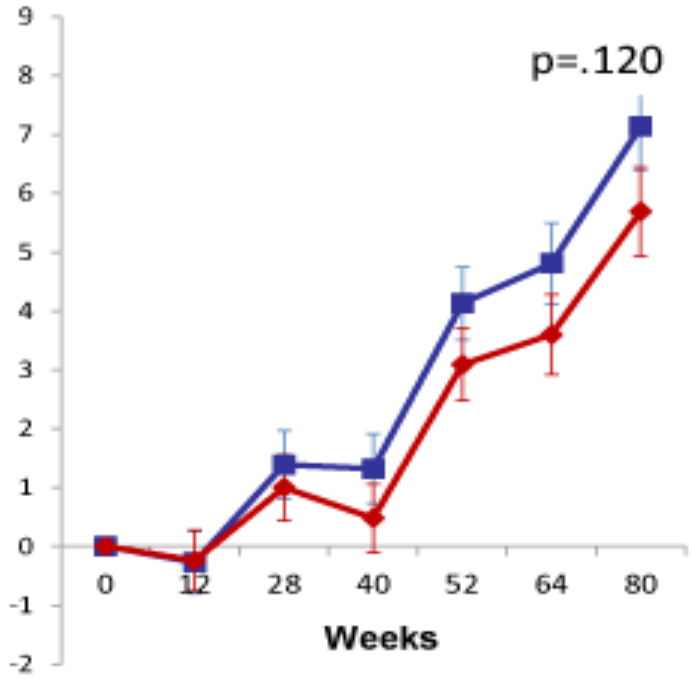
Solanezumab EXPEDITION Trial Results

ADAScog$_{14}$ in Mild* Population
EXPEDITION1, EXPEDITION2, and Pooled

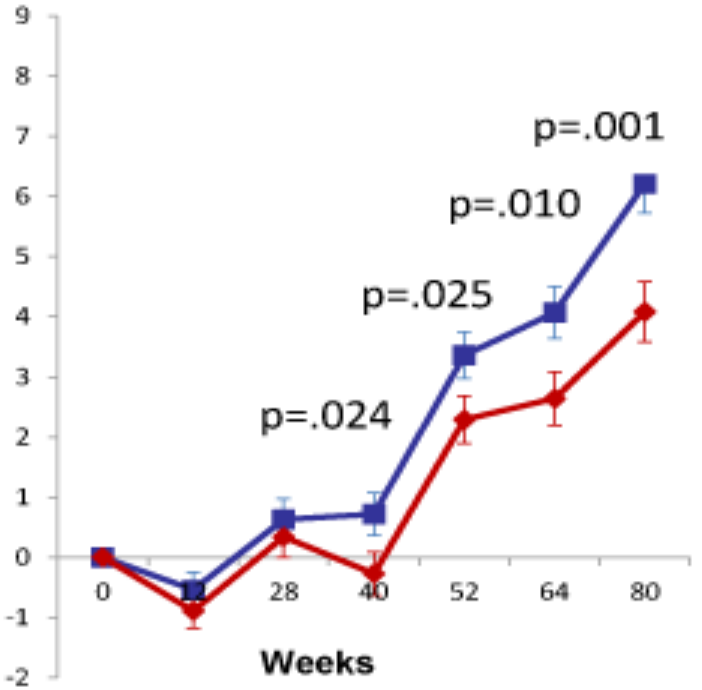
EXPEDITION1



EXPEDITION2



Pooled

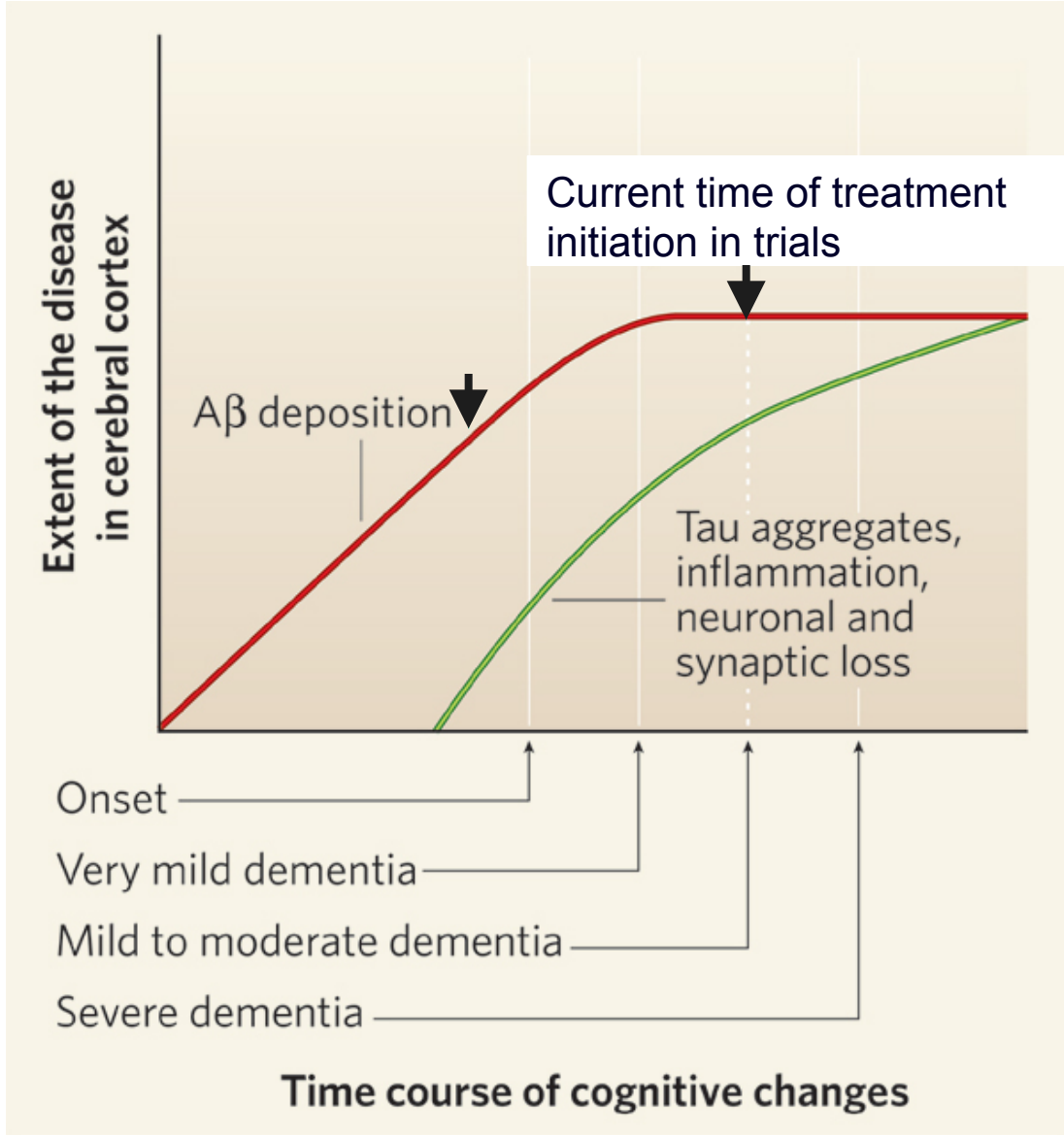


Pooled analysis represented 34% slowing in cognitive decline at 80 weeks.

Lilly
Answers That Matter.

* *Mild defined as MMSE 20-26 at Visit 1*

Time course of AD pathology and when current treatment trials are initiated by previous investigations in the field



Holtzman DM Nature 2008 454:418-20

Accumulation of Tau is a more robust predictor of symptoms than Aβ

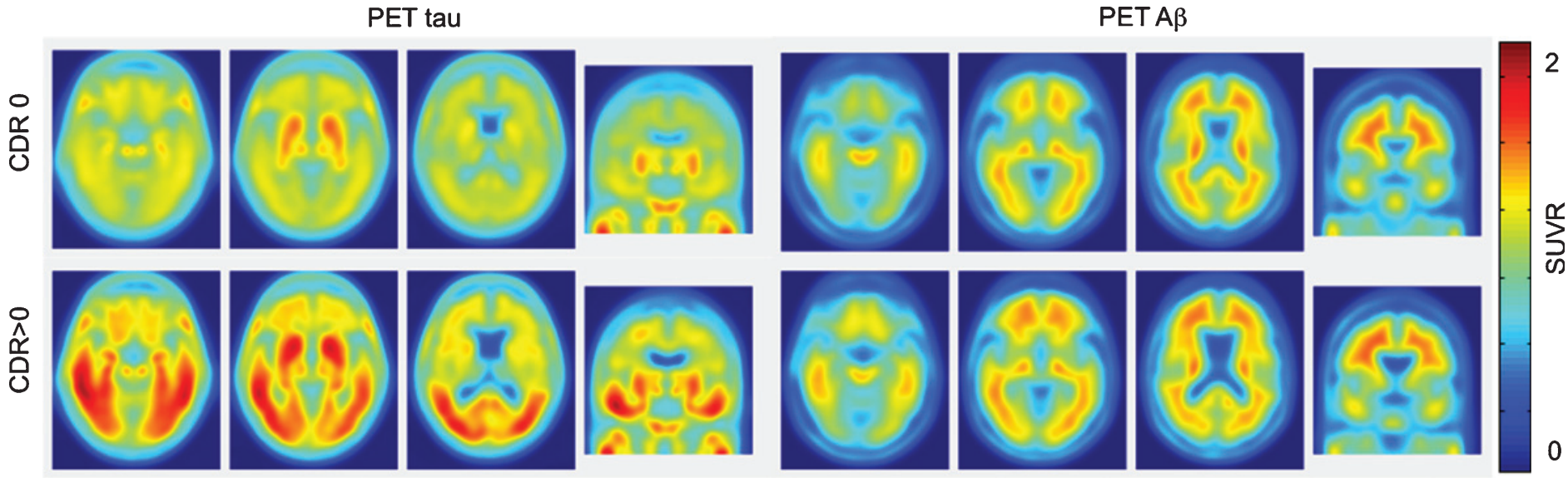


Fig. 3. Tau and Aβ PET images in cognitively healthy controls (top-CDR0) and AD patients (bottom-CDR>0). Notice that tau deposition is a better predictor of cognitive decline than Aβ deposition. Figure reprinted with permission from [73]. CDR, Clinical Dementia Rating; SUVR, standardized uptake value ratio.

Hane et al., Recent progress in ED res. 2017

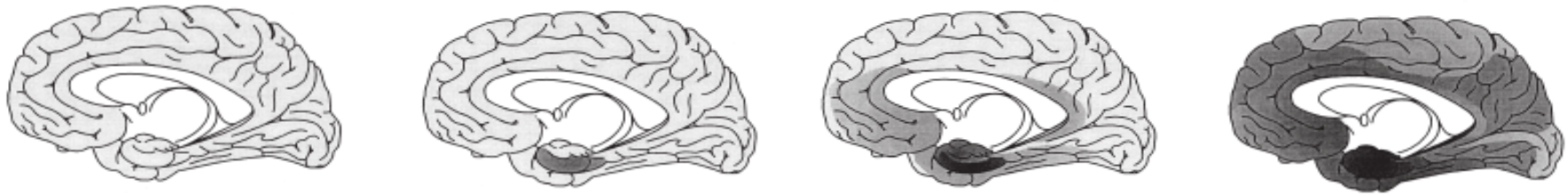
Neurodegenerative Diseases and tau: Potential contribution of protein aggregate spreading

- Proteopathies: Neurodegenerative Disorders in which there is aggregation of misfolded proteins

- Tauopathies feature tau aggregation in neurons and glia:

  - Alzheimer Disease (AD), Frontotemporal Dementia (FTD), Progressive Supranuclear palsy, (PSP), Cortico-basal degeneration (CBD)

  - Chronic Traumatic Encephalopathy (CTE)



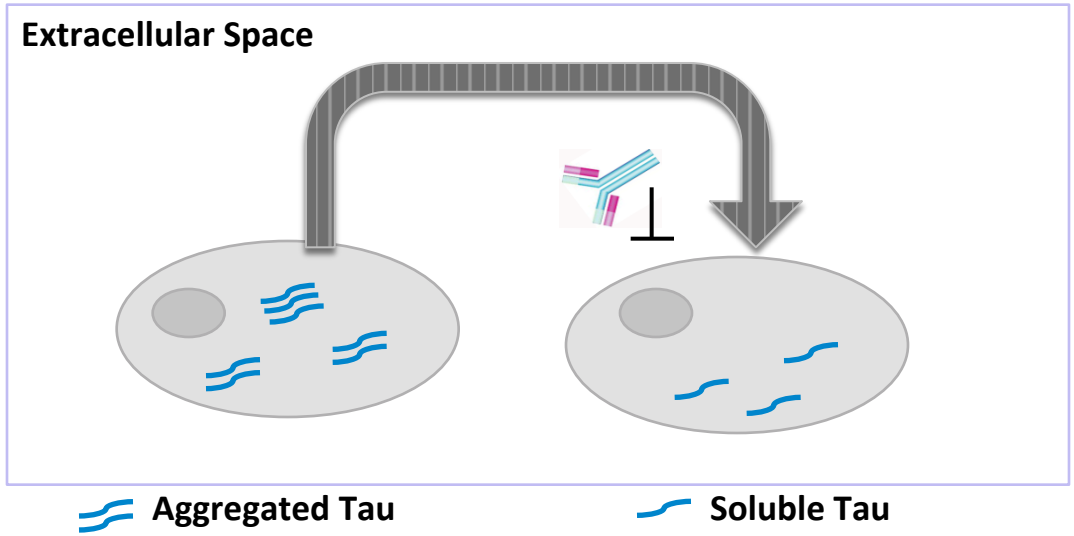
- Trans-cellular propagation of tau: a potential prion-like mechanism for disease progression

- There is increasing evidence that amyloid-β aggregates somehow drive tau propagation

- The presence of tau aggregates and accumulation strongly correlates with neurodegeneration

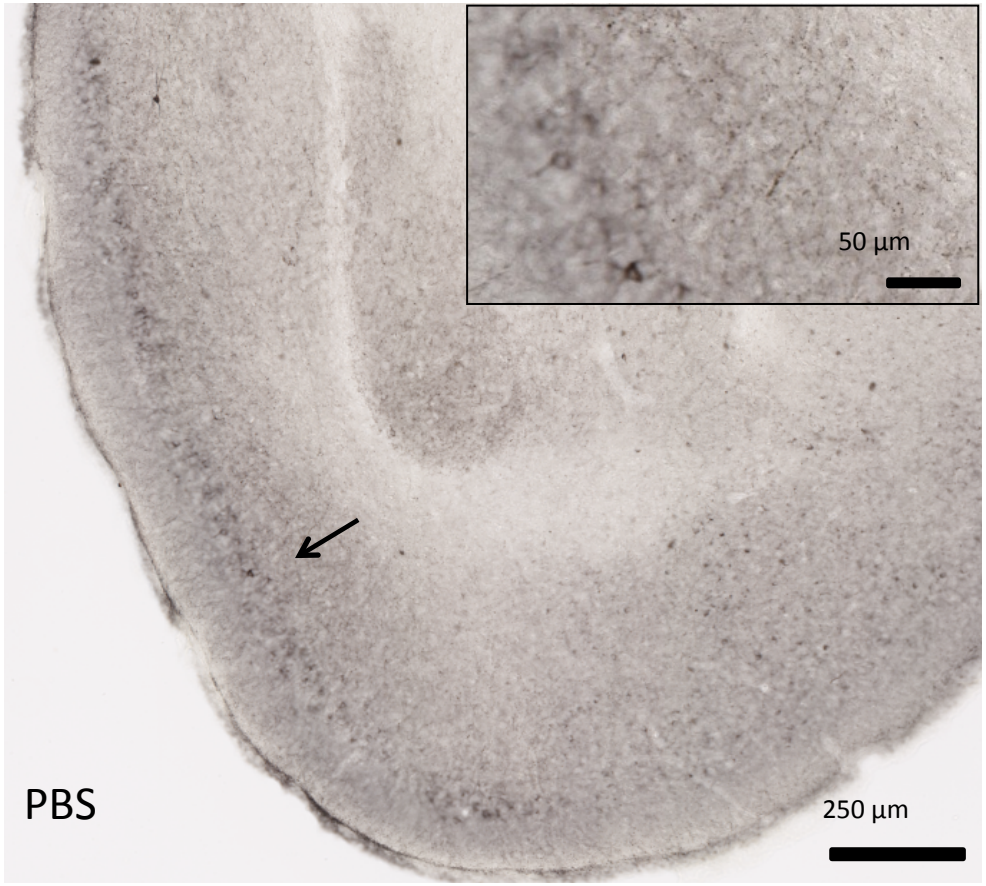
Braak and Braak Staging, 1991

Progression of Disease - Prion Mechanism

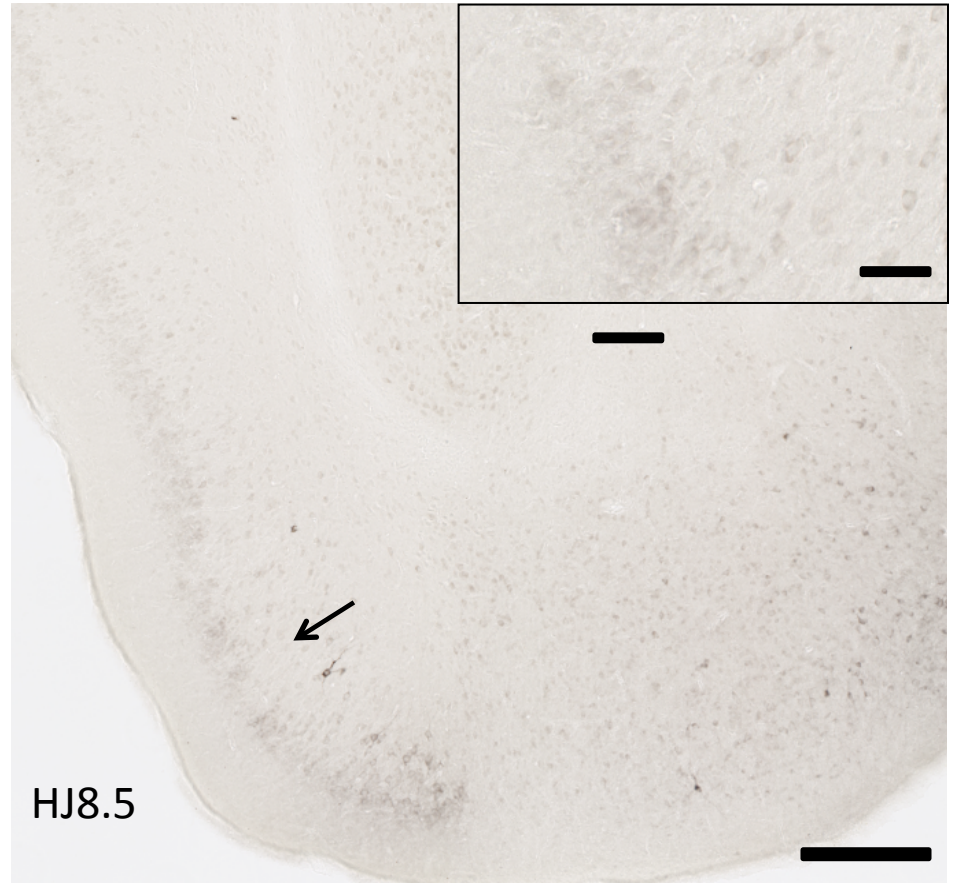


Prion diseases are transmitted by proteins (not bacteria or viruses) that act as unfolding "templates" to unfold and corrupt cellular proteins. It is thought that tau aggregates can be transferred to other neurons and cause their tau to become unfolded and form "tangles" inside neurons. A new approach to treating AD is to try to prevent the transmission of tau aggregates to other neurons with tau-binding antibodies (above and next slide) and to stop the aggregating process in the first place by blocking the "unfolded protein response" in neurons as in the following paper by the Mallucci lab.

Anti-Tau Antibody treatment reduces pathological tau



Control treatment



Anti-tau antibody treatment

Yanamandra et al. 2013 Neuron 80:402-14.

“Repurposed” drugs, Trazodone and Dibenzoylmethane have potential against AD

doi:10.1093/brain/awx074 BRAIN 2017: Page 1 of 16 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Repurposed drugs targeting eIF2α-P-mediated translational repression prevent neurodegeneration in mice

Mark Halliday,[1] Helois Radford,[1] Karlijn A. M. Zents,[2] Collin Molloy,[1] Julie A. Moreno,[1] Nicholas C. Verity,[1] Ewan Smith,[1] Catharine A. Ortori,[3] David A. Barrett,[3] Martin Bushell[1] and Giovanna R. Mallucci[1,2]

clinically relevant doses over a prolonged period of time, without systemic toxicity. Thus, in prion-diseased mice, both trazodone and dibenzoylmethane treatment restored memory deficits, abrogated development of neurological signs, prevented neurodegeneration and significantly prolonged survival. In tauopathy-frontotemporal dementia mice, both drugs were neuroprotective, rescued memory deficits and reduced hippocampal atrophy. Further, trazodone reduced p-tau burden. These compounds therefore represent potential new disease-modifying treatments for dementia. Trazodone in particular, a licensed drug, should now be tested in clinical trials in patients.

“Repurposed” drugs, Trazodone and Dibenzoylmethane have potential against AD

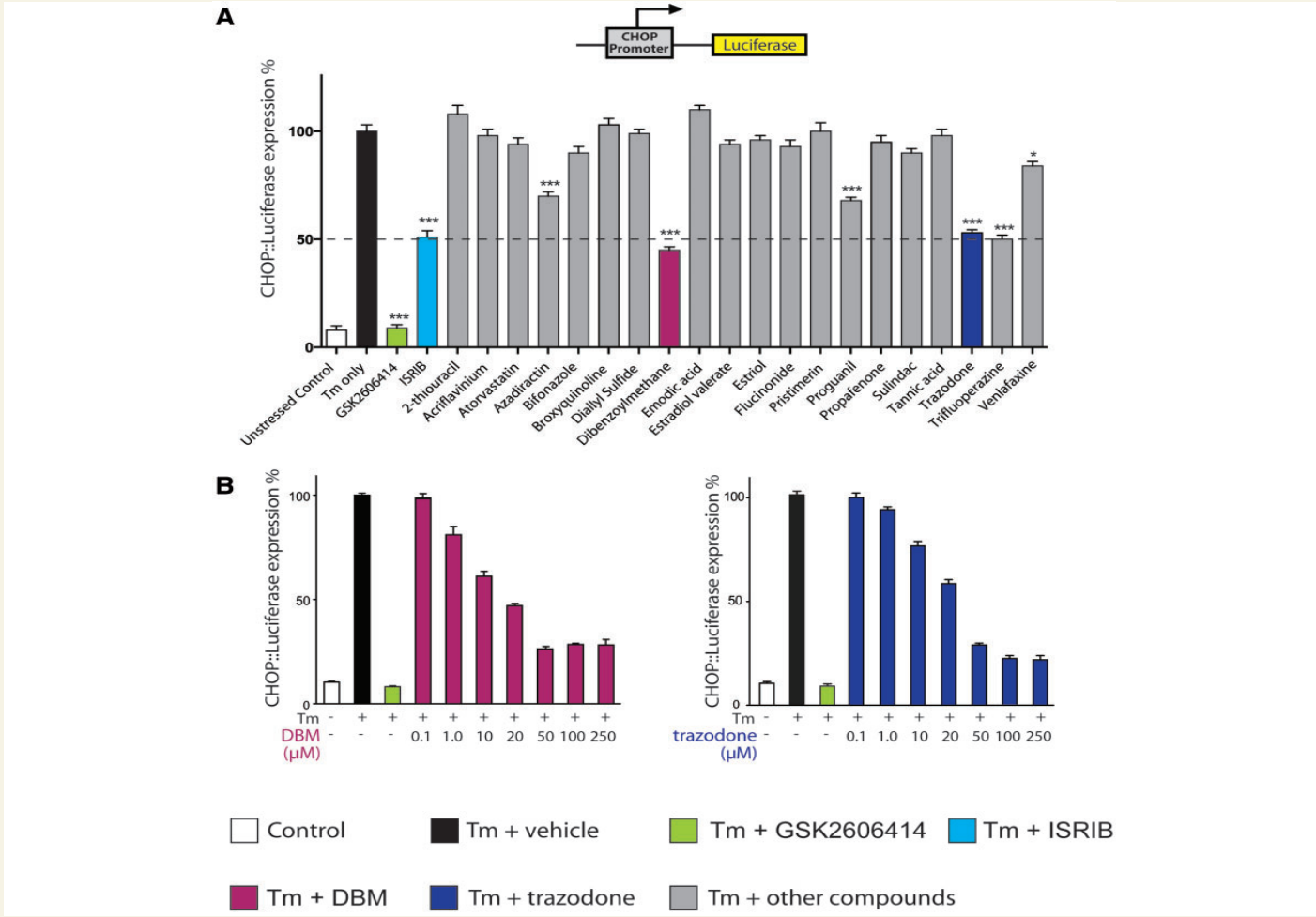
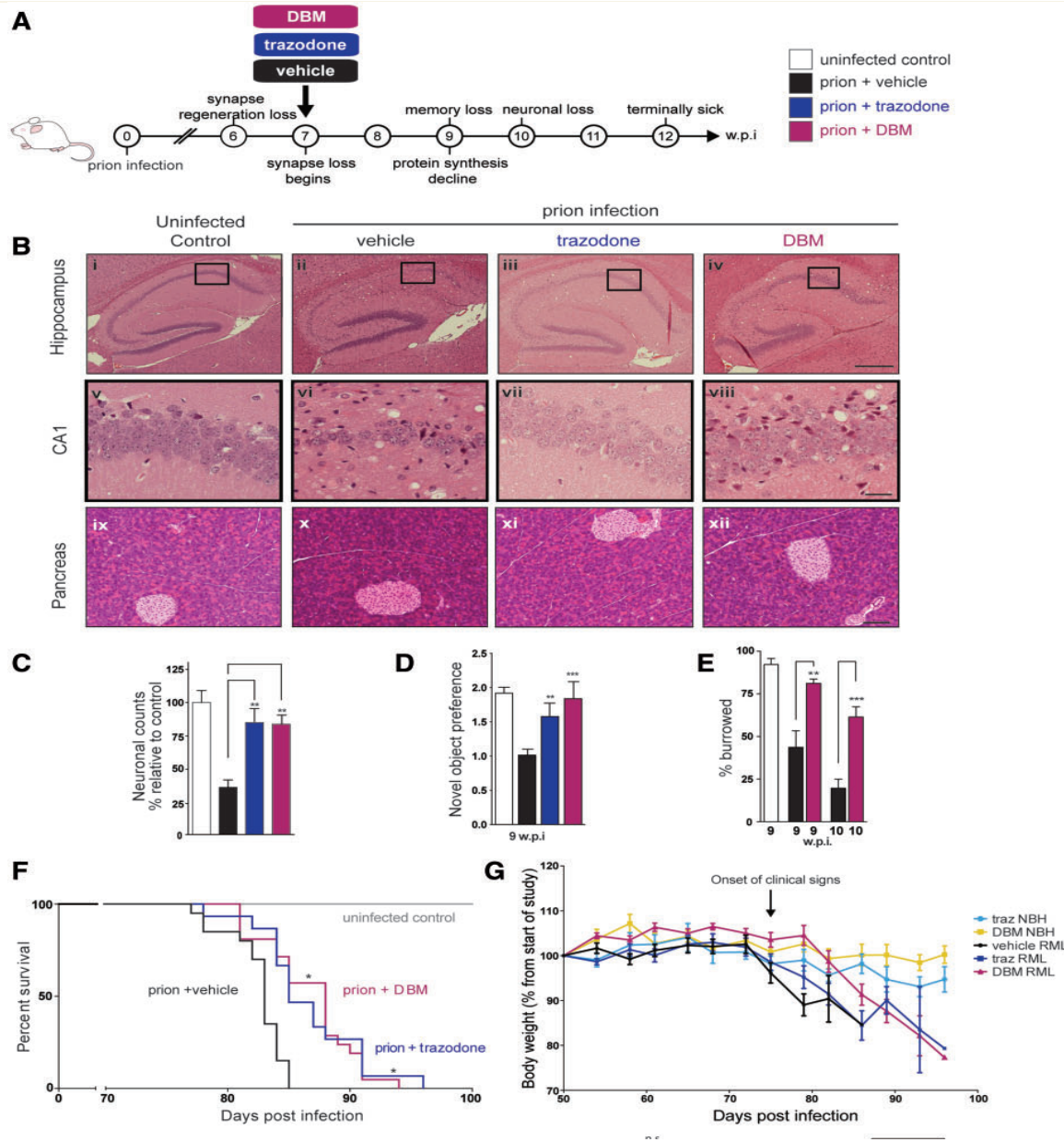


Figure 1 A screening approach uncovers two partial inhibitors of the UPR. (**A**) Luciferase expression in CHOP::luciferase cells treated with tunicamycin (Tm) (3 μg/ml) and compounds from primary screen (grey bars) (Supplementary Table 1), ISRIB (turquoise bar), GSK2606414 (green bar) or tunicamycin alone (black bar). ‘Hits’, including DBM (magenta bar) and trazodone (navy bar), repress luciferase expression to similar extent to ISRIB (dotted line). All drugs at 20 μM, except ISRIB, 1 μM; *n* = 3 and all experiments performed in triplicate. (**B**) DBM and trazodone inhibit luciferase expression in a dose-dependent manner. Concentrations of tunicamycin and GSK2606414 and *n* as in **A**.

Mallucci, Brain (2017)



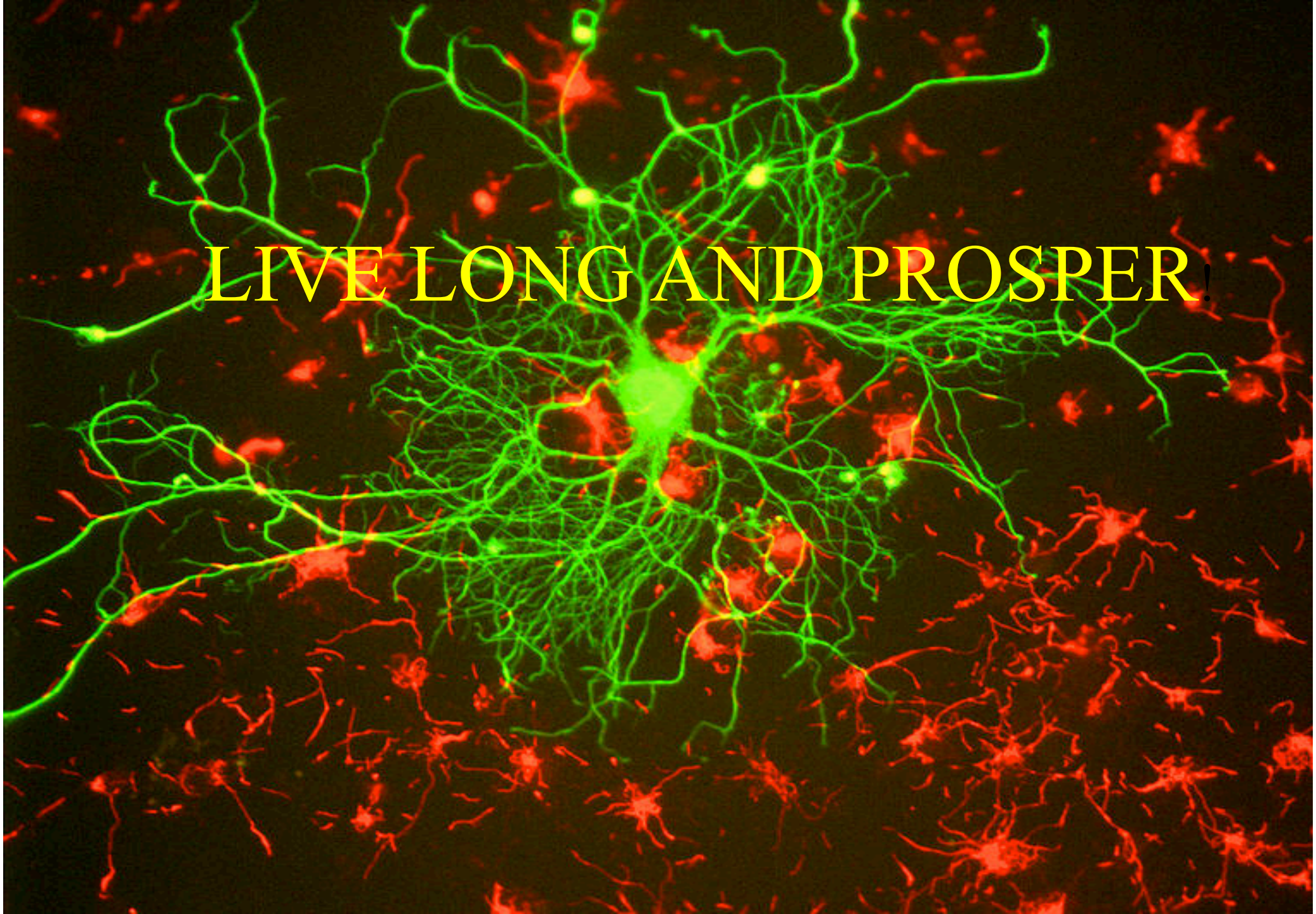
Mallucci, Brain (2017)

Summary

1. The underlying pathology of Alzheimer's disease begins ~ 15 years prior to symptom onset. It starts with amyloid-β accumulation followed by neuroinflammation and tau aggregation.

2. There are methods now available to detect amyloid-β and tau pathology and these methods can be useful to diagnose Alzheimer's disease prior to symptom onset.

3. Treatments to decrease the accumulation or remove amyloid-β are promising, especially now that trials are moving earlier in the course of disease. Treatments that decrease tau toxicity or prevent its spreading through the brain are just beginning but offer a novel way to prevent neurodegeneration.


LIVE LONG AND PROSPER!