AND NOW WHAT?
WHERE ARE WE HEADED IN AD DRUG DEVELOPMENT?

Paul Aisen December 6, 2019

Disclosures

- Grants and contracts: NIA, FNIH, Alz Assoc, Lilly, Eisai
- Consulting: Biogen, Roche, Merck, Samus, Immunobrain Checkpoint

- Initial title for this talk:

Failure after Failure: Where do we go from here?

- Oct 22, 2019: aducanumab is resurrected

- Revised title for this talk:

And now what? Where are we headed in AD drug development?

Tough couple of years: failure after failure

- Verubecestat (February, 2018)
- Atabecestat/EARLY (May, 2018)
- Lanabecestat (June, 2018)
- Crenezumab (January, 2019) *continues in API/ADAD*
- Aducanumab (March, 2019) *now continuing*
- Umibecestat/GENERATION (July, 2019)
- Elenbecestat (September, 2019)

Amyloid has been highest on our list of therapeutic targets for decades, but …

- Failure after failure
- After aducanumab, BACEi disappointments, many called for moving on, abandoning existing trials such as A4

Does amyloid deserve the attention it receives?

- So many negative trials
- But still
  - By far the strongest rationale
    - Amyloid accumulation begins the disease process
    - Amyloid accumulation is sufficient to predict dementia
    - Amyloid species are highly toxic in many model systems
    - All know genetic causes of AD are tightly linked to amyloid accumulation (APP, PS1,PS2 mutations; Down syndrome)
    - Genetic mutation that reduces amyloid generation confers protection (Icelandic APP mutation, Jonsson et al, Nature, 2012)

A major recent disappointment in the field

- BACE inhibitors carry risk of toxicity
  - Rapid onset cognitive worsening seen with multiple BACE inhibitors
  - Increase in hippocampal atrophy (non-progressive)
  - Similar to gamma secretase inhibitors?!

Even more disappointing: Aducanumab Phase 3 stopped early

- Futility analysis results announced March, 2019
- "Independent data monitoring committee advises aducanumab unlikely to meet primary endpoints"
- Very surprising result after highly encouraging Phase1b
- More scientists and companies give up on amyloid therapeutic hypothesis

But, on October 22, 2019 …

- Aducanumab resurrected
- Additional data collected after futility analysis datalock
- Full analysis hit primary endpoint, plus secondary outcomes, in one Phase 3 trial
- Second trial negative, but supportive data from those with adequate exposure
- Biogen will submit data to FDA for consideration of approval in early 2020

How could this happen?

- Clinical and cognitive data are noisy
- Futility analyses carry risk, loss of statistical power due to “early” decision making
- In this case, dose was increased during trial increasing the risk of misleading interim analysis

- Oct 22 announcement was a big turnaround for the amyloid hypothesis

So where does the amyloid hypothesis stand?

- Previous supportive findings
  - Solanezumab in Expedition: modest (15-20%) slowing of decline in mild dementia across 3 trials
  - Aducanumab Phase 1b: amyloid reduction and slowing of decline
  - BAN2401 Phase 2: amyloid reduction and slowing of decline
- Aducanumab Emerge trial
  - 22% slowing of clinical decline; supportive cognitive and biomarker data; effect would likely have been larger with completed study, highest dose throughout?
  - What about Engage? (supportive data in those with highest exposure)

Anti-amyloid trials

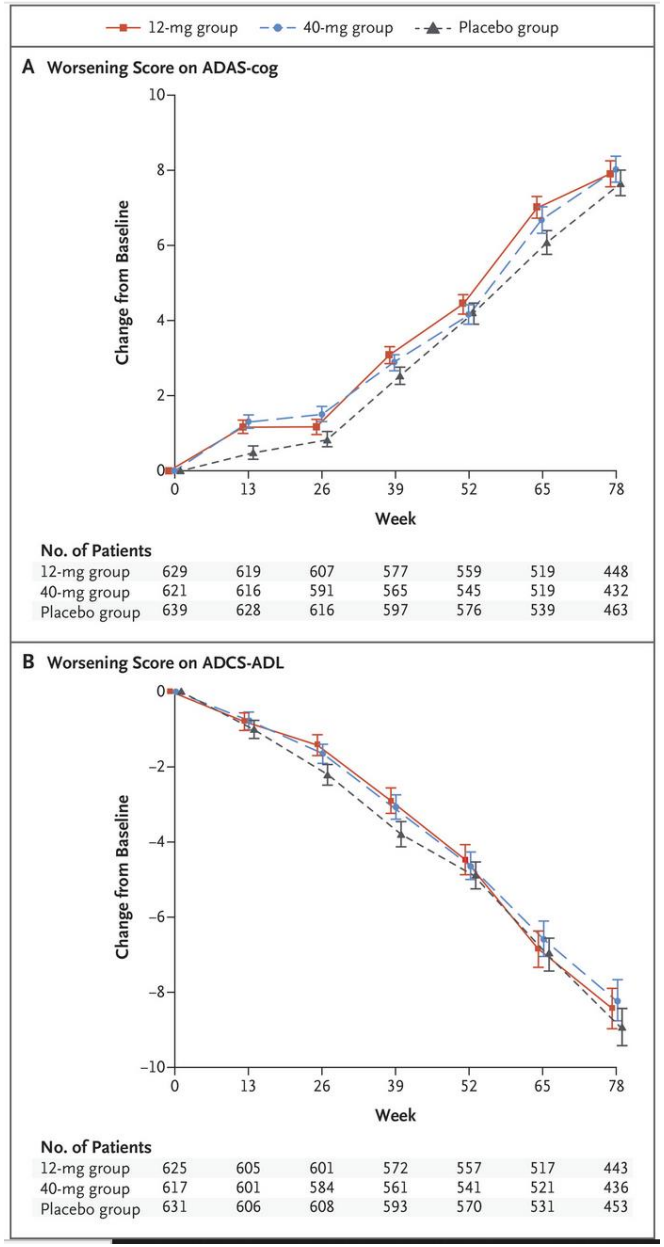
- Need highest tolerable dose
  - ARIA generally manageable
  - Doses of antibodies has been rising (aducanumab, ganterumab, solanezumab)
- Will earlier intervention (eg, in asymptomatic, amyloid positive individuals) yield bigger gains?
  - Seems very likely, though no data yet
- Combination approaches: target both amyloid and tau?
  - Too many uncertainties about anti-tau strategies?
  - Is targeting amyloid sufficient early on?

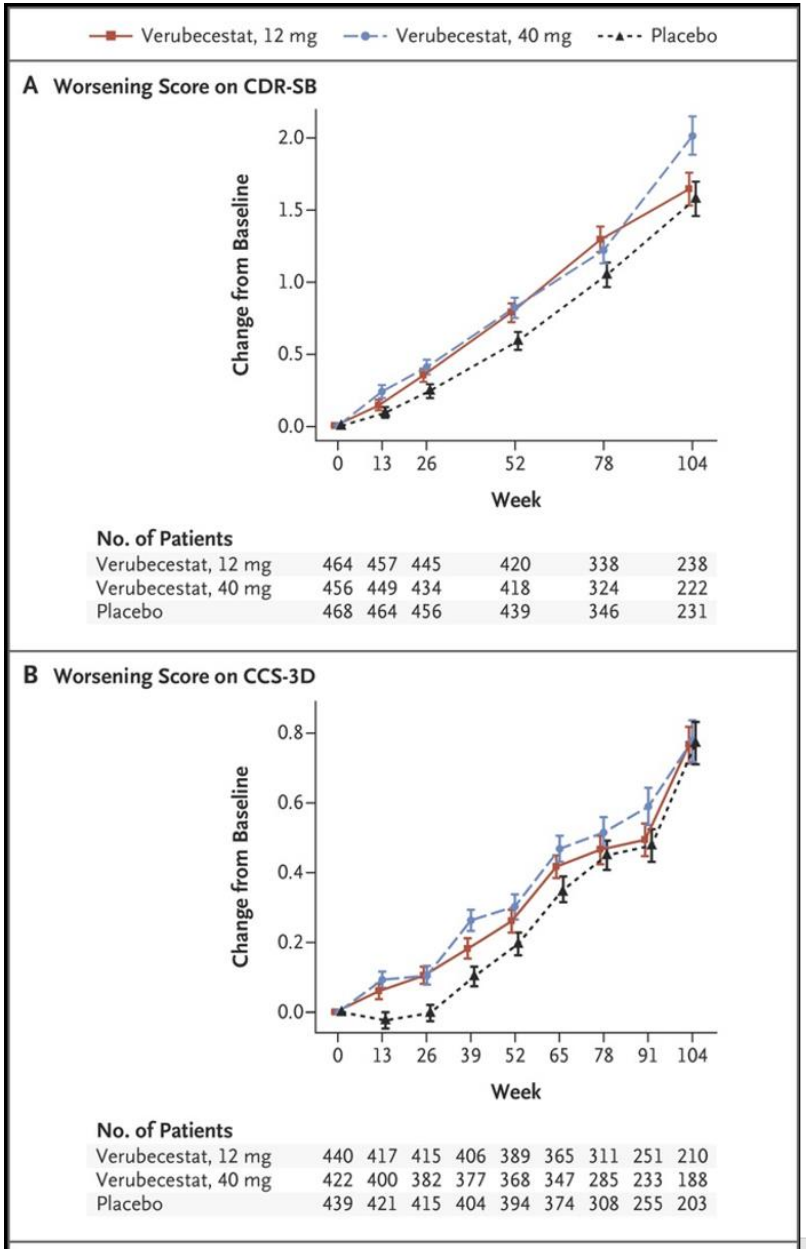
What about BACE inhibitiors?

BACE inhibition: is the cognitive worsening manageable?

- "Symptomatic issue," mild and non-progressive: verubecestat
  - What about MRI?
- Dose-related: atabecestat
- Reversible: atabecestat

Verubecestat in AD and prodromal AD

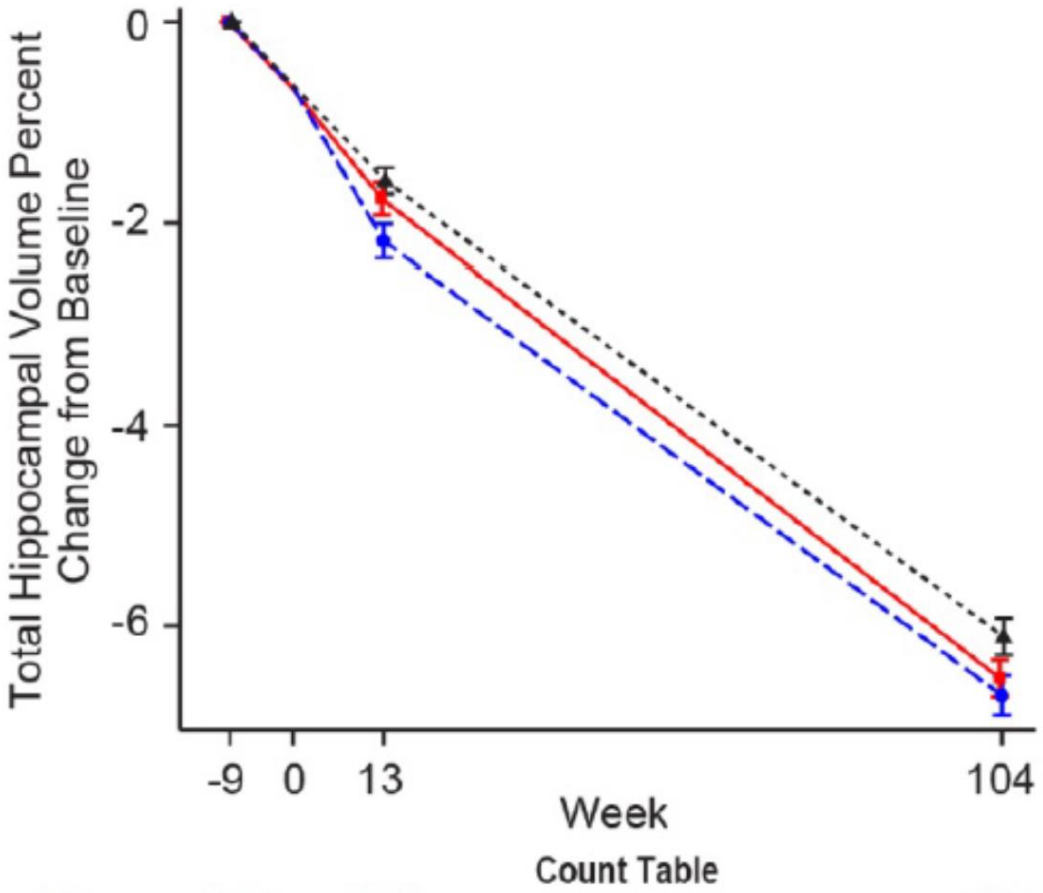




Egan et al, NEJM, 2018, 2019

Verubecestat increase in hippocampal atrophy in prodromal AD

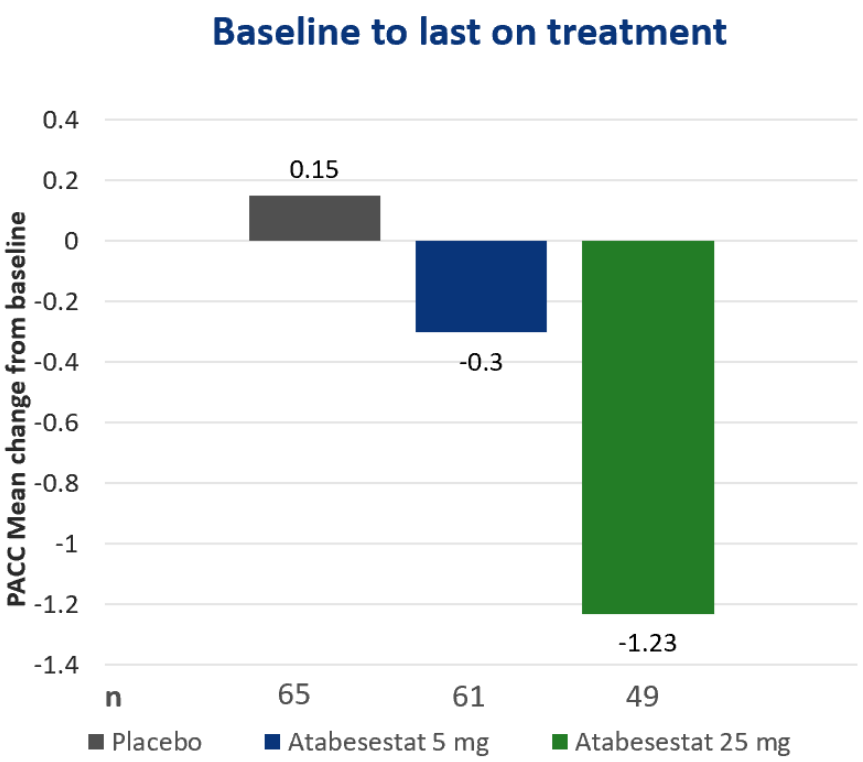
Figure S7. Model-based mean (SE) change from baseline in MRI hippocampal volume

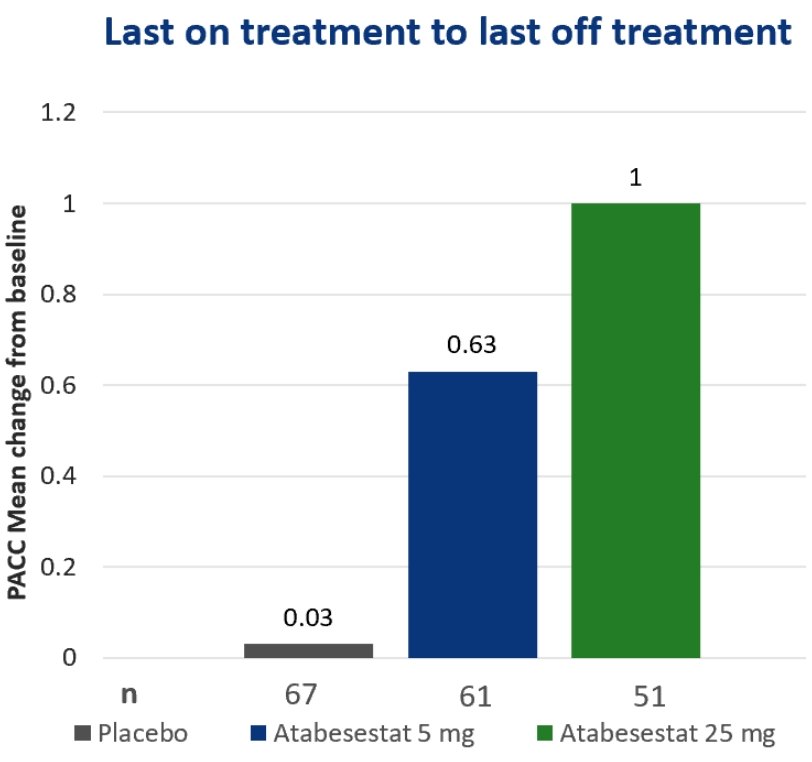


Count Table

12 mg	168	70	148
40 mg	181	70	150
Placebo	191	77	164

EARLY: cognitive effects of atabecestat





These data suggests that adverse cognitive effects may be dose-related and reversible

We should not give up on BACE inhibition

- The amyloid hypothesis remains *by far* the most compelling basis for disease-modification therapy
- BACE inhibition remains a powerful approach to primary prevention and very early treatment
- Modest, reversible cognitive toxicity can readily be monitored during a trial
- Modest inhibition (25-50%) should be studied in appropriate populations
- We must closely evaluate the coming datasets from elenbecestat and umibecestat trials
- We must continue to pursue basic mechanistic research
- It will not be easy to move forward with BACE inhibitors, but nothing that we do is easy

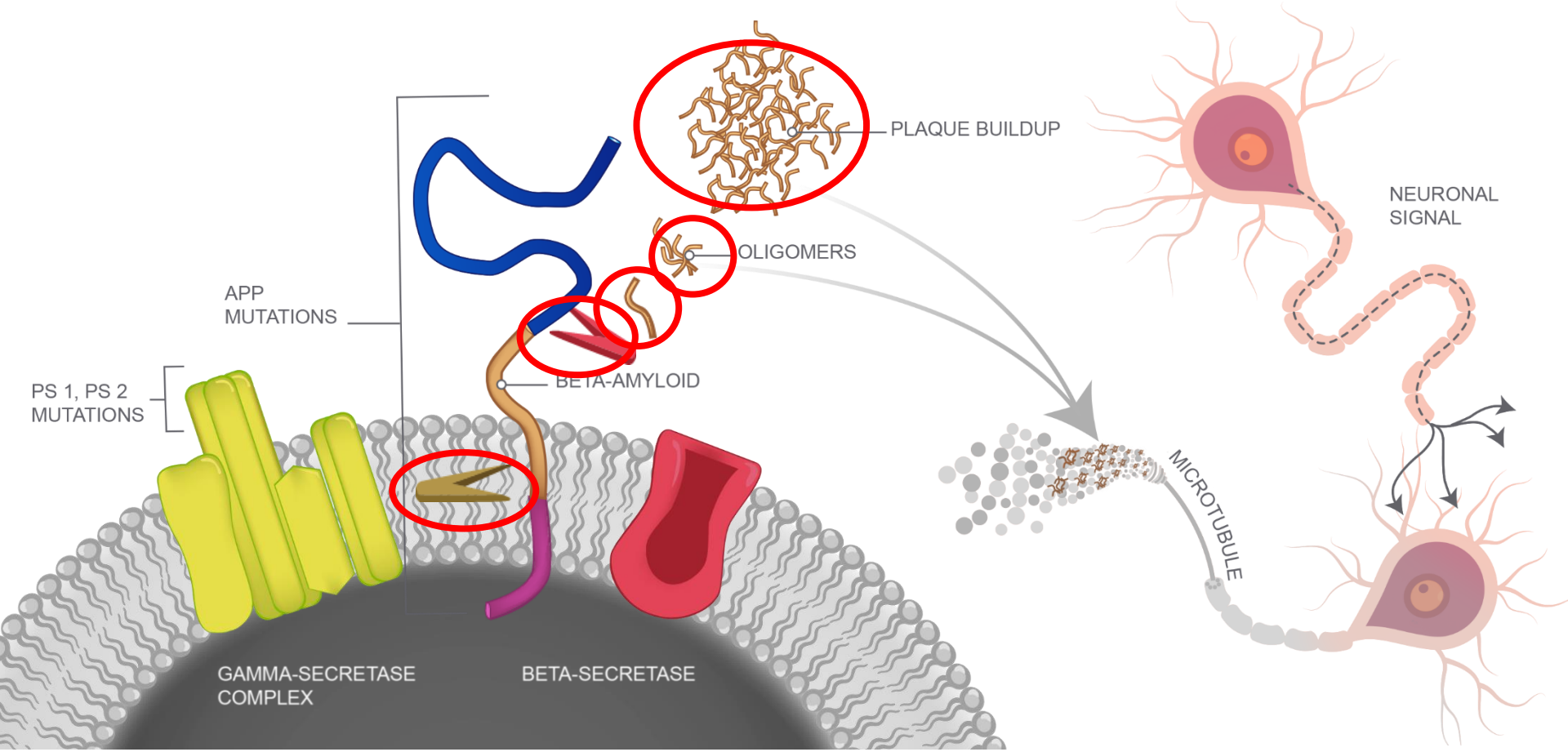
Costly errors?

- Over-generalizing trial failures
  - Each failure is very specific to trial conditions
- Intolerance to safety challenges
  - Giving up too soon (bapineuzumab?)
  - Keeping doses too low: ARIA
  - Or too high: BACE inhibitors
- Risk of interim analyses (aducanumab is just one example)

Good news for testing amyloid hypothesis

- We can measure brain amyloid longitudinally in humans
- Blood amyloid peptide ratios reflect brain amyloid load
- Brain amyloid can be removed
- Amyloid peptide generation can be inhibited (?)

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



What's coming in anti-amyloid studies?

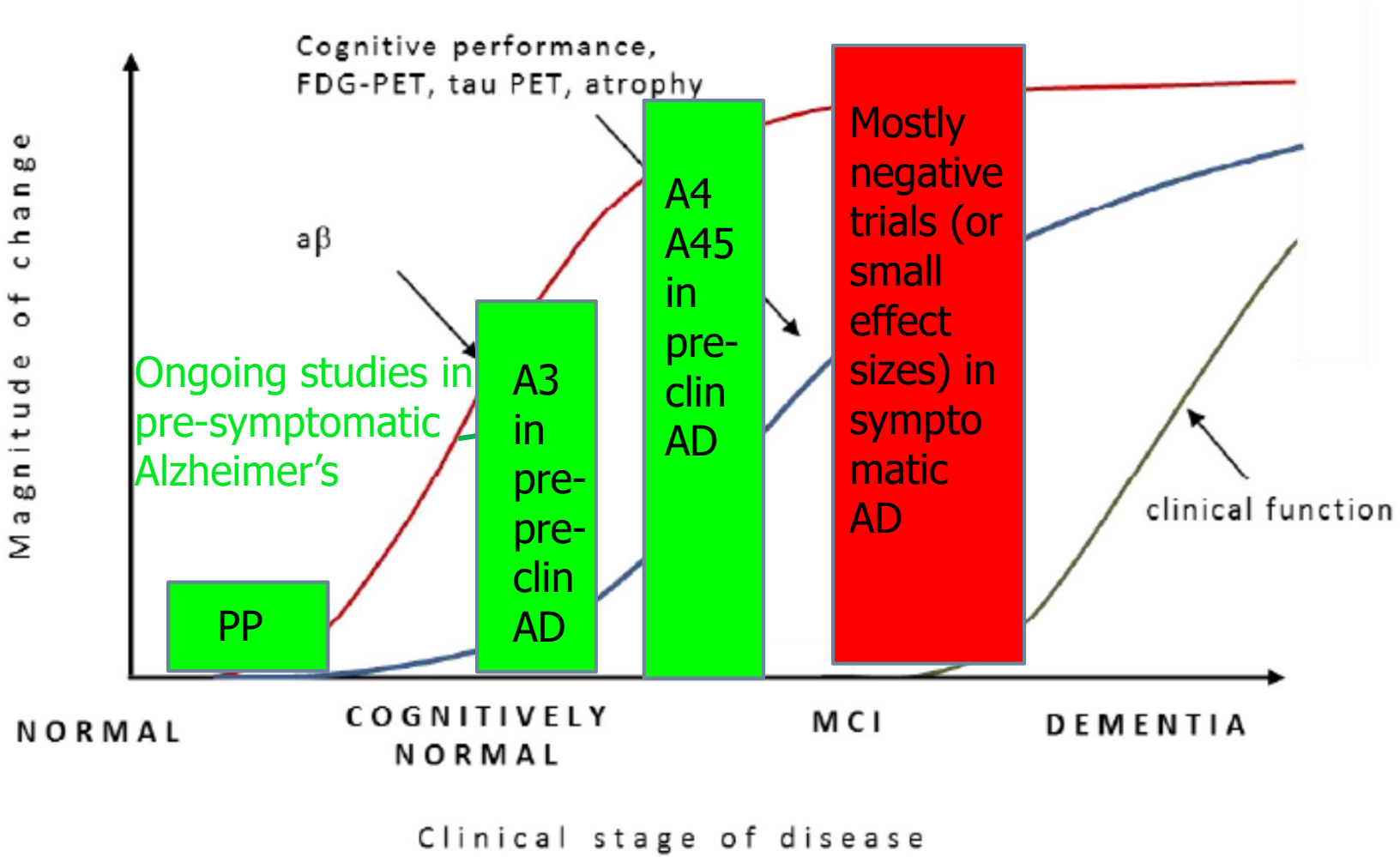
- Aducanumab submission to FDA
- DIAN: gantenrumab, solanezumab in ADAD
- API: crenezumab in ADAD, CAD106 in E4 homozygotes
- BAN2401(lecanemab) in early AD
- Gantenerumab in early AD
- Donanemab in symptomatic, amyloid and tau PET positive
- A4, A45, A3
- Many other early phase studies

A bit more on the A-platform trials

- A4, as compared to the marginally positive Expedition trials of solanezumab in mild AD dementia
  - Dose increased to 4x that of Expedition
  - Duration 3x that of Expedition
  - A decade earlier stage of AD
- A45: BAN2401 (lecanemab) in preclinical AD
- A3: BAN2401 (lecanemab) in pre-preclinical AD

- Optimism growing

When should we target amyloid?



Other approaches

- Tau
- Microglia
- APOE
- Target misfolded proteins
- Neuroprotection
- Anti-infectives?
- Anti-aging?
- Other: exercise, cognitive, multidomain, target deficiencies (DHA, testosterone)

Challenges with tau

- Absence of genetic support
- Can immunotherapy work against intracellular processes (or can it work to reduce spread)?
- What is the right target/epitope?

Microglia

- TREM2
- Role in plaque clearance

But:

- Complexity of microglial roles is challenging
- Need, specific target, plausible drug candidates
- No good biomarkers to aid development

APOE

- By far, the most important genetic risk factor for sporadic AD
- APOE4 increases risk, E2 decreases risk
- Intriguing case report (Arboleda-Velasquez et al, Nature Medicine, 04 November 2019)
  - Homozygous APOE3 mutation (Christchurch) protects against dementia despite huge amyloid load in a PS1 mutation carrier

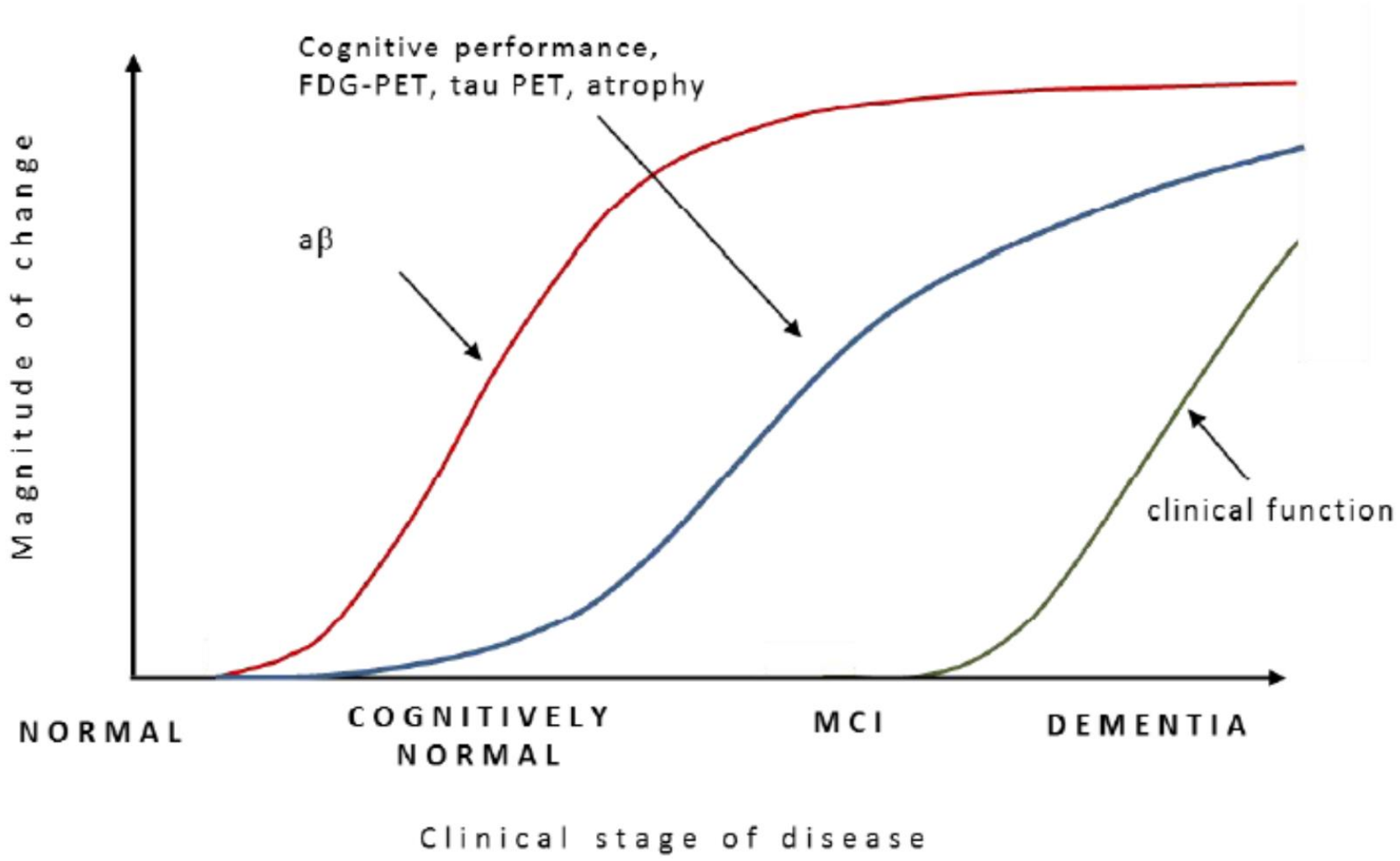
Targeting proteinopathy

- siRNA
- Epigenetic modulation
- Epichaperome
- Immunotherapy?

Essential to continue to test many other hypotheses until we have success

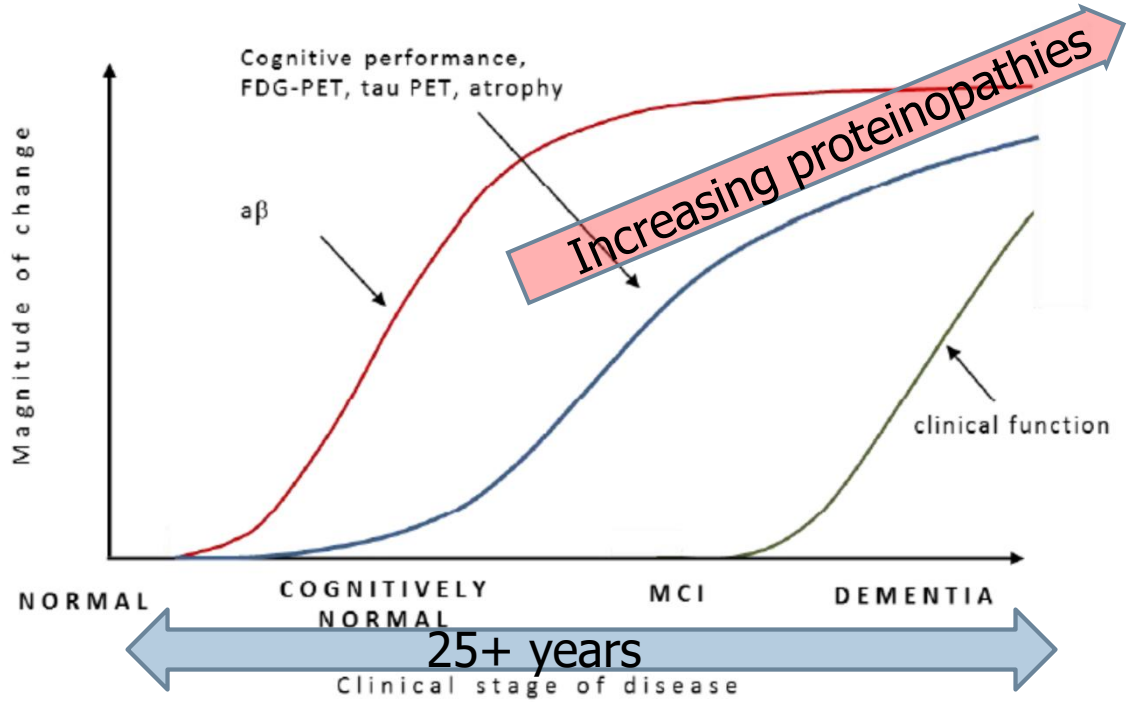
- Particularly in late stage disease, which is very complicated
  - Alpha synuclein
  - TDP-43
  - Vascular disease
  - …
- Must also test ways to increase brain resilience across the lifespan

Alzheimer's disease

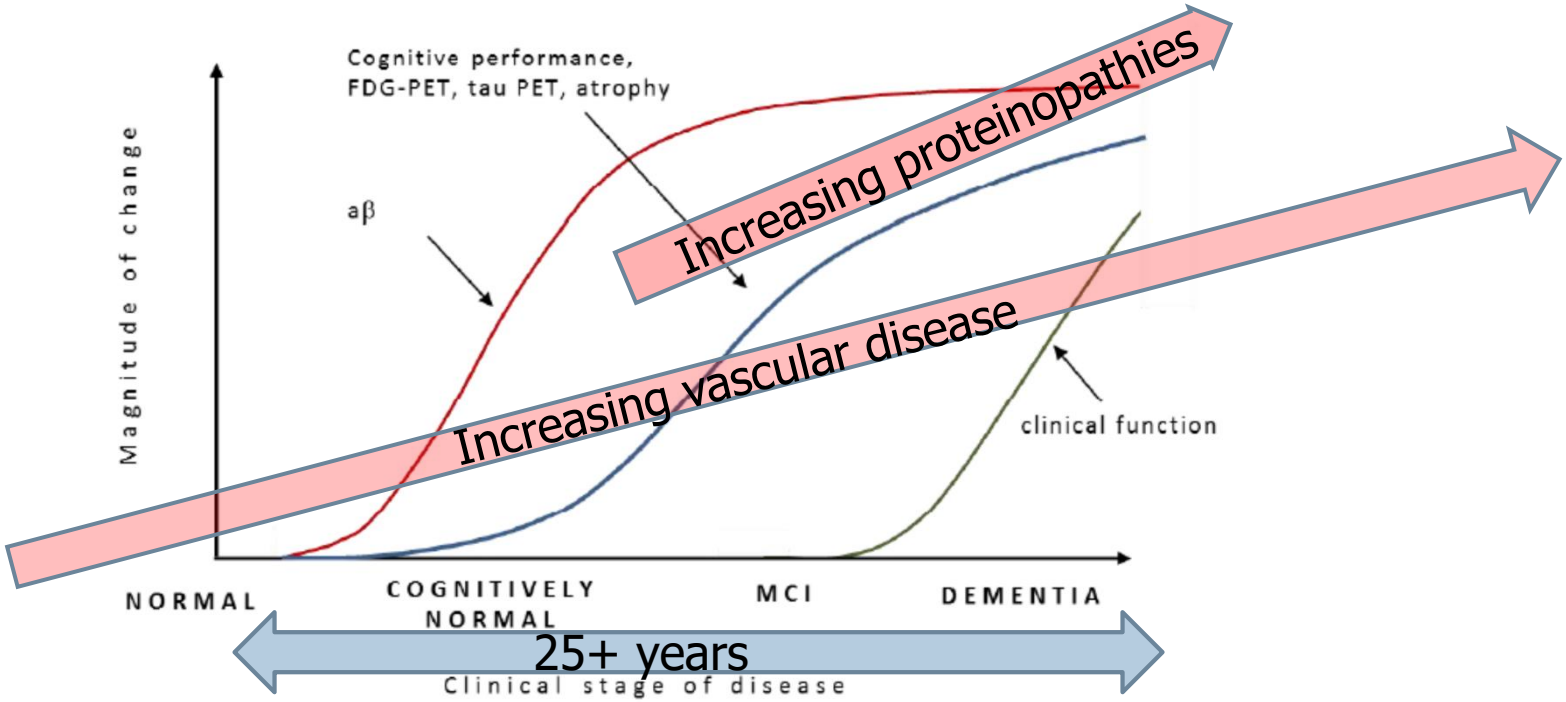


25+ years

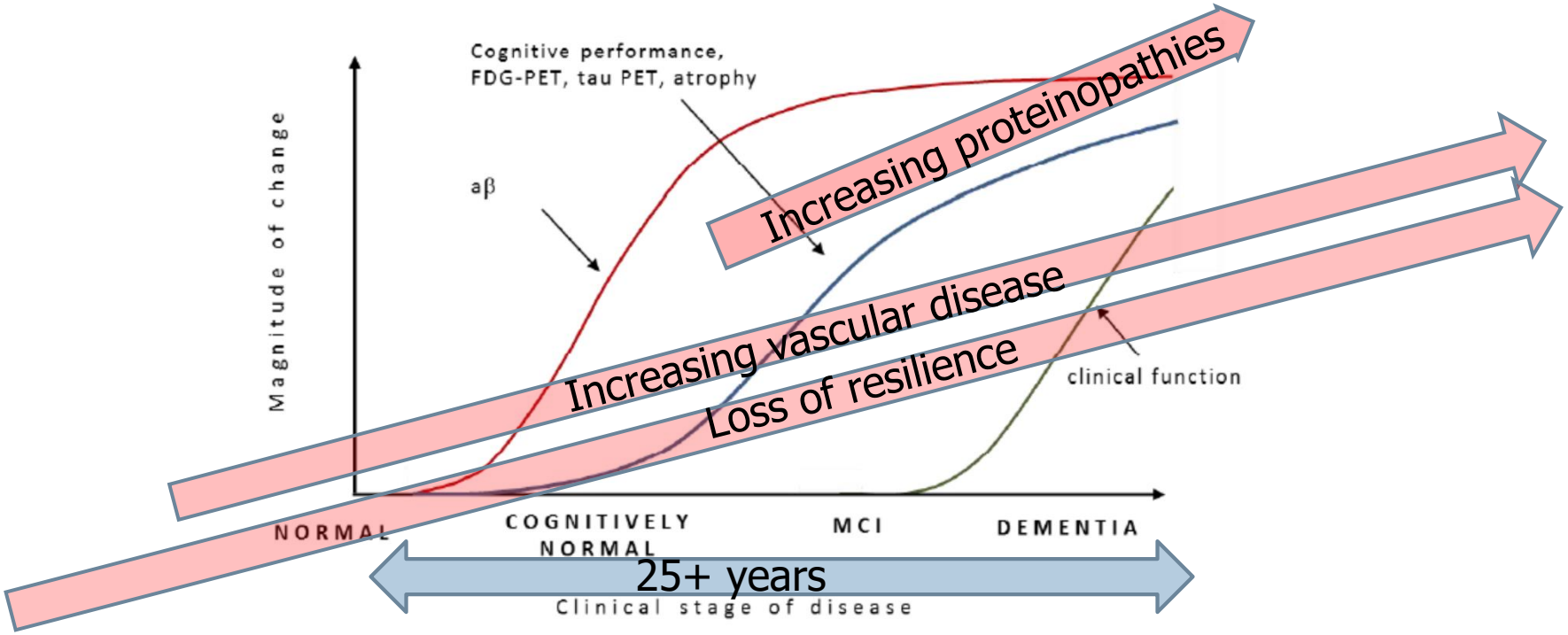
AD and its complications



AD and its complications



AD and its complications



Prevention and treatment of AD

- Lifelong: promote brain resilience
  - Diet, physical exercise, cognitive exercise, social engagement
- Starting in middle age:
  - Attention to vascular risk (diabetes, hypertension, cholesterol)
  - Monitor plasma abeta ratios for evidence of dysregulation (low dose secretase inhibition as needed)
- If amyloid accumulates in brain:
  - Reduction with amyloid lowering immunotherapy
  - Maintenance with immunotherapy or low dose BACEi
  - Anti-proteinopathy measures (against tau, synuclein, TDP-43)

Lessons from an eventful year

- Be wary of futility analyses and other statistical misadventures
- *The amyloid hypothesis will yield effective therapies*
  - Adverse effects of anti-amyloid therapies, including ARIA and cognitive worsening, may be manageable
- We must continue to pursue other strategies
- We can now take advantage of advances in blood-based biomarkers, even envision primary prevention of AD
- Collaboration and data sharing more important than ever

Many thanks to:

- Wonderful colleagues at ATRI, ACTC, TRC-PAD, ADNI, LEADS, MIND …
- Reisa Sperling, Ron Petersen, Jeff Cummings,

  Keith Johnson, Mike Weiner, Bruno Vellas …
- Lilly, Janssen, Eisai, Biogen, Merck, Roche, Novartis …
- NIA, FNIH, Alzheimer's Association …
- Generous involvement of study participants and partners