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THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Is Amyloid a Good AD Drug Target?

James Hendrix, Ph.D.

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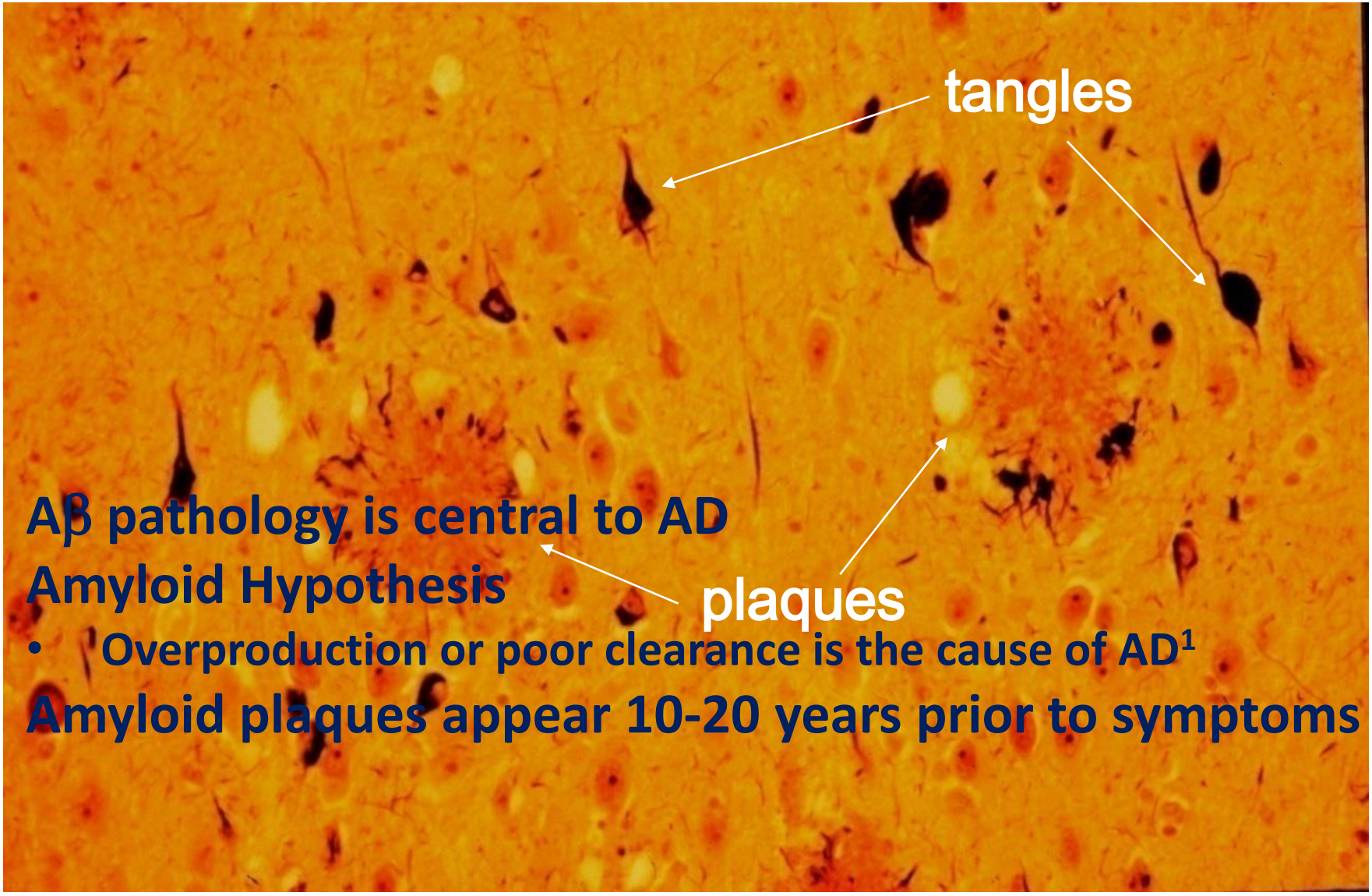
The Role of Amyloid in AD



Aβ pathology is central to AD

Amyloid Hypothesis

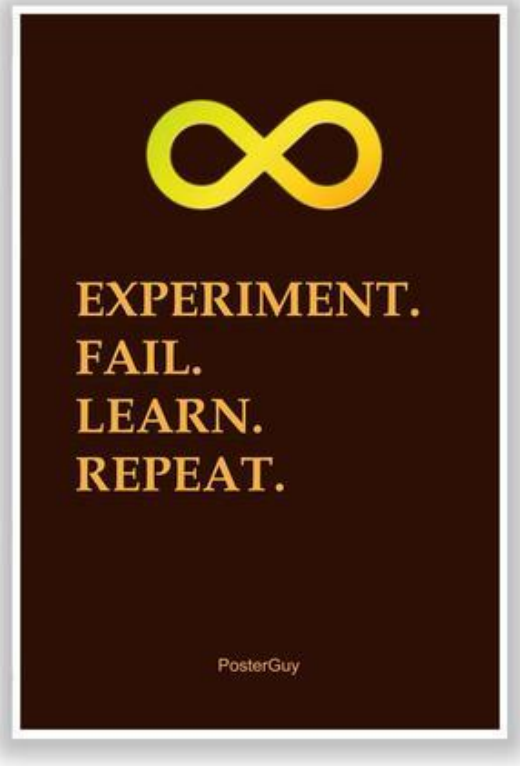
- **Overproduction or poor clearance is the cause of AD[1]**

Amyloid plaques appear 10-20 years prior to symptoms

[1] Selkoe, Hardy [2016], Hardy, Selkoe [2002] and Selkoe [1991]

Possible reasons amyloid trials fail

- **The amyloid hypothesis is wrong.**
- **The mechanism of action to reduce or remove amyloid is flawed**
- **The candidates were ineffective due to incorrect properties**
  - Potency
  - Target Engagement
  - BBB penetration and…
- **Flawed trial design**
  - Stage of disease – too late in progression
  - Lack of Biomarker Enrichment: Participants in the trial without high levels of Aβ.



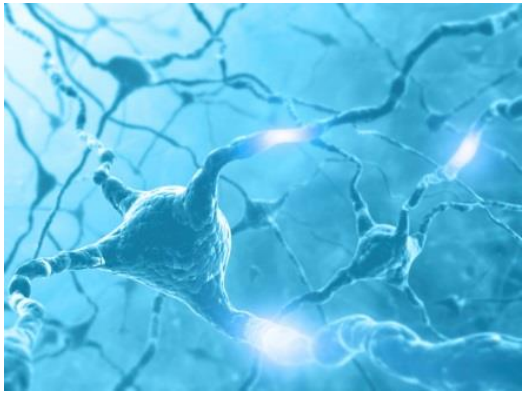
What have we learned from trials: Immunotherapy

- **Bapineuzumab**
  - Targeted Aβ Oligomers
  - Possible issues: staging of disease, dose selection, safety issues (ARIA), target engagement, minimal use of biomarkers
- **Solanezumab**
  - Targeting soluble Aβ peptides
  - Possible issues: staging of disease, dose selection, target engagement and / or BBB penetration
- **Gantenerumab, Crenezumab & Aducanumab**
  - Targeting alternative forms of aggregated Aβ, including oligomeric and fibrillar species and insoluble amyloid plaques
  - Improved BBB penetration
  - The use of biomarkers for trial enrichment
- **Isoform of Aβ (soluble, oligomeric, fibrillary or aggregated plaques)?**[2]
- **ARIA**
  - A sign of target engagement?
  - A therapeutic window issue?

[2]Murphy, NEJM [2018].

What have we learned from trials: BACE Inhibitors

- **Verbacestat**
  - Not effective in Mild to Moderate[3] or prodromal AD[4]
- **Lanabecestat**
  - Phase 3: Mild and Early AD
- **Elenbecestat**
  - Phase 3: Early AD
- **Are these still too late in disease progression?**
  - Does BACE need to work with clearance mechanisms (i.e. microglia)?[5]



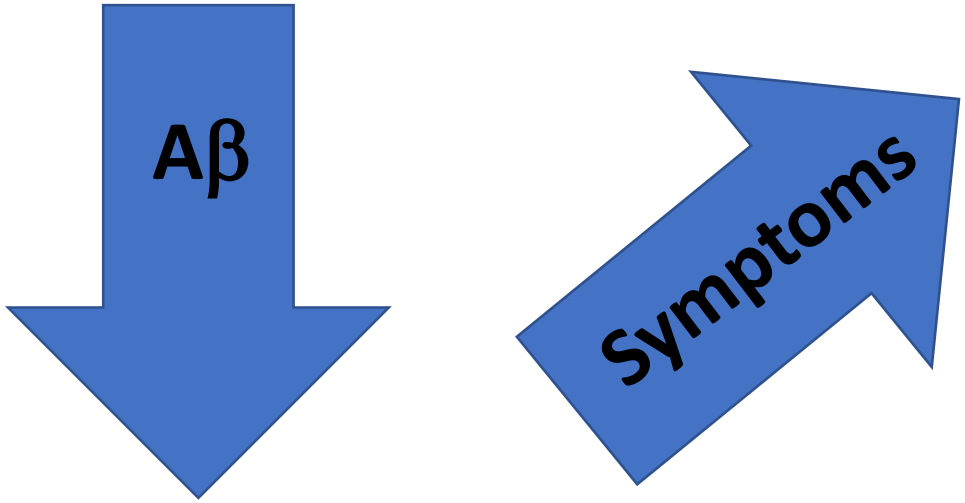
[3]https://www.alzforum.org/news/research-news/merck-pulls-plug-phase-23-bace-inhibitor-trial

[4]Merck Press Release, February 13, 2018

[5]Hu et al., 2018. *J. Exp. Med.* http://jem.rupress.org/cgi/doi/10.1084/jem.20171831?PR

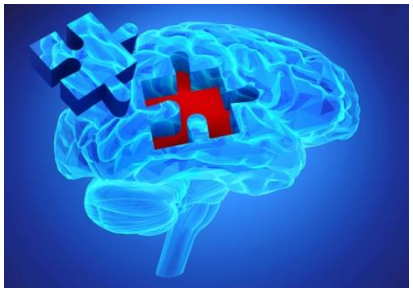
Have we answered the Key Questions Regarding Amyloid Therapies?

- Have we seen a candidate that has been shown to lower Aβ levels in the brain and provide no treatment of cognitive or behavioral symptoms?



- Does the failure of the first anti-amyloid approaches mean that all anti-amyloid approaches will fail?

Strategies for Success?



- **Secondary Prevention?**
  - Since amyloid appears before symptoms, perhaps attacking amyloid with a secondary prevention strategy is warranted.
  - A4 and DIAN could answer this if their drug candidates move the biomarkers
- **Combination Approaches?**
  - Aβ Clearance (immunotherapy) + Aβ production (BACE)
  - Aβ Clearance or Production + Anti-Tau mechanisms
  - Aβ Clearance or Production + Neuroinflammatory Treatments
- **Novel Aβ related targets?**
  - New approaches to activate Aβ autophagy
  - Targets upstream of Aβ processing (i.e. upstream of BACE)
  - Impact of other processes on Aβ
    - Inflammation / Immunity
    - Oxidative Stress
    - Etc.

What will the future hold?

If God had intended man to fly, he would have given him wings.

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