Is Amyloid a Good AD Drug Target?

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The Role of Amyloid in 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 A\(\beta\) Oligomers
  - Possible issues: staging of disease, dose selection, safety issues (ARIA), target engagement, minimal use of biomarkers

- **Solanezumab**
  - Targeting soluble A\(\beta\) peptides
  - Possible issues: staging of disease, dose selection, target engagement and/or BBB penetration

- **Gantenerumab, Crenezumab & Aducanumab**
  - Targeting alternative forms of aggregated A\(\beta\), including oligomeric and fibrillar species and insoluble amyloid plaques
  - Improved BBB penetration
  - The use of biomarkers for trial enrichment

- **Isoform of A\(\beta\) (soluble, oligomeric, fibrillar or aggregated plaques)?**

- **ARIA**
  - A sign of target engagement?
  - A therapeutic window issue?

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\[^2\]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)?\(^5\)

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\(^4\)Merck Press Release, February 13, 2018

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?
  • $A\beta$ Clearance (immunotherapy) + $A\beta$ production (BACE)
  • $A\beta$ Clearance or Production + Anti-Tau mechanisms
  • $A\beta$ Clearance or Production + Neuroinflammatory Treatments

• Novel $A\beta$ related targets?
  • New approaches to activate $A\beta$ autophagy
  • Targets upstream of $A\beta$ processing (i.e. upstream of BACE)
  • Impact of other processes on $A\beta$
    • 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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