Is it time to move past the amyloid hypothesis?

An affirmative response

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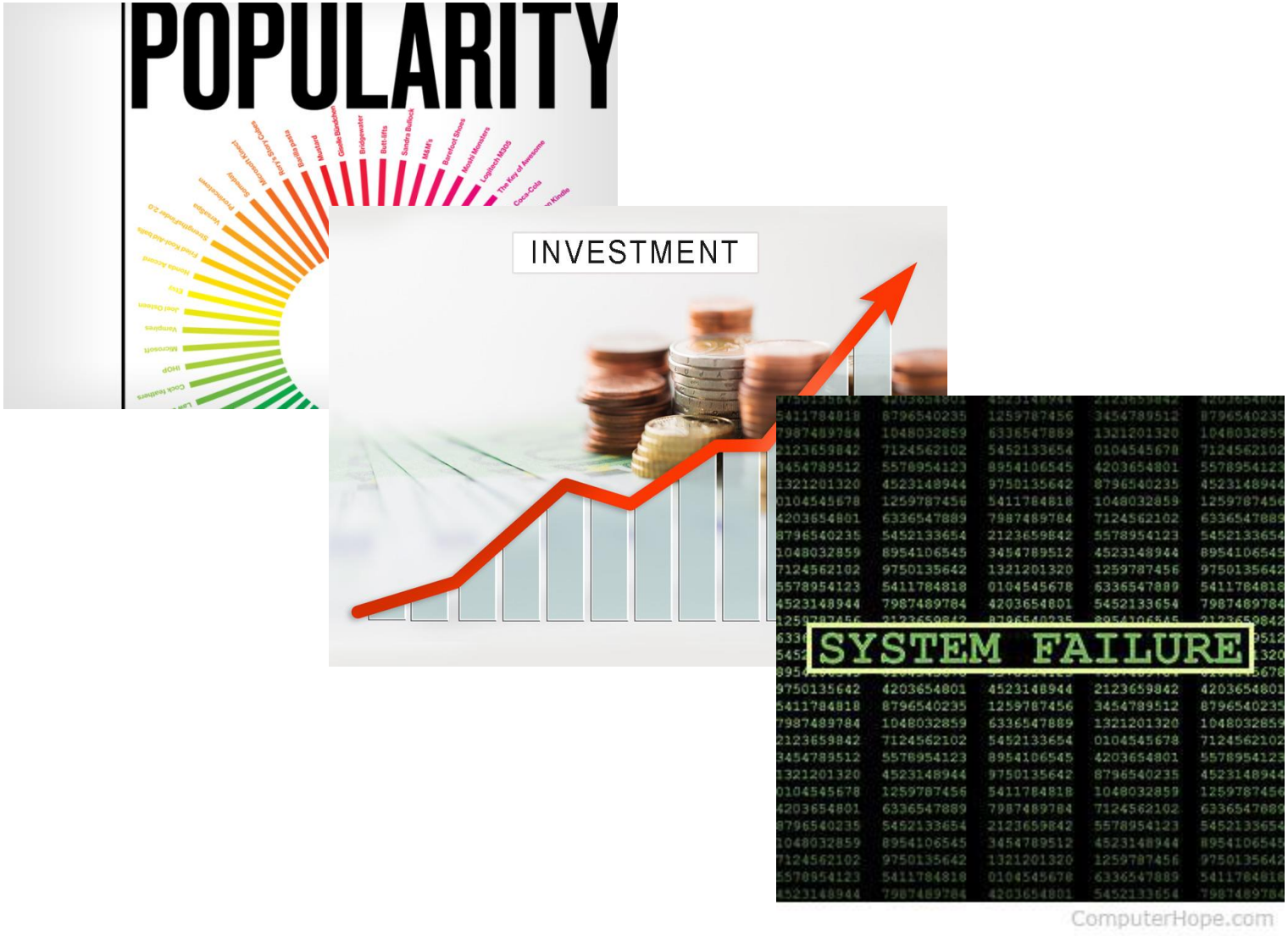
Disclosure

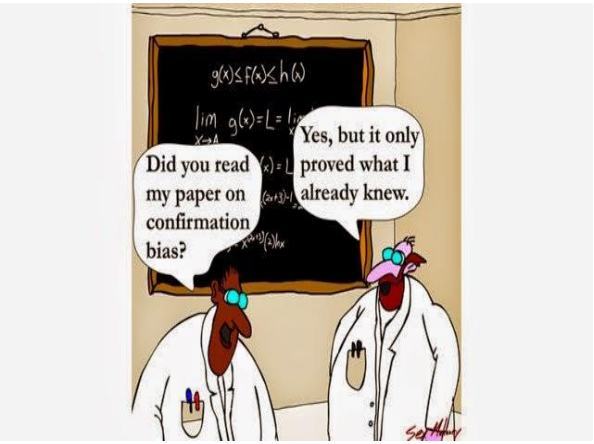
- I am a full-time employee of AbbVie
- The material and discussion that follow represent my personal view and should in **no** way be interpreted as AbbVie's position on this topic
- I am solely responsible for the material that follows, therefore any errors or omissions are my fault.

Why are we even discussing this?



The current state of affairs

- There are lots of emotions attached to both sides of the debate
  - "I cannot give any scientist of any age better advice than this: the intensity of the conviction that a hypothesis is true has no bearing on whether it is true or not." Peter Medawar, Advice To A Young Scientist



- Confirmation vs. falsifiability
  - It is easy to obtain confirmations, or verifications, for nearly every theory—if we look for confirmations. Confirmations should count only if they are the result of risky predictions... A theory which is not refutable by any conceivable event is non-scientific. Irrefutability is not a virtue of a theory (as people often think) but a vice. Every genuine test of a theory is an attempt to falsify it, or refute it. — Karl Popper

Why is it time to move on?

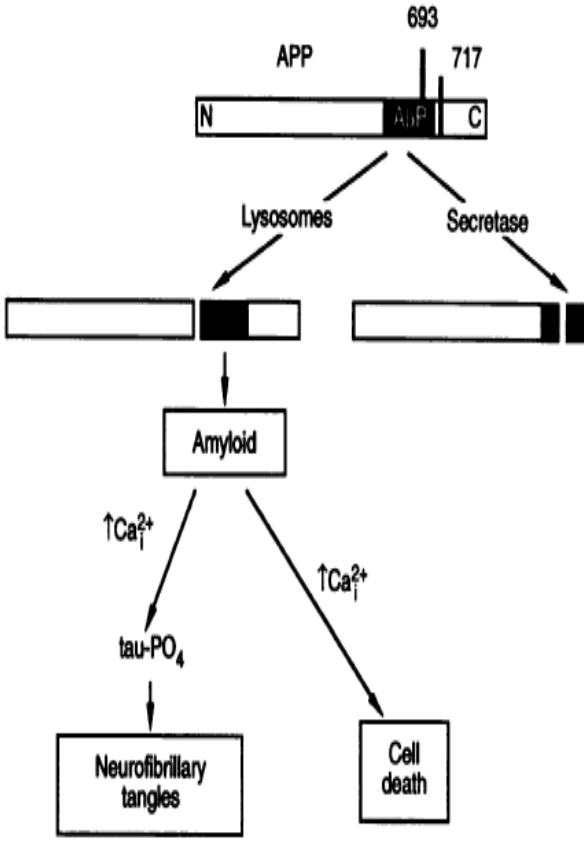
- The hypothesis' foundations are not solid
- The hypothesis is liable to revision and circularity instead of falsification
- The pre-clinical models derived from this hypothesis are not valid
- Despite evidence of pharmacological targeting, reduction of a-beta has no effect on core cognitive symptoms

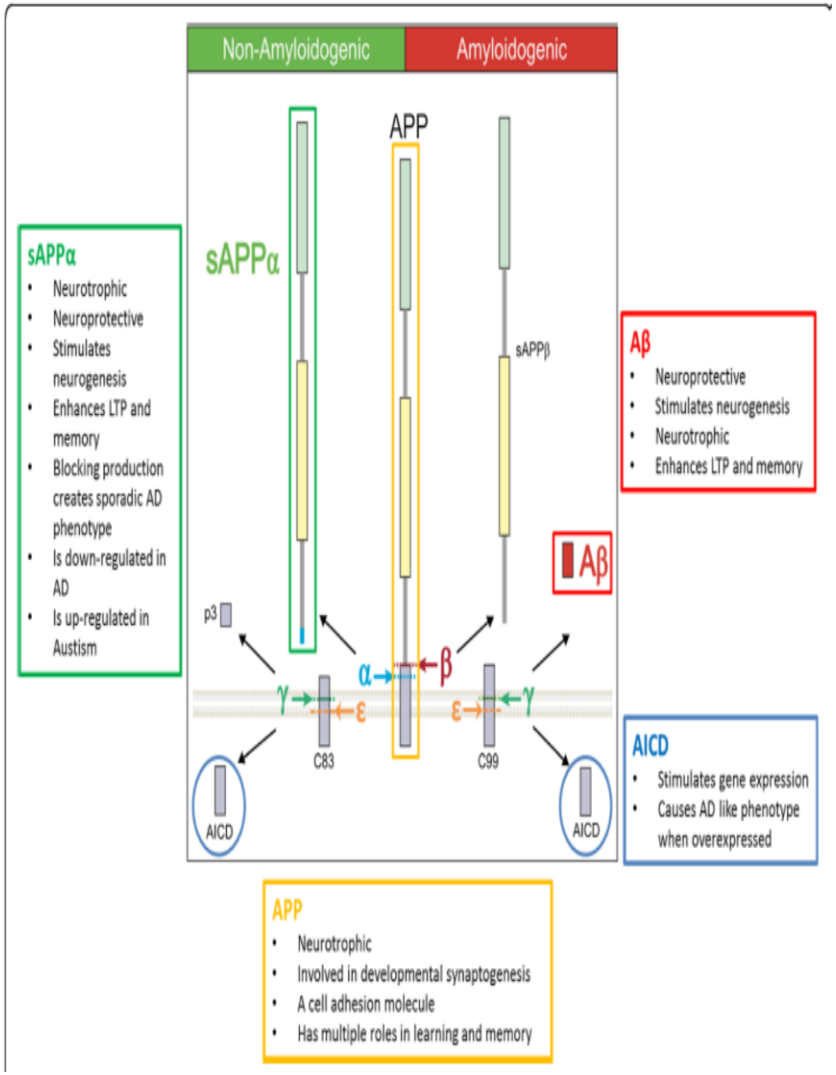
Initial proposition

- β-amyloid deposition is “the causative agent of AD pathology and that the NFTs, vascular damage and dementia follow as a result of this deposition”
- β-amyloid itself or APP cleavage products are neurotoxic and lead to NFT formation and cell death
- Linkage between β-amyloid and NFT not clear but thought to be mediated through increased intraneuronal Ca^{+2}
- This proposition is based on observations from patients with DS and APP mutations
  - Hardy & Higgins 1992

Initial Model

Fig. 1. The amyloid cascade hypothesis. Processing of APP can occur via two pathways: (i) Cleavage within AβP by the secretase, which generates peptide products that do not precipitate to form amyloid and (ii) cleavage in the endosomal-lysosomal compartment, resulting in intact AβP that precipitates to form amyloid and, in turn, causes neurofibrillary tangles and cell death, the hallmarks of Alzheimer's disease.





Predictions from initial model

- If you have enough β-amyloid in the brain, you should have dementia: Falsified (Rowe 2010)
- If your remove β-amyloid from the brain, your dementia should not progress (or maybe even improve): Falsified (AN-1792)
- If β-amyloid deposition is causal and upstream of NFTs, plaques and tangles should be spatially related: Falsified (Armstrong 1993)
- If β-amyloid deposition is causal and upstream, it should correlate with core symptoms of AD: Falsified (Rodrigue 2012 [sAD], Quiroz 2018 [fAD])

The problem with circular definitions

- Instead of rejecting the hypothesis, however, the field has essentially redefined the disease. The result is a dangerous circular logic that is holding back the field. It has been proposed that if people have plaques in their brain but are cognitively normal, they nonetheless have an early, ‘preclinical’ stage of AD.
- Since amyloid deposits are integral to defining AD, and since we can detect amyloid before the onset of overt cognitive decline, the argument is that the amyloid pathophysiology must precede the clinical symptoms and therefore defines an early disease stage. This argument only makes sense, however, if we have complete confidence that Aβ directly causes AD.
- It is the equivalent of saying that once plaques are found in the coronary arteries, a person is having a heart attack and, if there are no plaques in the arteries, no myocardial event can be defined as a heart attack. This is not a useful concept

Herrup 2015

Bad Science: Proving the negative

- ~40% of non-demented elderly meet neuropathological criteria for AD
- 24% of CN subjects (aged > 60) meet criteria for +amyloid using PET (Rodrigue 2012)
- Just how impaired should a **CN** subject be in order to fit the model that β-amyloid deposition causes impairment?
  - Keep in mind that CN persons who are pathologically or imaging + have been oligomeric + for even longer periods of time (We will get back to this later).

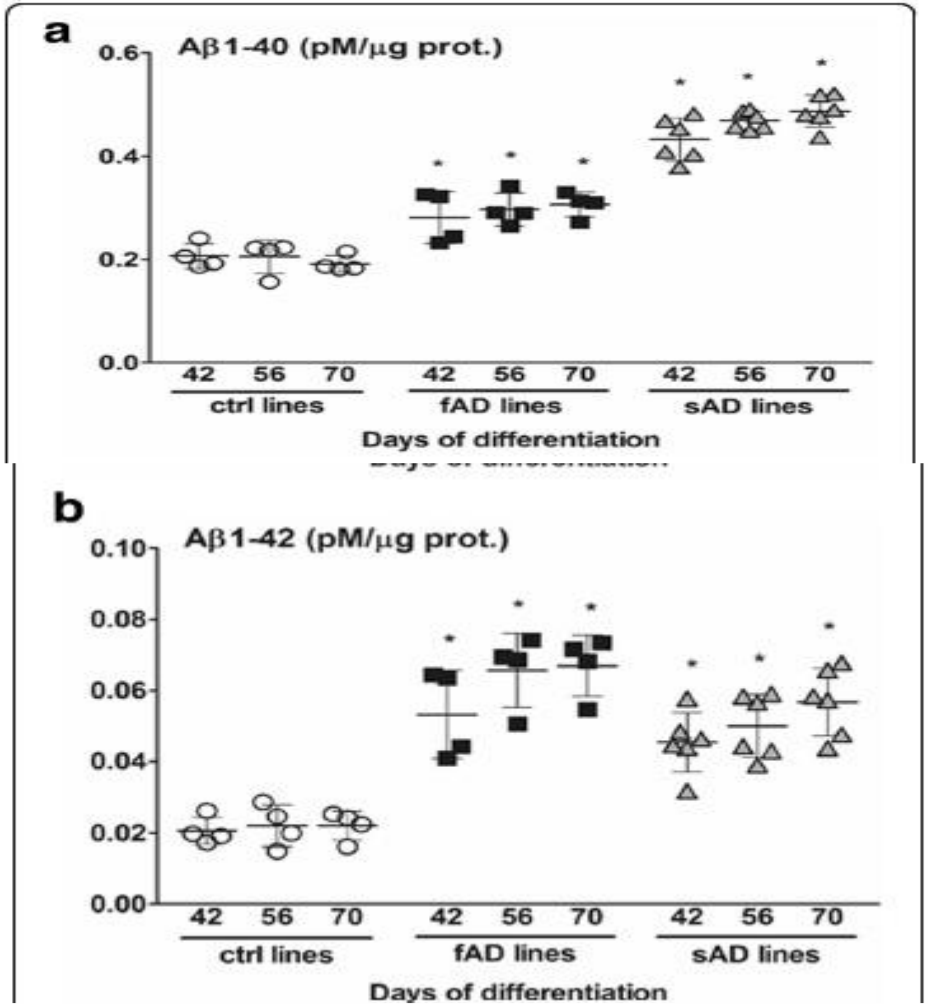
Reality Check on Trisomy 21

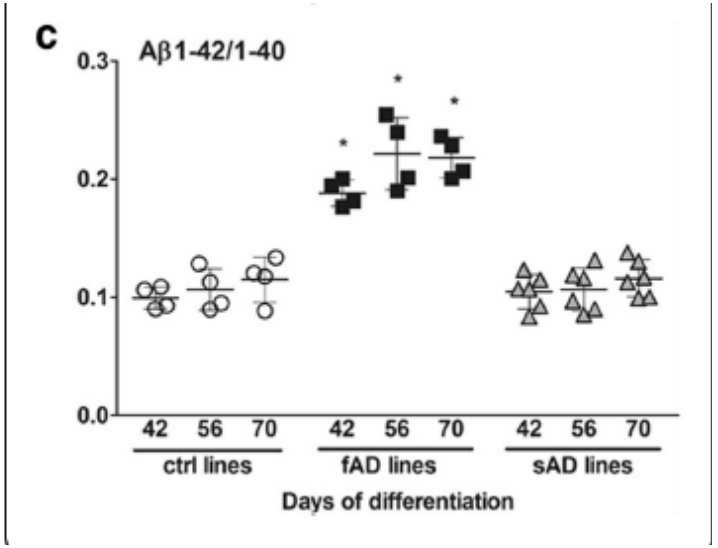
- APP cDNA maps to Chromosome 21
  - Many individuals with DS (TS21) meet neuropathological criteria for AD by age 40 (Zigman 2008)
  - Over-expression of APP → ↑β-amyloid → AD in DS and by extension to LOAD
- BUT
  - Not all persons with DS develop dementia despite ↑β-amyloid pathology
  - APOE has an independent role in DS
  - β-amyloid pathology in DS is not the same as in AD (Armstrong 1994)
  - There are other genes of interest in Chr 21 that can affect neurons

The next iteration

- Discovery of the PS1/PS2 mutations and that EOAD/fAD is due to over-production of β-amyloid$_{1\text{-}42}$
  - Increased production of β-amyloid$_{1\text{-}42}$ plays a critical role in the initiation of AD due to its increased tendency to aggregate compared to other species.
- BUT
  - There are PSEN1 mutations that do NOT affect the 1-42/1-40 ratio (Shioi 2007)
  - Patients with the same PSEN1/2 mutations have clinically heterogeneous presentations/progression (Gomez-Isla 1999)

B-amyloid production from iPSCs derived from fAD and sAD patients





Ochalek 2017

TG model paradox

- β-amyloid pathology in TG models using mutations associated with fAD should replicate β-amyloid pathology from sAD
  - The ability to clear/reduce β-amyloid pathology in TG models and stabilize or improve function/behavior implies that the same should be possible in man (otherwise why bother doing the experiment?)
- BUT
  - No accounting for time-scale differences and post-translational modification (demonstrably different properties)
  - No accounting for comorbidities (CVD)
  - No accounting for additional risk factors (eg APOE)
  - No accounting for limited cognitive repertoire/testing in rodents
  - No development of NFTs or consistent neurodegeneration
  - Inconsistent correlation between pathology and behavior
  - Complete failure to predict efficacy (or lack thereof) in man

And then came the oligomers

- Incubation of “non-toxic” β-amyloid monomers leads to aggregation and toxicity (Pike 1991)
- In-vitro β-amyloid preparations revealed the presence of “protofibrils” (Harper/Walsh 1997)
- A lack of correlation between insoluble β-amyloid burden and deficits in spatial reference memory implied the existence of a smaller, soluble pool that was responsible for cognitive deficits (Westerman 2002)

Is the oligomeric version falsifiable?

- No clarity as to which species is relevant to sAD
- Different species may be technical artifacts (buffers, detergents etc.)
- Cannot be studied in-vivo
- Concentrations use in experiments are not relevant to in-vivo settings
- Oligos associate with lipoproteins in-vivo which may mitigate neurotoxicity

Benilova et. al. 2012, Morris et. al. 2014

Finally..

- The amyloid hypothesis needs to be discarded or at a very minimum rebuilt from scratch.
  - The circular definition of AD as being synonymous with β-amyloid deposition should not be allowed
  - Modifications of the hypothesis should be allowed only when falsification has been demonstrated, not when inconvenient data are obtained
  - Reliance on genetic forms of the disease (< 5% of AD patients) should not be allowed to dominate the field in terms of pathogenesis, animal model development , target identification and therapeutics.
  - Increased reliance on data from GWAS analyses of sporadic LOAD
  - Increased reliance on data suggesting the critical role of glia, inflammation and mitochondria.

References

- Morris GP, Clark IA and B Vissel. Inconsistencies and Controversies Surrounding the Amyloid Hypothesis of Alzheimer's Disease. Acta. Neuropath Comm 2014;2:135
- Herrup K. The case for rejecting the amyloid cascade hypothesis. Nat. Neuroscience 2015; 18: 794-798
- McGowan E, Eriksen J and M Hutton. A decade of modeling Alzheimer's disease in transgenic mice. Trends in Genetics 2008;22:281-289.
- Benilova I, Karran E and DeStrooper B. The toxic ab oligomer and Alzheimer's Disease: an emperor in need of clothes. Nat. Neuroscience 2012;15: 349-