

CAN THE AMYLOID HYPOTHESIS BE RESCUED? NO

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Disease-modifying treatment for Alzheimer's disease (AD) has focused mainly on beta-amyloid (a-beta) reduction. Four major strategies have been tested clinically: prevent or reduce its formation, remove existing deposits using active or passive immunization, prevent or reduce its aggregation, enhance its clearance. As documented by PET and autopsy studies, some approaches have succeeded in decreasing beta-amyloid in the brain of mild-moderate patients but none has produced clinically significant results in phase III.

Most recently, antibodies recognizing both soluble and aggregates of a-beta (Bapineuzumab) or soluble but not plaques a-beta (Solanezumab) have been tested in phase III. The results are consistent with target engagement of soluble (Solanezumab) and both soluble and aggregated a-beta (Bapineuzumab), however, neither vaccines showed a clinical benefit with respect to designated primary outcomes. Several methodological issues have been considered as a cause of failure, including poor penetration, too low dosage, misdiagnosis and too advanced disease stage. However, the main reason could be that the amyloid cascade hypothesis does not fully integrate a large body of data relevant to the emergence of clinical AD. Most important is the fact that amyloid deposition is not strongly correlated with cognition in multivariate analyses, contrary to neuronal and synaptic loss, and tangles and hyperphosphorylated tau pathology which are closely associated with memory deficits. Targeting tau pathology may thus be more effective clinically. Potential therapeutic compounds include kinase inhibitors, phosphatase activators, phospho-tau antiaggregants and microtubule stabilizers. Also, numerous immunization studies in animal models indicate that it is possible to reduce intracellular levels of tau and P-Tau with an improvement in cognitive performance. Although, the potential risk of tau immunotherapy in humans should not be underestimated, several tau-related vaccines are presently in advanced preclinical stage and two of them have entered clinical trials. The ongoing development of markers of Tau for PET detection makes it possible to directly evaluate the relation between tau reduction and clinical results.

Reference

E. Giacobini and G. Gold . Alzheimer disease therapy—moving from amyloid-beta to tau. *Nature Reviews Neurology* (2013), vol.9.677-686