Are Anti-amyloid Therapies Still Worth Being Developed as Treatments for Alzheimer’s Disease?

Despite limited pharmaceutical success thus far, amyloid peptides may yet prove useful in the treatment of Alzheimer’s and delay disease progression.

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Drug discovery in the domain of Alzheimer’s disease is essentially benchmarked by clinical trial failures (dimebon, tramiprosate, tarenflurbil, semagacestat, the vaccine AN1752).\(^1\)\(^-\)\(^6\) Difficulty in finding an AD treatment arises from lack of knowledge of the origin of this disease. Although the etiology of the familial form of AD is known, that of the sporadic form, which represents 95 percent of the cases, remains unidentified.\(^7\)

Consequently, most animal models currently used in the proof-of-concept stage of preclinical studies in AD R&D were developed based on knowledge acquired from studying the familial form of AD. This represents a second obstacle in finding AD treatments, as these models have limited usefulness for studying the sporadic form of the disease and as an investigational tool in drug development. A third obstacle lies in the multiplicity of the deleterious pathways that are activated during the progression of the disease, probably at distinct time points. These multiple pathways explain the limited efficacy of the classical single-target drugs. Future treatments for AD will necessarily include drugs aimed at different targets. Alternatively, in accord with the current trend, they will evolve toward the development of compounds\(^8\) that target several mechanisms leading to different pathological endpoints.

For a long time, the scientific community has primarily focused on improving cholinergic network dysfunction for the treatment of AD. This led to the development of the therapeutically class of acetylcholinesterase inhibitors (AchEI), with tacrine as the class leader. The clinical benefits of tacrine were modest and hampered by its significant liver toxicity.
The new generation of AchEI represented by galantamine, rivastigmine, and donepezil did not improve the delay in symptom onset compared to tacrine, and the true benefit of these AchEI for the treatment of mild, moderate, and severe Alzheimer’s disease as well as mild cognitive impairment remains controversial. A 2006 Cochrane review of efficacy of donepezil, the leading AchEI on the market, in AD treatment concluded that, although this AchEI is clinically effective, the treatment effects are small and not always apparent in practice. In addition, the long-term cost effectiveness of donepezil is unknown, and the scientific relevance of the use of AchEI to treat AD has been questioned. Nevertheless, except for AchEI, no major advances in AD drug development have been made. Even the beneficial effects of the low-affinity N-methyl-D-aspartate (NMDA) receptor antagonist are still unclear. Recent Cochrane reviews confirm a small beneficial effect of the NMDA receptor antagonist, memantine, at six months in moderate to severe AD. On the other hand, they rule out any beneficial effect of this agent in mild to moderate AD. Other studies reported that memantine has no benefit as a monotherapy in Alzheimer’s disease but proved to be beneficial when associated to donepezil. Memantine was also shown to induce subtle psychotic symptoms in an AD patient, raising concerns about this treatment.

In the endeavor to find a cure for Alzheimer’s disease, many efforts have been devoted to targeting the once considered main actor of the disease, namely the amyloid peptide. Although the real contribution of amyloid peptide to the disease remains unclear, years of research continuously provided compelling evidence that some of the amyloid forms present in the brain are detrimental to the neuronal cells’ survival. This situation rationalized the development of drugs meant to reduce the amyloid burden in the diseased brain, the so-called anti-amyloid. As of today, three main approaches have been used. The first approach was the inhibition of peptide synthesis. The amyloid peptide is generated through the cleavage of the transmembrane protein Amyloid Precursor Protein by two proteases, the beta-secretase or BACE-1 and the gamma-secretase. The development of BACE-1 inhibitors is still at the discovery or early pre-clinical stage due to their challenging peptide-like structure that prevents them from crossing the blood-barrier. In addition, recently generated BACE1-/- mouse strains exhibited a high mortality rate and the survivors were much smaller than their wild-type littermates, and adult BACE1-/- mice displayed hyperactive behaviors that were related to the inactivation of voltage-gated sodium channels and a modification of the synaptic current. Therefore, it appears that although compelling evidence supports the development of beta-secretase inhibitors, a broader, more cautious, and better understanding of BACE1 is necessary prior to seriously envisioning a clinical trial. On the other hand, many small molecules specific inhibitors of gamma-secretases were developed and several clinical trials have been launched. Unfortunately, tarenflurbil and semagacestat, the first gamma-secretase inhibitors/modulators tested in clinical trials, failed in phase III at demonstrating any therapeutic efficacy.
A second approach developed was the vaccine against amyloid peptide, also called active immunization. The rationale was to have the patients’ immune system target the amyloid peptide. However, the widely reported failure of the vaccine AN1792 in phase I studies for safety reasons represented a major setback for the development of this type of treatment. The meningoencephalitis cases observed during the AN1792 clinical trial were attributed to the nature of the epitope used, which led to the development currently ongoing of vaccines based on different epitopes meant to not trigger such dramatic immune reaction. Nevertheless, regardless of the epitope to be used, the risk of inducing an autoimmune disease with a vaccine targeting a native protein has never really been debated, leaving open the question of what will happen to the physiological functions of A'1-42 following vaccination.

An alternative to the active immunization is the administration of humanized immunoglobulins specifically raised against the amyloid peptide. Several clinical trials are currently being or have already been conducted to assess safety/tolerability and clinical efficacy of such concept (Bapineuzumab, solanezumab and PF-04360365). First reports showed that either the immunoglobulin treatment did not lead to any cognitive improvement or the effect of the treatment on the ADAS-cog score has not been recorded, which at best questions the clinical efficacy of humanized monoclonal antibody in the treatment of Alzheimer’s disease. The high percentage (9.5 percent) of vasogenic edema reported after one single injection of bapineuzumab, although reversible, raises the question of long-term treatment safety on the blood-brain barrier integrity in particular. The mechanism of action of these humanized IgGs is poorly understood; since immunoglobulins do not cross the blood-brain barrier, the common assumption is that they would trigger an output flow of amyloid from the brain across the blood-brain barrier involving a still-to-identify transporter. Further fundamental work is definitively required not to kill in the egg this seducing therapeutic strategy and to make it sustainable on the long-term.

Since this histological alteration was first diagnosed by Alois Alzheimer in 1907, amyloid plaques were described as playing a major role in the disease progression. Although amyloid plaques are commonly present in otherwise healthy subjects and sometimes in higher amounts than in patients suffering from Alzheimer’s disease, the thought that they contribute to the disease still carries some weight and dissolving these insoluble structures remains a current therapeutic concept. Kinetic studies showed that amyloid peptide has to self-assemble to form oligomers as a preliminary step towards plaque formation. Interestingly, the Amyloid Derived Diffusible Ligands (ADDLs), another amyloid species that also results from the self-aggregation of the monomeric amyloid peptide into oligomers containing 4 to 24 monomers, is known as a highly neurotoxic molecular entity and has been purported to bear most of the deleterious effects of the amyloid peptide described in Alzheimer’s disease. Both plaques’ purported deleterious role and ADDLs provided at the time the rationale and justification for the development of small molecules inhibitors of amyloid aggregation as a potential treatment for Alzheimer’s disease. Many pharmaceutical companies as well as academia were extremely creative in developing various compounds that showed remarkable anti-Alzheimer properties in vitro and in vivo but for which clinical data are still lacking.

Unfortunately, the conjunction of concurring circumstances threw an undeserved shade over the development of aggregation inhibitors: the complexity and multifactorial origin of the disease that makes it difficult for a monotherapy to be clinically relevant, the discovery of pathological pathways seemingly offering a more drugable potential, and finally the amyloid plaques themselves whose neurotoxicity ceased to look so evident as the lack of correlation between amyloid load and cognitive was established. However, it may be discussed that, under the light of new discoveries, restricting the therapeutic targeting of amyloid peptide to oligomers species might have significantly narrowed the interest for amyloid aggregation inhibitors. Indeed, compelling evidence suggests that the monomeric form of amyloid peptide exerts detrimental effects on neurons survival con-
tributing therefore to the disease progression.\textsuperscript{30,32} In particular, the capacity of amyloid peptide to enter the mitochondria and to damage the respiratory chain has been recently established in our laboratory\textsuperscript{33} and by others.\textsuperscript{34} We showed that such compound, as long as it crosses the blood-brain barrier, displayed tremendous beneficial effect on the cognitive performances, neuroinflammation and brain histological modifications in an animal model of Alzheimer disease.\textsuperscript{35,36} We also demonstrated that an amyloid ligand would be capable of removing the amyloid peptide that accumulates in the mitochondria during the progression of the disease and consequently to protect the mitochondria respiratory chain from amyloid insult.\textsuperscript{33} Few examples of amyloid peptide ligands currently at various stages of their development are given in the figure on p.23. It is noteworthy that three of these compounds are naturally occurring in plants, epigallocatechin gallate, curcumin and caprosinol; two of them, curcumin and caprosinol, have showed an excellent toxicity as well as an interesting pharmacokinetic profile.\textsuperscript{35-38}

The use of aggregation inhibitors, which pharmacologically are amyloid ligands, regains interest as these compounds could be used to prevent the amyloid peptide from entering the mitochondria or to “clean-up” altered mitochondria overloaded with the peptide. These small molecules would therefore not only be used for their anti-aggregating properties but also for their ability to bind and inactivate/scavenge the amyloid peptide under its monomeric forms. The initial rationale behind the development of such compounds was to dissolve the amyloid plaques and to prevent their formation. However, few decades later, it appears that the insoluble plaque burden is not so much an actor of the Alzheimer’s disease physiopathology and should no longer be considered as a therapeutic target. This would not compromise in my opinion the development of amyloid ligands, as instead of targeting the already constituted plaques we would just have to realign the aiming at the amyloid monomer.


Anti-amyloid Therapies for AD?