

Emerging Therapies for Alzheimer's Disease

a report by

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There is consensus among researchers that the biological basis of Alzheimer's disease (AD) lies in the abnormal accumulation of toxic amyloid protein in the brain.^{1,2} In brief, the amyloid hypothesis of AD states that the amyloid precursor protein (APP), encoded on chromosome 21 and ubiquitously expressed as a glycosylated transmembrane protein, is abnormally cleaved into many products, including the toxic amyloid- β_{42} ($A\beta_{42}$). This occurs when APP is processed via an amyloidogenic pathway via sequential cleavage by β -secretase and γ -secretase, leading to the production of $A\beta$. Aggregated $A\beta_{42}$ then forms insoluble plaque, which is laid down in the brain. These plaques and/or the upstream events in their formation are believed to underlie the neuronal loss and cognitive decline of AD.^{3,4} As a result, future therapies hoping to modify the disease itself must focus on this process. Whether addressing the actual accumulation and deposition of amyloid protein or the downstream oxidative damage induced by amyloid protein, researchers are basing emerging drug therapies on this model of the disease.

As a result, disease-modifying therapies can be designed to intervene at several different points along the disease pathway. These approaches include: the inhibition of secretase enzymes to prevent the formation of $A\beta_{42}$; specifically modifying the γ -secretase enzyme, which is likely to be instrumental in the production of toxic $A\beta_{42}$, and shunting production away from this toxic product; preventing the aggregation of $A\beta_{42}$, which is believed to be a central step in plaque deposition; and increasing the body's clearance of toxic $A\beta_{42}$.⁵ Currently, therapies available for AD can treat only symptomatic manifestations of the disease. These include drugs that increase intrasynaptic acetylcholine levels and modulate glutamatergic transmission in the brain. However, no currently approved treatments intervene to halt or reverse the disease process itself, which makes the approaches described above exciting lines of enquiry. The current status of many of these emerging therapies will be described in the following sections.

Inhibiting $A\beta_{42}$ Production

The blockade of either β -secretase or γ -secretase would ultimately prevent

production of $A\beta_{42}$. As such, these enzymes have been widely studied targets for therapy. However, blocking these enzymes has proved to be quite difficult.⁵ As the β -secretase active site is quite large, passage of similarly large inhibitor molecules through the blood-brain barrier has been difficult.⁶ On the other hand, γ -secretase inhibitors have run into problems in development due to intolerable side effects.^{7,8} Despite these challenges, trials examining both types of inhibitor are ongoing. In fact, LY450139 (Lilly), a γ -secretase inhibitor, is currently the subject of phase III trials.^{7,8} Phase II trials were a collaborative effort of the Alzheimer's Disease Cooperative Study Group and the sponsor company. This was a multicenter, randomized, double-blind, dose-escalation, placebo-controlled trial focused largely on safety and tolerability. Biomarker analysis of the treatment group showed that plasma $A\beta_{40}$ decreased by 58.2% in the 100mg/day group and by 64.6% in the 140mg/day group. However, the decrease in cerebrospinal fluid (CSF) $A\beta_{40}$ was smaller and not statistically significant. In addition, plasma $A\beta$ response to the drug was biphasic, suggesting that a period of reduced $A\beta$ is transient and followed by a period of elevated $A\beta$.^{7,8}

As difficult as designing a compound to inhibit β -secretase has been, many researchers continue to pursue this line of investigation. For example, the biotech company CoMentis has begun a phase I study of CTS-21166, a reported high-potency, highly selective brain-penetrating β -secretase inhibitor.⁹ The β -secretase inhibitor TAK-070 (Takeda) has also entered clinical trials.¹⁰ Another interesting approach to decreasing $A\beta$ levels may be through the well-studied lipid-lowering statin drugs. Many studies have identified a significant connection between elevated cholesterol levels and enhanced production of toxic $A\beta$ from APP.^{11,12} Early trials have shown that statins increase the serum APP/ $A\beta$ ratio, and one recent trial demonstrated that subjects taking statins had less cerebral amyloid burden. However, this finding was tempered by the fact that statin use was not similarly correlated to cognitive changes.¹³ Among their various anti-amyloid effects, statins activate an $A\beta$ -destroying enzyme, α -secretase. This is a new strategy that is especially interesting since α -secretase mutations have recently been implicated as risk factors for AD.

Modifying γ -Secretase Activity

Rather than blocking γ -secretase activity outright, researchers have designed drugs to modify the actual products of γ -secretase to shorter, non-toxic proteins, which are non-amyloidogenic.⁵ These drugs change the activity of γ -secretase on the APP. Phase II clinical trials were recently completed on tarenflurbil (Flurizan, Myriad Genetics), a small-molecule selective amyloid-lowering agent that modulates γ -secretase activity as described above. Pre-clinical studies of tarenflurbil established an effect in genetically altered Alzheimer's 'knockout' mice whereby memory is improved on a test of the mouse's ability to remember the location of a



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platform in a pool of water.¹⁴ Phase II studies demonstrated significant effects on Alzheimer's Disease Assessment Scale–Cognitive Subscale performance and global function, as tested by the Clinical Dementia Rating Scale Sum of Boxes test.^{5,15} However, phase III trials of tarenflurbil recently failed to show efficacy. Body fluid analyses are ongoing in order to determine whether the desired A β ₄₂-lowering effect was actually achieved. Many other compounds that modulate γ -secretase activity are currently under study, including non-steroidal anti-inflammatory drugs, which act on γ -secretase to reduce A β ₄₂ and increase the shorter, less amyloidogenic 38-amino acid peptide.¹⁶

Decreasing A β ₄₂ Aggregation

Many researchers believe that soluble A β ₄₂ molecules do not become particularly toxic until they aggregate into fibrils and plaques.⁵ This has led to therapies targeting the aggregation of A β ₄₂. Tramiprosate (Alzhemed, Neurochem), an A β ₄₂ aggregation inhibitor, has been well studied and showed initial promise.¹⁷ Unfortunately, the study was ultimately halted due to the failure of large phase III trials.¹⁸ However, Elan Pharmaceuticals is currently studying a molecule known as ELND005 in a phase II safety and efficacy study. ELND005 is a scyllo-inositol molecule that acts as an A β aggregation inhibitor that may help to prevent or inhibit the build-up of amyloid plaques in the brain. Studies of the drug using mouse models of AD found that the drug modified the disease process when used as a prophylactic or therapeutic.¹⁹ In addition, phase I studies found this drug to be well tolerated, orally bioavailable, and with CSF concentrations in humans that had been effective in mouse models of AD. Several other aggregation inhibitors are in pre-clinical and clinical development.

Increasing Clearance of A β ₄₂

A potential 'Alzheimer's vaccine' has long been an interest for researchers and a hope for patients and families. The idea of using the body's own immunity to combat amyloid plaques has great appeal, but the most promising candidate of this approach to modifying AD ran into serious problems. The drug in question, AN-1792, was designed to present the body with A β proteins in order to induce active immunity against A β ₄₂ and amyloid plaques. Studies of AN-1792 in mouse models of AD appeared positive, with evidence that plaques were both prevented and reduced.²⁰ Unfortunately, when trials began in elderly human subjects with AD, approximately 6% of patients developed aseptic meningoencephalitis, necessitating the termination of the study.²¹

Interestingly, subsequent analysis of the data showed that subjects who developed high titers of antibodies to A β ₄₂ seemed to decline more slowly, and autopsy reports indicated that despite diagnostic neuropathological features of AD, these patients also had regions in the brain where amyloid appeared fully cleared.²² As a result of the serious adverse events seen in the AN-1792 study, many researchers have turned to immunotherapies that rely on passive

immunity against amyloid plaques. Along these lines, the monoclonal anti-A β antibody bapineuzumab is currently the subject of phase III trials.²³ In contrast to AN-1792, bapineuzumab is a humanized antibody that does not require the body to mount an immunological response to target A β . It is hoped that by using a passive approach, the adverse effects seen in the AN-1792 trial will be circumvented while simultaneously retaining the benefits. In addition, two other monoclonal antibodies, LY2062430 (Lilly) and RN1219 (Pfizer), are currently the subject of clinical trials.

Future Directions

Another interesting line of recent research involves the role of oxidative stress and mitochondrial dysfunction in the pathogenesis of AD. Several studies have implicated oxidative stress in the exacerbation of plaque formation and the alteration of APP and A β metabolism.²⁴ It has also been shown that A β exerts toxic effects on mitochondria, perhaps by altering mitochondrial permeability.²⁵ Along these lines, dimebon (Medivation), a drug believed to inhibit mitochondrial permeability, as well as being a weak cholinesterase inhibitor and N-methyl-D-aspartate-receptor antagonist, has recently demonstrated encouraging results in phase II study. This randomized, placebo-controlled trial showed significant improvement over placebo on measures of cognition, activities of daily living, and global function.²⁶ This effect was seen at six months, and an additional 26-week extension of the study showed maintenance of the benefits from dimebon. The drug was well tolerated and is now the subject of phase III trials.

Although all of the potential therapies discussed above hold promise, many researchers hold out even greater hope for treatments that may ultimately effect neural regeneration itself. Although the concept of neurogenesis in the adult brain is a new one,²⁷ it presents researchers with perhaps the most tantalizing mode of treating patients with AD, apart from completely preventing the disease. If the process of neurogenesis could be better understood, perhaps researchers could learn to promote the formation of new neurons in the diseased portions of the brains of those with AD.⁵ Tuszynski et al. tried just such an approach when they implanted genetically modified nerve-growth-factor-secreting cells into the nucleus basalis of eight patients with early-stage AD.^{5,28} This approach appeared safe and tolerable in these patients. This is clearly an area of development that will require many more years of study, and many molecules purported to stimulate neurogenesis are currently being studied.

Conclusion

Although slow in arriving, many of the approaches described above, whether inhibiting A β production, modifying secretase activity, reducing A β aggregation, or increasing clearance of A β , hold promise for actual modification of the AD process itself, rather than simply managing symptoms. Hopefully, these emerging treatments will provide patients and families with new, more effective ways of combating AD in the very near future. ■

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