EDITORIAL

Novel Therapeutics for Alzheimer's Disease

Alzheimer's disease (AD), the most common form of dementia in the elderly, was first described roughly 100 years ago in Bavaria by Dr. Alois Alzheimer. AD is a progressive and fatal neurodegenerative disease that impairs memory and overall cognition. Although drugs currently available treat the symptoms with only minimal and temporary benefit, the coming years are expected to see the results of several clinical trials on novel therapeutics aimed at retarding disease progress. This could not come at a better time, given that there are currently more than 5 million documented patients in the United States, with the number of new cases growing by more than 10% per year. Medicare expenditures for AD in 2005 were $91 billion, and this is projected to increase to $160 billion by 2010. If AD remains an unmet medical need, Medicaid and Medicare expenses for AD and related disorders will reach $184 billion by 2010, which will be approximately 27% of the expected budget for Medicare and Medicaid.

After age, family history is the second greatest risk factor for AD, and four different genes have been established to predispose to AD: amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and apolipoprotein E (*APOE*). All four AD genes have pointed to the excessive accumulation of cerebral amyloid β peptide (Aβ) as the major culprit in AD pathogenesis.[1] Aβ is the main component of senile plaques and β-amyloid deposits in the brain. Clinical trials of therapies aimed at modifying Aβ production, enhancing Aβ clearance, or neutralizing Aβ neurotoxicity are currently underway. Aβ is produced by the activities of two enzymes, β-secretase and γ-secretase, which serially cleave APP to produce Aβ. The peptide can be produced as 37- to 43-amino acid species, although the most common form is Aβ_{40}. The second most common form ($\sim$10% of total Aβ) consists of 42 amino acids (Aβ_{42}), and is considered the most toxic and amyloidogenic species of Aβ. After Aβ is made in the brain, it is usually shuttled into the bloodstream for degradation. The balance of Aβ production in the brain versus clearance out of the brain determines how much Aβ will accumulate and potentially form toxic β-amyloid aggregates. If production is too high or clearance is too low, Aβ can aggregate into clusters called oligomers before being deposited into senile plaques. Although earlier, controversial hypotheses (e.g., the amyloid cascade hypothesis) have traditionally favored senile plaques as the cause of Alzheimer's disease, it now appears that the Aβ oligomers, which precede plaques, may be the actual neurotoxic entities in Alzheimer's disease. As Aβ oligomers accumulate in the brain, neurotransmission can be impaired—ultimately leading to cognitive decline and dementia. This is referred to as the synaptic Aβ hypothesis of AD.[2]

In this issue of *Neurotherapeutics*, we have enlisted several experts in the field to review the most promising new therapeutics currently under development for the treatment and prevention of AD. Given the overwhelming evidence supporting a central role for Aβ in AD pathogenesis, the first set of reviews focuses on therapies targeting the cerebral accumulation of Aβ. The issue begins with a review by Randall J. Bateman and William E. Klunk (pages 381–390), which focuses on various methodologies for measuring the effects of disease modifying therapies aimed at reducing cerebral Aβ levels. Dr. Bateman's review comprehensively covers how physiological Aβ measurements, β-amyloid imaging, and other biomarkers can be most effectively used in preclinical studies and clinical trials to determine whether Aβ levels correlate with improved cognition in AD. In addition, Dr. Bateman presents various clinical and preclinical scenarios for using Aβ measurements and imaging as a means for characterizing disease progress of AD at the biochemical and physiological levels.

Michael S. Wolfe (pages 391–398) reviews clinical strategies for curbing production of Aβ as a treatment for AD, including therapies aimed at blocking the generation of the peptide with γ-secretase inhibitors (GSI). Given that γ-secretase cleaves a number of other substrates, Dr. Wolfe notes that GSIs can be toxic by blocking proteolysis of other substrates, such as the Notch receptor. Thus, he also discusses compounds known as γ-secretase modulators (GSM), which selectively alter Aβ production (away from Aβ_{42}) without hindering signal transduction from the Notch receptor. GSMs carry considerable promise as AD therapeutics. Ibuprofen (and other nonsteroidal anti-inflammatories [NSAIDs]) was first reported to have GSM properties, lowering the Aβ_{42}:Aβ_{40} ratio. Myriad Pharmaceuticals (Salt Lake City, UT) has since developed a NSAID, an R-enantiomer of flurbiprofen, with the trade name Flurizan. Although the phase II trial did not

show statistically significant effects on AD, phase III clinical trials on high-dose Flurizan are underway, with reports expected this year. Meanwhile, a novel GSM, E2012, is being developed by Eisai (Tokyo, Japan; Ridgefield Park, NJ) in partnership with TorreyPines Therapeutics (La Jolla, CA). In February 2007, a phase I clinical trial of E2012 was put on hold because some side effects were observed in the eyes of rats after 13 weeks of treatment. After further testing, the side effect was not observed, and the hold was lifted in April 2008. Meanwhile, TorreyPines and other companies, including Eli Lilly (Indianapolis, IN) and Merck (Whitehouse Station, NJ), are continuing attempts to develop more potent GSMs.

An alternative approach to curbing Aβ production involves inhibiting the other enzyme required to generate Aβ, β-secretase (memapsin 2, BACE1), In their review, Jordan Tang and colleagues (pages 399–408) describe attempts to discover BACE inhibitors. β-Secretase is considered an attractive target because it is the first step in the pathway leading to the production of Aβ, and knockout of the BACE1 gene leads to relatively mild phenotypes. Like γ-secretase, however, β-secretase has in vivo substrates beyond APP, including a sodium channel subunit and neuregulin 1, which modulates myelination. Tang and colleagues describe a rational drug design strategy based on the structure of β-secretase and summarize progress on an orally available β-secretase inhibitor drug candidate, CTS-21166 from CoMentis (South San Francisco, CA). A phase I study indicated that CTS-21166 was safe and well tolerated. A phase II study is expected later this year.

In reviewing therapeutic approaches aimed at clearing Aβ out of the brain, Berislav V. Zlokovic (pages 409–414) discusses the role of the neurovasculature and vascular factors in the clearance of Aβ. He specifically focuses on the role of the receptor for advanced glycation end products (RAGE) and the low density lipoprotein receptor related protein 1 (LRP1) in maintaining normal levels of Aβ in the brain by controlling its transport across the blood–brain barrier. Dr. Zlokovic also summarizes the role of impaired vascular remodeling and dysregulation of cerebral blood flow in the disease process. Finally, he covers novel therapeutic strategies based on neurovascular targets, including RAGE, LRP, and other genes implicated in AD neurovascular dysfunction (e.g., mesenchyme homeobox gene 2 and myocardin).

Another strategy for clearing Aβ applies immunotherapy with anti-Aβ antibodies. More than a dozen different pharmaceutical and biotechnology companies are attempting to use various antibodies targeting Aβ to reduce cerebral Aβ levels. Roger M. Nitsch and Christoph Hock (pages 415–420) summarize the various approaches based on Aβ immunization. There are two basic strategies: active vaccination and passive immunization. Active vaccination involves immunizing a patient with aggregated Aβ. The first clinical trial (Wyeth–Elan, Madison, NJ, and Dublin, Ireland) using this approach was terminated because several of those treated developed encephalitis. In the alternative strategy, passive immunization, antibodies targeted against Aβ are purified and injected intravenously into the bloodstream. With regard to mechanism of action, the antibodies either bind to Aβ peptides that have been exported from the brain and do not let them re-enter the brain, or a small fraction of the antibodies enter the brain and activate microglial degradation of Aβ. This is a promising strategy, and one that is being pursued by at least 15 different companies and is currently in large phase III trials at Wyeth–Elan (Bapineuzumab; formerly AN-1792).

An alternative approach to clearing Aβ from the brain involves blocking the peptide's ability to form oligomers and aggregates, or even dissolving them. One of the first trials along these lines was carried out by Neurochem (Bellus Health, Laval, Quebec, Canada) on the drug Alzhemed, an orally available drug known as a GAG-mimetic. This drug is designed to bind to Aβ peptides and prevent them from aggregating. Phase II and III trials of this drug failed, most likely due to the potency of the drug rather than the antiaggregation approach as such. Neurochem may attempt a revised phase III trial in the future. Another trial aimed at blocking Aβ aggregation is being conducted by Transition Therapeutics (Toronto, Ontario, Canada), with the drug AZD-103, an inositol compound aimed at preventing Aβ aggregates. AZD-103 was well tolerated in a phase I clinical study. Transition Therapeutics has now partnered with Elan to carry out a phase II clinical trial.

Ashley I. Bush and I (pages 421–432) describe another therapeutic strategy for clearing Aβ based on the metal hypothesis of AD, which contends that copper and zinc drive the formation of toxic forms of Aβ, such as oligomers. We first proposed this hypothesis in 1993 and later cofounded Prana Biotechnology (Parkville, Victoria, Australia) to apply it to AD drug discovery. In our review, we describe the effects of PBT2, a metal protein attenuation compound (MPAC) that strips zinc and copper from Aβ and thereby prevents it from aggregating and forming oligomers that can impair neurotransmission. PBT2 has been shown to dramatically reduce Aβ aggregation and accumulation in transgenic AD mouse models. It is also able to block the detrimental effects of Aβ on neuronal synapses, neurotransmission, and cognition. Phase IIa clinical trial results have been encouraging: after 12 weeks of oral administration in 78 patients with mild-to-moderate AD, PBT2 significantly lowered $A\beta_{42}$ levels in the cerebrospinal fluid and significantly improved cognition based on two neuropsychiatric tests

for executive memory. The drug had no side effects or adverse events and was well tolerated.

Cholinergic drugs, which include acetylcholinesterase (AChE) inhibitors such as donepezil, rivastigmine, galantamine, and tacrine, are currently the most prescribed for treating AD; they are considered symptomatic treatments. Abraham Fisher (pages 433–442) reviews novel cholinergic treatments with a focus on muscarinic and nicotinic agonists. Based on recent preclinical studies, Dr. Fisher suggests that cholinergic agonists might be useful not only for treating symptoms, but also as disease-modifying agents for AD. He summarizes evidence that some cholinergic drugs, the M1 agonists, ameliorate AD pathology via M1-mediated activation of key transduction pathways, including protein kinase C (PKC)- and mitogen-activated protein kinase (MAPK)-dependent pathways, that are linked to activation of α-secretase, which obviates Aβ production. In addition, he describes how activation of M1 can decrease tau hyperphosphorylation via activation of PKC and inhibition of GSK-3β. Dr. Fisher also reviews evidence that regulation of nicotinic receptors (e.g., α7) can be used under conditions of elevated Aβ to potentially reduce tau pathology in AD.

Focusing on tau as a therapeutic target in AD, Anja Schneider and Eckhard Mandelkow (pages 443–457) review tau-based therapeutics for AD and related dementias. In addition to senile plaques, neurofibrillary tangles are characteristic hallmarks of brain pathology in AD and tauopathies such as Pick's disease (PiD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Drs. Mandelkow and Schneider present evidence that hyperphosphorylation and aberrant aggregation of tau plays a central role in neurodegeneration and neuronal dysfunction in AD and tauopathies. They then summarize therapeutic strategies aimed at regulating tau phosphorylation and aggregation, as well as those targeted at dissolving tau aggregates (e.g., by activation of degradation pathways or anti-tau immunotherapy). Alternative therapeutic strategies reviewed include stabilizing microtubule networks, which cannot bind hyperphosphorylated tau, or modulating the splicing machinery to decrease levels of four-repeat tau, which is more prone to aggregation.

Another receptor-based target being pursued for AD therapeutics is the serotonin 5-HT$_6$ receptor, which is expressed mainly in the CNS, in regions associated with cognitive function. Neil Upton and colleagues (pages 458–469) describe the use of 5-HT$_6$ receptor antagonists as cognitive enhancers in AD. Recent studies have shown that blockade of 5-HT$_6$ receptors leads to an improvement of cognitive performance and also engenders anxiolytic and antidepressant-like activity. Dr. Upton and colleagues point out that the effects of 5-HT$_6$ antagonists involve enhancements of multiple neurotransmitter systems leading to learning-associated neuronal remodeling. They also summarize the cognitive-enhancing effects of the 5-HT$_6$ receptor antagonist SB-742457 in AD patients. This compound has also been tested in two phase 2 clinical trials. Dr. Upton and colleagues summarize the findings in which SB-742457 was well tolerated and led to improvement in both cognitive and global function in AD. Besides ameliorating cognition, 5-HT$_6$ antagonists may also protect against Fyn-dependent activation of Erk1/2 and thus block deleterious effects of activated Fyn on Aβ toxicity and tau phosphorylation.

Two final reviews address novel AD therapies targeted at problems in energy metabolism in the brain. In the first of these, Samuel Henderson reviews region-specific declines in brain glucose metabolism in AD and discuss glucose hypometabolism as a possible target for intervention in the disease process. Dr. Henderson focuses on therapeutics aimed at supplementing the glucose supply of the brain with ketone bodies (e.g., acetoacetate, β-hydroxybutyrate, and acetone). Direct infusion of ketone bodies or ketogenic diets have demonstrated efficacy in animal models of neurodegenerative disorders and in AD clinical trials. Ketone bodies can increase mitochondrial efficiency, thereby supplementing neuronal reliance on glucose for energy. Thus, therapies based on ketone bodies may allow for intervention early in the progression of AD.

A second review covering therapeutics that can ameliorate problems with energy metabolism in the AD brain is provided by Gary Landreth and colleagues (pages 481–489). Dr. Landreth focuses on the nuclear receptor PPARγ, which is a ligand-activated transcription factor involved with regulating glucose and lipid metabolism, as well as with inflammatory gene expression. Dr. Landreth and colleagues summarize recent data showing how agonists of the PPARγ receptor can ameliorate disease-related pathology and improve cognition in animal models of AD. They also discuss recent clinical trials in which the PPARγ agonist, rosiglitazone, was shown to improve memory and cognition in AD patients. The initial suggestion that PPARγ might be considered for treating AD came from the known effects of PPARγ agonists on insulin activity, energy metabolism, lipid metabolism, and inflammation. Although various mechanisms of action have been proposed for PPARγ agonists in AD, Dr. Landreth and colleagues review how they act through multiple parallel pathways to affect AD pathogenesis.

In summary, many of the most promising current clinical trials aimed at modifying disease progression (as opposed to just treating the symptoms) in AD are targeting Aβ and tau abnormalities in the brain, and others are

targeting energy metabolism. The field eagerly awaits the results of these clinical trials—with cautious optimism and with high hopes. Ultimately, our best chance for effectively treating and preventing AD will most likely involve a cocktail of therapies that will, on the one hand, safely and specifically regulate cerebral Aβ levels and, on the other hand, enhance cognition and ameliorate neuronal energy metabolism. With several active clinical trials and other promising drugs now headed toward the clinic, the hope is that we will soon have novel AD therapeutics that successfully slow or reverse disease progress in AD.

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