Drugs of the Future 2008, 33(9): 811-822

CCC: 0377-8282/2008

Meeting Report

Towards early detection and treatment of Alzheimer's disease

Highlights from the 11th International Conference on Alzheimer's Disease and Related Disorders (ICAD)

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CONTENTS

Abstract

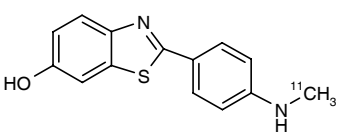
The 11th International Conference on Alzheimer's Disease and Related Disorders (ICAD) 2008, held in Chicago on July 26-31, gathered nearly 5,400 neurologists and neuroscientists from over 70 countries around the world. At this year's meeting, special attention was devoted to biomarker studies and novel diagnostics to improve the early detection of this devastating neurological disorder. Here, we highlight relevant topics covered during this exciting conference, in particular the latest developments in biomarkers and therapies for Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is a progressive, fatal neurodegenerative disorder and the most common cause of dementia in the elderly, followed by vascular dementia. Currently, the diagnosis of AD mostly occurs when the patient is already cognitively impaired and exhibits extensive neuropathology involving neuronal loss. The lack of clinical success of current treatments may be due to the fact that the disease is identified when it is already well established. Current research is focused on the discovery of novel biomarkers and diagnostic techniques that will allow AD diagnosis in earlier stages, especially when the patient's cognitive function is still not affected. Furthermore, the development of new disease-modifying drugs targeting the two typical neuropathological features –amyloid deposits and neurofibrillary tangles– will provide more effective treatments, especially when combined with currently available neurotransmitter-based therapies.

Biomarker studies

The development of amyloid plaques and neurofibrillary tangles may begin many years before the onset of cognitive symptoms. According to John C. Morris from Washington University, the clinically recognized stage of AD (dementia of the Alzheimer type) may probably be the end stage of this process (1). Thus, to identify patients before symptom onset, *i.e.,* preclinical AD, may be crucial to provide early pharmacological intervention to prevent the development of neuronal loss and preserve normal brain function. Thus, Dr. Morris and his team have led research assessing biomarkers that will allow the detection of this presymptomatic stage of AD. One of them is imaging brain amyloid plaques with the **[^{11}C]-labeled Pittsburgh Compound B** (PIB), a diagnostic compound in phase I/II trials at the University of Pittsburgh and Uppsala University for the diagnosis of Alzheimer's-type dementia. Due to a high affinity for β-amyloid (Aβ) protein and its ability to cross the blood–brain barrier, it allows the imaging of amyloid plaque deposits in living patients using positron emission tomography (PET). This technique combined with the detection in cerebrospinal fluid (CSF) of relevant AD biomarkers, such as $A\beta_{40}$, $A\beta_{42}$, tau and phosphorylated tau, has allowed the establishment of some useful diagnostic correlations. In fact, research led by Dr. Anne M. Fagan from the same group at Washington University has demonstrated that in volunteers rated cognitively normal or having very mild or mild AD, individ-



[^{11}C]-Pittsburgh Compound B

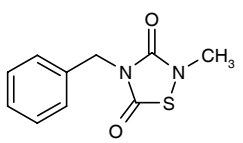
uals with positive PIB binding exhibited low levels of CSF $A\beta_{42}$, and conversely, PIB-negative subjects had high CSF $A\beta_{42}$ levels, regardless of their cognitive status. Moreover, several nondemented individuals were PIB-negative and had low CSF $A\beta_{42}$, while some very mild AD patients were PIB-negative and showed high CSF $A\beta_{42}$, which may indicate that a reduction in CSF $A\beta_{42}$ levels may precede the development of PIB positivity in the preclinical stage of AD (2). Previous studies have also identified a high CSF tau/$A\beta_{42}$ ratio as an indicator of future dementia in cognitively normal elderly subjects (3).

Two studies at Trinity College in Dublin, Ireland, and the University of Munich, Germany, investigated whether CSF β-secretase (BACE1) could be a biomarker for predicting the conversion of mild cognitive impairment (MCI) to AD. Researchers measured BACE1 levels in 80 AD patients, 59 subjects with MCI and 69 healthy elderly controls and discovered that MCI patients displayed increased BACE1 activity compared to AD patients and healthy controls. In addition, BACE1 activity significantly correlated with BACE1 protein and Aβ levels. Further clinical follow-up of 47 MCI individuals demonstrated that BACE1 levels and ApoE-ε4 genotype, a known genetic risk factor for AD, were the strongest predictors of conversion to AD after controlling for age and gender. After a mean follow-up period of 2.3 years, 15 MCI subjects progressed to AD (4, 5). A further study showed that MCI patients who progressed to AD had higher baseline CSF BACE1 levels than those who remained stable or those who developed other forms of dementia (6).

New therapies

Antiamyloid therapies

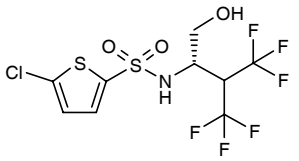
Researchers at the Hospital de la Santa Creu i Sant Pau, Barcelona, in collaboration with NeuroPharma, tested the effects of a novel glycogen synthase kinase GSK-3 inhibitor, **NP-031112**, in a newly developed double transgenic mouse (APP^{sw}/tau^{vlw}) that features both tau and amyloid pathology, hence mimicking human AD. Daily oral treatment with NP-031112 (200 mg/kg) for 3 months in APP^{sw}/tau^{vlw} mice starting at 12 months of age resulted in improved performance on the Morris water maze compared to untreated mice. In addition, treatment caused a significant decrease in hippocampal tau hyperphosphorylation and in amyloid burden in entorhinal and cingulate cortex. NP-031112 also reduced astroglial proliferation in hippocampus and entorhinal cortex, indicating antiinflammatory activity. Importantly, treatment significantly prevented neuronal loss in the CA1 region of the hippocampus and in entorhinal cortex, areas typically affected in AD. Neuronal survival in NP-031112-treated animals remained at the same levels as in untreated animals at 12 months of age. These results suggest that GSK-3 inhibition may be an effective strategy for the treatment of AD (7, 8).



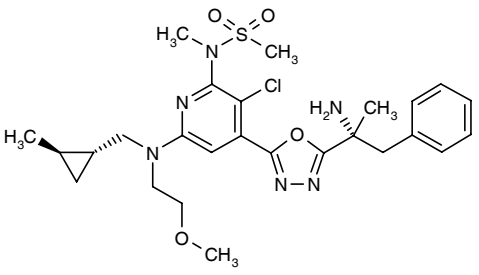
NP-031112

GSI-953 (**begacestat**) is a γ-secretase inhibitor in phase I clinical development at Wyeth for the treatment of AD. Data from preclinical investigations detailed the rationale for continued development of the compound. *In vitro,* GSI-953 was found to inhibit Aβ production with low-nanomolar potency in cellular and cell-free assays. Cellular assays of Notch processing revealed > 16-fold selectivity for the inhibition of amyloid precursor protein (APP) cleavage, suggesting that GSI-953 might not provoke the side effects associated with inhibition of Notch processing related to γ-secretase inhibition. In Tg2576 mice, GSI-953 reduced Aβ in plasma, CSF and brain, with a minimal effective dose of 1 mg/kg p.o. A dose of 10 mg/kg was also associated with improvement in cognitive deficits (9). Further investigations in Tg2576 mice found that high doses of GSI-953 significantly reduced $A\beta_{40}$ levels in brain, CSF and plasma, while a lower dose significantly reduced $A\beta_{40}$ only in brain and plasma. In clinical studies in which healthy young subjects and AD patients received single oral doses of GSI-953, plasma but not CSF $A\beta_{40}$ levels were dose-dependently reduced. The GSI-953 plasma:CSF ratio was approximately 10 in both mice and humans. These results suggest that brain concentrations of GSI-953 that reduced brain Aβ in the mouse model were achieved at the doses tested in humans (10).

Merck & Co. researchers have developed **TC-1**, a BACE inhibitor shown to reduce brain Aβ levels in monkeys following oral administration in recent studies. *In vitro*, TC-1 potently inhibited BACE1 and BACE2 with IC_{50} values of 0.3 and 17 nM, respectively. TC-1 (3 and 10



Begacestat

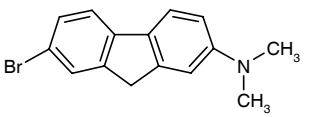


TC-1

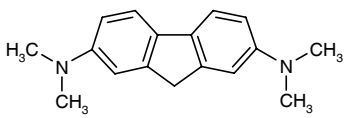
mg/kg) was orally administered to conscious rhesus monkeys (N = 6) together with the cytochrome P-450 CYP3A4 inhibitor ritonavir to enhance TC-1 plasma levels. Treatment induced a significant, dose- and time-dependent reduction in CSF levels of $A\beta_{40}$ (42%) and $A\beta_{42}$ (43%). CSF soluble APPβ, but not APPα, levels were also significantly decreased (41%), as well as plasma $A\beta_{40}$ concentrations (61%). A good correlation was observed between sAPPβ and CSF $A\beta_{42}$ and between CSF $A\beta_{42}$ and $A\beta_{40}$ upon TC-1 treatment. However, the correlation between CSF $A\beta_{40}$ and plasma $A\beta_{40}$ was found to be variable. Preliminary experiments in APP/YAC transgenic mice, an accelerated model of AD, have shown that TC-1 treatment (100 mg/kg) also markedly reduced brain Aβ (11).

Scientists at the University of California, Davis, have tested two fluorene compounds, **K-01-162** and **K-01-186**, identified from libraries of blood–brain barrier-permeable, highly specific, small-molecule amyloid ligands developed for radioligand imaging. These compounds have been found to bind to intracellular Aβ oligomers (AβO), which may play a role in the early pathogenesis of AD, and decrease synaptotoxicity. Both compounds were able to disaggregate AβO and prevent progressive Aβ aggregation. Additionally, K-01-162 was evaluated in a 5xFAD murine model of AD, showing a decrease in soluble Aβ species and amyloid plaque burden after short-term intracerebroventricular infusion. These preliminary results suggest that both K-01-162 and K-01-186 may hold promise for the treatment of AD (12).

Pfizer scientists reported on the preclinical profile of their novel γ-secretase inhibitor **PF-3084014**. When administered subcutaneously it showed a linear efficacy–exposure relationship in both guinea pigs and APP transgenic Tg2576 mice, with a brain-to-plasma ratio of approximately 1 in guinea pigs. Aβ N^1-terminal variant (Aβ1-X) levels were reduced by up to 80% in brain and plasma, and by up to 70% in CSF in guinea pigs (10 mg/kg s.c.), and these results were similar to those in mice (18 mg/kg s.c.), where levels decreased by 71% in the brain, 78% in the CSF and 84% in the plasma. As with other nonselective γ-secretase inhibitors, the $A\beta_{40}$ fragment was more potently inhibited by PF-3084014 than $A\beta_{42}$. Unlike other γ-secretase inhibitors, PF-3084014 at low doses only led to a minor elevation of plasma Aβ1-X, with no rebound following a period of inhibition (13).



K-01-162

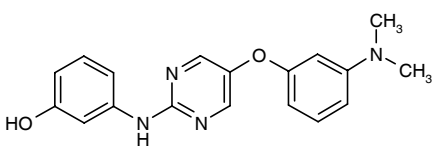


K-01-186

Researchers at Abbott disclosed promising preclinical results for novel antibodies against AβO, such as **A-887755**, a passive immunotherapy for the treatment of AD. A-887755 selectively targeted AβO, discriminating not only monomers, fibrils or sAPPα *in vitro*, but also Aβ monomers in human AD CSF and plasma samples (14). Studies in Tg2576 mice with synaptic modifications in the CA1 hippocampal region demonstrated that A-887755 successfully prevented spine density deficit in apical dendrites proximal to soma (15). Further assays in APP transgenic mice demonstrated that A-887755 at 500 μg for 6 weeks increased novel object recognition, reduced plaque formation and enhanced dentate gyrus PSD-95 and neocortex pPAK synaptic markers (16).

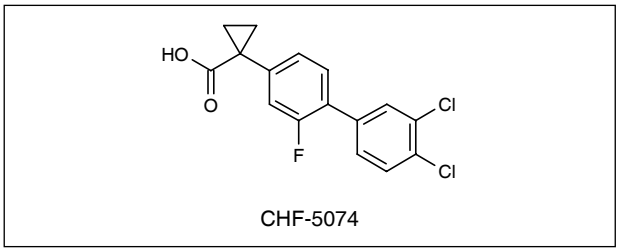
Following the discovery of RS-0406, a small molecule that demonstrated the ability to inhibit the toxicity of Aβ assemblies *in vitro*, investigators at Senexis modified the compound to improve its potency and eliminate potential metabolic/toxicological liabilities. This resulted in **SEN-1269**, which was found to inhibit the process of Aβ aggregation in a thioflavin-T fluorescence assay and to protect neuronal cell lines against an $A\beta_{42}$ insult. Concentration-dependent binding to $A\beta_{42}$ oligomers was also demonstrated with SEN-1269. *In vivo*, SEN-1269 rescued the deficit in long-term potentiation caused by naturally derived oligomers of Aβ. In rats undergoing an alternating-lever cyclic-ratio schedule procedure, exogenously applied, naturally derived AβO impaired performance on the lever-pressing task. SEN-1269 100 nM to 1 μM protected against this impairment, resulting in fewer lever-switching errors and incorrect lever perseverations (17).

NeuroPharma investigators have reported the discovery of an extract from the sponge *Stylissa* spp. that inhibits GSK-3 kinase, and have developed a synthetic analogue of oroidin, one of the active components of the extract. This analogue, **NP-103**, was found to concentration-dependently inhibit endogenous tau phosphorylation in SH-SY5Y human neuroblastoma cells at the epitope Ser396, a site specifically phosphorylated by GSK-3β in cells, without cytotoxic effects. NP-103 inhibited the activity of recombinant human GSK-3β and GSK-3α *in vitro* with IC_{50} values of 0.56 and 0.29 μM, respectively. Further experiments showed that ATP can overcome GSK-3β inhibition by NP-103, indicating that NP-103 is a competitive inhibitor of ATP binding. Evaluation of the inhibitory profile of NP-103 using different human kinases indicated that the compound is a selective inhibitor of GSK-3 (18).

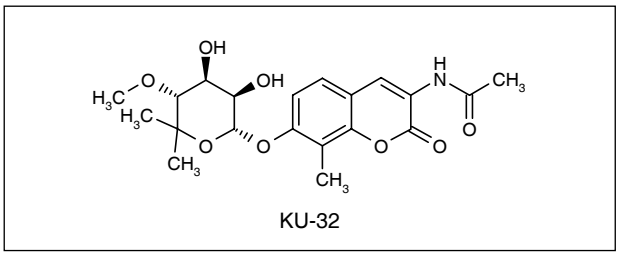


SEN-1269

After treatment with **CHF-5074**, reductions in brain Aβ levels were observed in experiments in transgenic mice expressing mutant human APP and in guinea pigs expressing Aβ peptides of the human sequence. In the mouse study, treatment consisted of 6 months of CHF-5074 at 375 ppm in the diet, ibuprofen 375 ppm in the diet or a standard diet. CHF-5074 significantly reduced the area occupied by plaques in the cortex (–34.3%) and hippocampus (–44.5%) compared to controls. The number of plaques was also significantly reduced by the treatment. In addition, plaque-associated microglia were significantly reduced in CHF-5074-treated mice compared to controls in cortex and hippocampus, and CHF-5074-treated mice performed significantly better than controls on the distance moved in the Morris water maze. CHF-5074 treatment did not affect mortality or weight gain compared to controls (19). In the guinea pig model, the effects of single oral doses CHF-5074 of 10 or 100 mg/kg were compared to vehicle. CHF-5074 significantly reduced brain $A\beta_{42}$ levels compared to vehicle (47.8% at 24 h after 100 mg/kg), but not brain $A\beta_{40}$ levels or plasma $A\beta_{40}$ or $A\beta_{42}$ levels. Brain levels were dose-proportional and the mean brain-to-plasma ratios were 3.3% and 9.3%, respectively, for doses of 10 and 100 mg/kg (20).



CHF-5074



KU-32

Anti-tau therapies

Recently disclosed preclinical results from studies with a novel heat shock protein HSP90 *C*-terminal inhibitor, **KU-32**, suggest that it may be useful in the therapy of AD, as it appears to demonstrate efficacy without toxicity, which is commonly found in this class of compounds. In primary cortical neuron cultures, KU-32 decreased Aβ-induced tau phosphorylation via upregulation of HSP70. *In vivo* assays in a tau-mutant mouse model demonstrated that chronic treatment with KU-32 (2 mg/kg 5 times/week for 8 weeks) significantly decreased not only soluble tau, but also hyperphosphorylated, sarkosyl-insoluble tau, compared to controls. KU-32 was also found to cross the blood–brain barrier in mice, with terminal half-lives of 27.4 and 23.7 min in plasma and brain, respectively (21).

Neurotransmitter therapies

Researchers at Memory Pharmaceuticals have discovered **MEM-68626**, which has been selected for clinical development from a series of 5-HT_6 receptor antagonists due to its ability to improve learning and memory processing in MCI and AD. In a young rat model of episodic memory, MEM-68626 enhanced both memory acquisition and consolidation. Furthermore, the compound was able to restore the cognitive function of aged impaired rats in a model of spatial reference memory. The pharmacokinetics of MEM-68626 allowed once-daily oral administration (22).

Diagnostics

Adlyfe's novel **Pronucleon™** peptide imaging agents have been previously found to measure insoluble and soluble Aβ plaques in CSF and blood, which may make them effective tools for the preclinical diagnosis of AD and for determining the efficacy or monitoring the effects of antiamyloid therapies (23). *In vitro* staining assays with Pronucleon™ peptides were performed in transgenic mice expressing human APP and post-mortem human AD brain sections, which showed a plaque-like morphology correlated with thioflavin-S staining results. Some of the Aβ structures, such as amorphous or α-helical structures, were not detected by Pronucleon™ peptide technology. The imaging agents were able to cross the blood–brain barrier and label amyloid plaques in the hippocampus and cortex of hAPP mice after intranasal administration. Results in aged hAPP mice with intranasal and i.v. administration of Pronucleon™ peptides matched completely with the thioflavin-S staining technique but only partially with the anti-Aβ (6E10) test (24).

Update on clinical studies

Antiamyloid therapies

Several presentations at the meeting further examined the activity of the BACE1 inhibitor **CTS-21166** (ASP-1702), complementing previous reports detailing reductions in plasma Aβ in healthy subjects. The drug is being developed as part of a collaboration between Astellas Pharma and CoMentis. A series of experiments characterizing the pharmacological profile of CTS-21166 revealed a K_i of 2.5 nM against BACE1 and selectivity *versus* a broad panel of enzymes, channels and receptors. Excellent oral bioavailability (20-60%) was noted in multiple species, and oral administration of the agent was associated with reduced Aβ in plasma, CSF and brain of wild-type rodents (25). In studies in Tg2576 transgenic mice, CTS-21166 was given as single oral doses of 30, 100 and 300 mg/kg or b.i.d. for 5 days at doses of 10, 30 and 100 mg/kg. Single doses of CTS-21166 100 mg/kg significantly improved memory deficits in the animals, and soluble cortical $A\beta_{40}$ was reduced 23% after a single dose

of 300 mg/kg. Five days of dosing at 10 and 30 mg/kg b.i.d. restored the memory deficit, and soluble cortical $A\beta_{40}$ was reduced by 15-20% after 5 days of dosing at 10-100 mg/kg b.i.d. Good brain penetration and plasma levels were seen with both single and multiple doses (26). In hAPP transgenic mice, the administration of CTS-21166 4 mg/kg/day for 6 weeks reduced soluble brain $A\beta_{40}$ and $A\beta_{42}$ by 38% and 35%, respectively, and reduced plaque area and count by approximately 40%. The treatment was well tolerated and no effects on the myelination of peripheral nerves, motor function or strength were noted (27). Two phase I studies in healthy male volunteers have also been conducted, with i.v. doses of 7.5-225 mg in one trial and an oral dose of 200 mg in the other. All doses were well tolerated. Intravenous infusion was associated with dose-proportional increases in exposure and oral bioavailability was good (40.5%), with low intersubject variability (28).

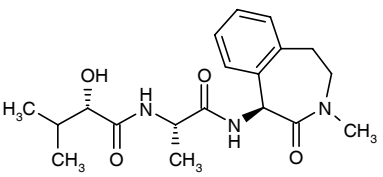
In a 12-week phase II study in patients with mild to moderate AD (n = 52) and healthy volunteers (n = 16), i.v. administration of **LY-2062430,** Lilly's humanized monoclonal antibody targeting soluble Aβ, was well tolerated and associated with increases in patients' blood and CSF $A\beta_{42}$. This randomized, placebo-controlled trial evaluated LY-2062430 at doses of 100 and 400 mg given once a week or every 4 weeks in patients, while volunteers received a single 100-mg dose or placebo. Brain imaging and CSF evaluation showed no evidence of inflammation or bleeding. Cognitive scores were not affected by treatment, and a substudy in 24 patients and 13 volunteers revealed no change in brain Aβ plaque burden. Treatment was also associated with increased total $A\beta_{40}$ and $A\beta_{42}$ in CSF and plasma, while the unbound fraction of CSF $A\beta_{42}$ increased dose-dependently. The effects observed may be due to plaque dissolution. A phase III study of LY-2062430 is planned for 2009 (29).

Bapineuzumab (AAB-001) is a humanized monoclonal antibody targeting the Aβ *N*-terminus that is currently in phase III trials at Elan and Wyeth Pharmaceuticals for the treatment of mild to moderate AD. Results from a phase I study evaluating the safety and tolerability of bapineuzumab in mild to moderate AD patients were disclosed at the meeting. Patients (N = 234) were randomized to receive either bapineuzumab (0.15, 0.5, 1.0 or 2.0 mg/kg; n = 124) as 6 separate infusions (13 weeks apart) or placebo (n = 110). The primary endpoint was to identify within-cohort treatment differences from baseline through week 78 on cognitive measures (Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-cog], Neuropsychiatric Test Battery [NTB]). Although no dose–effect was observed, bapineuzumab showed a trend towards improvement in all cognitive measures, which reached statistical significance in those patients who received the 6 infusions. Post hoc analysis revealed no difference between ApoE4 carriers and noncarriers. Interestingly, the subset of noncarriers receiving all bapineuzumab infusions showed an improvement of +7.3 points in the ADAS-cog. Magnetic resonance imaging (MRI) findings were comparable in both groups. However, treated ApoE4 noncarriers showed a significantly lower decline in brain volume and a nonsignificant enlargement in ventricular volume compard to placebo patients. Phosphorylated tau in CSF also tended to be lower in bapineuzumab-treated patients, but no changes were seen in Aβ or total tau. These results support further investigation of bapineuzumab in phase III clinical trials (30).

Bristol-Myers Squibb's novel γ-secretase inhibitor **BMS-708163** has shown a promising pharmacokinetic and safety profile with potent effects on APP (IC_{50} = 0.30 nM for inhibition of $A\beta_{40}$; IC_{50} = 58 nM for inhibition of Notch) signaling. In preclinical studies in dogs and rats, BMS-708163 administration led to a decrease in brain and CSF $A\beta_{40}$ levels, without Notch-related gastrointestinal and lymphoid toxicity. This effect was also observed in single- and multiple-dose studies in humans where BMS-708163 dose-dependently decreased brain and CSF $A\beta_{40}$ levels. A linear pharmacokinetic profile was identified up to a dose of 200 mg. In general, BMS-708163 was well tolerated at up to 400 mg as single doses or up to 150 mg as multiple doses for 28 days (31).

Dose adjustments for LY-450139 (**semagacestat**), a γ-secretase inhibitor in phase III development at Lilly for the treatment of AD, do not appear to be necessary in Japanese subjects based on ethnicity. This was the conclusion of a safety, tolerability, pharmacokinetic and pharmacodynamic study of the drug in Japanese subjects given 40, 100 or 140 mg LY-450139 or placebo daily for 14 days. No serious adverse events, no clinically significant Q-T_c prolongation and no other clinically important cardiovascular changes were seen. Several laboratory values (uric acid, potassium, inorganic phosphorus) showed trends toward changes compared to placebo. LY-450139 was rapidly absorbed and displayed a mean half-life of 2.8 h. A maximum reduction in $A\beta_{40}$ concentrations of 57.7% at 140 mg was recorded, and the area above the plasma $A\beta_{1\text{-}40}$ concentration–time curve at 100 and 140 mg was significantly different from placebo. LY-450139 was well tolerated, with the only adverse event, rash, noted in 1 of 6 subjects administered the highest dose (32).

The pathological formation of AβO has been shown to be mediated, at least in part, by metals like zinc and copper, found near excitatory NMDA synapses. Therefore, researchers at Prana Biotechnology are currently investigating the utility of **PBT-2**, a metal protein-attenuating compound (MPAC) for the treatment of AD. Results were reported from a 12-week phase IIa trial conducted in 78



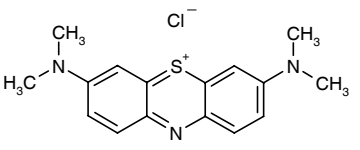
Semagacestat

patients with early AD who were randomly assigned to receive either 50 mg (n = 20) or 250 mg oral PBT-2 (n = 29) or placebo (n = 29). Both doses of PBT-2 were well tolerated during the study period, with a frequency of adverse events comparable across all groups. The most commonly reported treatment-emergent adverse events were headache, dizziness, somnolence, nasopharyngitis and fatigue. No clinically relevant adverse findings were observed. Patients treated with the highest dose of PBT-2 showed a significant reduction of CSF $A\beta_{42}$ levels with a least squares mean change from baseline of –39.2 pg/ml compared to 17.1 pg/ml with placebo. $A\beta_{40}$ levels also decreased on 250 mg PBT-2, but this did not reach statistical significance compared to placebo. Treatment did not affect CSF concentrations of total and phosphorylated tau or plasma levels of $A\beta_{42}$ or $A\beta_{40}$. Additionally, PBT-2 significantly improved two measures of executive function in the NTB: the Category Fluency Test and the Trail Making Test Part B. Other measures of efficacy (memory z-score, ADAS-cog) were not modified by treatment. Additional longer and larger studies are required to effectively measure the effect of PBT-2 on cognition (33, 34).

Further preclinical studies have shown that PBT-2 inhibited free radical-dependent formation of AβO and rescued Aβ-induced inhibition of long-term potentiation in hippocampal slices. In transgenic AD mice, treatment with PBT-2 significantly improved performance on the Morris water maze, which was associated with a reduction in brain Aβ and phosphorylated tau levels and an increase in markers of synaptic plasticity (35).

Anti-tau therapies

TauRx Therapeutics disclosed new findings from multiple preclinical and clinical studies of its oral tau aggregation inhibitor **methylthioninium chloride** (MTC; rember™) assessing the drug's effects on cognitive function in AD. In studies in transgenic murine models of AD, MTC treatment led to a significant decrease in tau-positive neuron counts in the hippocampus and entorhinal cortex with an overall reduction of tau pathology (36). Furthermore, a study in a pharmacological model of AD (scopolamine-induced amnesic mice) indicated that the drug also has symptomatic activity as it reversed short- and long-term memory, as well as learning deficits, to a degree greater than rivastigmine (37). Two weeks' pretreatment with MTC at 15 and 45 mg/kg also reversed age-dependent spatial problem-solving cognitive deficits in transgenic mice (38).

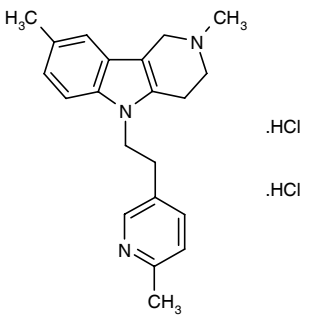


Methylthioninium chloride

A clinical study in 332 subjects with mild or moderate AD randomized to receive MTC at 30, 60 or 100 mg t.i.d. or placebo was performed over a 24-week period. At the end of the study, regional cerebral blood flow declined in AD patients treated with placebo, but this was only partially decreased after a dose of 60 mg MTC in the hippocampal, median temporal and temporal regions (39). An ^{18}F-FDG PET assay in a subgroup of these patients (n = 18) revealed that MTC significantly increased glucose metabolism in the median temporal lobes compared to the placebo group, but because the sample size was small further investigations may be required (40). Another clinical trial in the same population (N = 321) demonstrated that at a dose of 60 mg MTC significantly enhanced cognitive function by improving the ADAS-cog score by –5.4 units relative to placebo only in patients with moderate AD. However, further analysis at week 50 demonstrated an 81% reduction in cognitive decline in both mild and moderate AD patients. Cognitive improvement was associated with positive results in SPECT and PET scans, which showed decreased intensity in regions associated with tau pathology, thus indicating the disease-modifying nature of MTC. The minimum effective dose was suggested to be 60 mg t.i.d. The most commonly reported adverse events were diarrhea, dysuria, urinary urgency and falls, which are similar to those reported with acethylcholinesterase inhibitors (41).

Neurotransmitter therapies

Results from an open-label extension of a phase II study and an analysis of treatment effect by disease severity have added to data showing a benefit for **dimebolin hydrochloride** (Dimebon; Medivation) treatment in patients with AD. The study included 183 patients with mild to moderate AD who were randomized to receive dimebolin 20 mg t.i.d. or placebo. As previously reported, significant improvements in efficacy measures (ADAS-cog, Clinician's Interview-Based Impression of Change Plus Caregiver Input [CIBIC-plus], Mini-Mental State Examination [MMSE], Alzheimer's Disease Cooperative Study-Activities of Daily Living [ADCS-ADL], Neuropsychiatric Inventory [NPI]) were seen with dimebolin at 1 year compared to placebo. Further analysis revealed

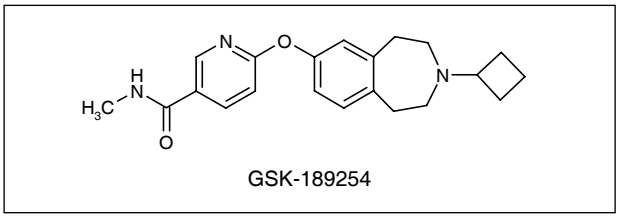


Dimebolin hydrochloride

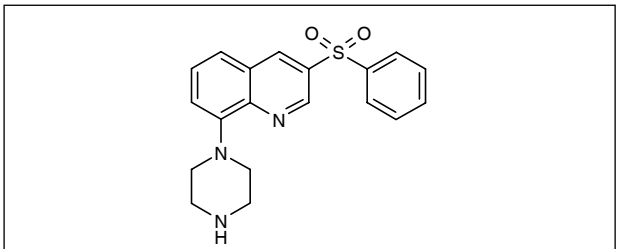
improvements in cognition and memory, activities of daily living, behavior and global function in patients with both mild and moderate disease, and that those with moderate disease had greater benefit. Patients with mild AD given dimebolin remained above baseline for 1 year on the ADAS-cog, while patients with moderate AD treated with dimebolin had an improvement of 9.7 points over placebo on the ADAS-cog. A 6-month extension study showed that patients treated with dimebolin for 18 months had their levels of memory and thinking, behavior, activities of daily living and overall function preserved from the time of trial entry. Dimebolin was well tolerated over 18 months of treatment. Patients initially treated with placebo for 12 months and then crossed over to dimebolin stabilized on all key measures after declining during the months of placebo treatment. A phase III study of dimebolin in AD is under way (42).

Functional MRI conducted during cognitive tasks has shown that the histamine H_3 receptor antagonist **GSK-189254** affects cognition. The effects were studied in 16 healthy right-handed male volunteers who received GSK-189254 1 mg and placebo in a double-blind, crossover design. The cognitive tasks performed during imaging were paired associates learning (PAL) and delayed match to sample (DMTS). GSK-189254 did not affect performance on either task. During the PAL task, the functional MRI BOLD (blood oxygen level-dependent) signal during learning decreased in the region of the posterior hypothalamus on placebo, but increased on GSK-189254. This suggests an effect of GSK-189254 on histaminergic neurons, which are located in the tuberomamillary nucleus in the posterior hypothalamus. The increase in hypothalamic signal was also significantly associated with increased speed in response latency during learning on GSK-189254. During the DMTS task, activation at the parieto-occipital junction was increased on GSK-189254 and the increase in activity was correlated with shorter response latency. As impairments in PAL and DMTS are seen in AD, the study indicates the means by which GSK-189254 may improve cognition in these patients (43). GlaxoSmithKline's GSK-189254 is in phase I development for AD and in phase II for narcolepsy.

SB-742457 is a novel, selective and potent 5-HT_6 receptor antagonist developed by GlaxoSmithKline, which has been found to enhance cognition in aged rats. The compound (1.5 mg/kg p.o.) was also able to significantly improve spatial learning ability and reverse scopolamine-induced amnesia in a range of animal models of cognition, including the Morris water maze and passive avoidance tests in aged animals. The benefits on memory retention were more prolonged with SB-742457 compared to donepezil (0.03 and 0.3 mg/kg) (44). Furthermore, the compound was studied in two clinical trials in subjects with mild to moderate AD over 24 weeks. Efficacy was measured using the CIBIC-plus, and the change from baseline ADAS-cog score at week 24 (intention-to-treat last observation carried forward [LOCF] analyses). In the first study (AZ3106242; N = 197), either SB-742457 (15 mg/day titrated to 35 mg/day at week 4) or donepezil (5 mg/day titrated to 10 mg/day at week 4) was administered, but the study was not powered enough to show formal statistical differences between treatment groups and placebo (45). Therefore, in a second trial (AZ3100603; N = 371), following increasing SB-742457 doses of 5, 15 and 35 mg/day, some evidence of a linear trend in beneficial response for both cognition and global function at week 24 LOCF was noted. There was no placebo decline for CIBIC-plus or ADAS-cog after 24 weeks. A subgroup analysis demonstrated a trend towards superior improvement in ADAS-cog in patients with baseline MMSE scores of 18 or less compared to those with MMSE score > 18. The adverse event profile was similar across all groups and the most frequently reported were headache and urinary tract infections (46).



GSK-189254



SB-742457

A phase IIa study revealed significant effects for monotherapy with the 5-HT_4 agonist **PRX-03140** (Epix Pharmaceuticals, GlaxoSmithKline) on the ADAS-cog after 2 weeks of treatment in patients with mild AD. Patients received placebo or PRX-03140 at doses of 50 or 150 mg p.o. given once daily, or donepezil 10 mg plus PRX-03140 5, 25, 50, 100 or 200 mg or placebo p.o. once daily. After 2 weeks, the mean ADAS-cog change for monotherapy with 150 mg PRX-03140 was 3.6 points, which was significantly superior to placebo. When given with donepezil, no significant effects on ADAS-cog scores were seen for PRX-01340 compared to placebo. A trend towards an effect on the EEG α:θ ratio with PRX-03140 150 mg was also seen. PRX-03140 was well tolerated as monotherapy and in combination with donepezil at up to 100 mg. Two other studies of PRX-03140 have been initiated, including a 3-month monotherapy study and a 6-month study of PRX-03140 given together with donepezil 10 mg (47).

AD immunotherapy

Baxter researchers are currently investigating the efficacy of **intravenous immunoglobulin** (IVIG), which has

previously shown cognitive improvement in mild to moderate AD patients when continuously administered for 6 months, as an antiamyloid immunotherapy. Interim results from a 6-month, double-blind, placebo-controlled phase II study followed by a 12-month rater-blinded extension phase conducted by Weill Cornell Medical College researchers in 24 AD patients who received IVIG doses ranging from 0.2 to 0.8 g/kg every 2 weeks showed statistically significant improvement in CGIC scores at 3, 6 and 9 months. Treatment also resulted in improved ADAS-cog measures, which only reached statistical significance at 9 months. The most effective dose was found to be 0.4 g/kg every 2 weeks, with associated improvements in ADAS-cog and CGIC scores and measures of daily functioning over baseline (48).

Researchers at the Karolinska Institute in collaboration with Novartis have reported results from the first-in-human study (CCAD106A2101) of **CAD-106**, an immunotherapeutic vaccine comprising the $A\beta_{1-6}$ peptide coupled to Qβ virus-like particles. CAD-106 demonstrated amyloid plaque-lowering activity in preclinical studies. The safety, tolerability and immunogenicity of CAD-106 were evaluated in a 52-week, two-center, randomized, double-blind, placebo-controlled trial in patients with mild to moderate AD (N = 31). The study assessed two patient cohorts and results are currently available from the first cohort of patients. Twenty-four patients were assigned to CAD-106 treatment (50 μg s.c. on weeks 0, 6 and 18) while 7 received placebo. Increased Aβ-specific IgG antibodies were observed in 16 of 24 CAD-106-treated patients. Following the first injection, an increase in Aβ-specific IgM antibodies was noted, whereas IgG titers increased after the second and third immunization, reaching similar levels. This pattern was considered as a classic immune response to active immunization. Antibody titers specific to Qβ virus-like particles displayed a similar profile to Aβ-specific antibodies. Moreover, human serum was reactive against amyloid plaques and relative staining intensities matched those of Aβ antibody titers. Concerning its safety profile, the most frequently reported adverse events were gastrointestinal disorders, fatigue, injection-site erythema and injection-site rash. CAD-106-associated serious adverse events included loss of consciousness, noncardiac chest pain, head trauma, aortic stenosis and syncope. No clinically relevant findings on MRI, cerebrospinal fluid, laboratory or electrocardiographic parameters were observed. Treatment was not associated with meningoencephalitis. Further evaluation of dose regimens will be assessed in the second cohort (49).

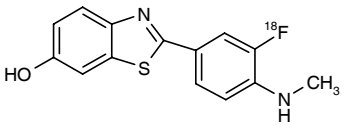
Diagnostics

Avid Pharmaceuticals reported the development of a novel [^{18}F]-labeled PET amyloid imaging agent, namely **[^{18}F]-AV-45**, currently undergoing phase II clinical trials. In contrast to PIB, [^{18}F]-AV-45 is a longer-lived tracer that after injection to AD patients showed rapid brain uptake, with retention in areas of high amyloid deposition and levels that were maintained in the brain between 50 and 90 min postinjection, while healthy controls showed rapid washout. Also, AD patients exhibited higher standardized uptake value ratio (SUVR) values in the cortical target areas compared with healthy volunteers. This pattern of tracer kinetics is suitable for obtaining high-quality images via PET imaging beginning 50 min after administration of [^{18}F]-AV-45. These results encouraged ongoing phase II studies and suggest that this novel radiotracer may be useful for the development and monitoring of novel amyloid-reducing therapies (50).

Researchers at GE Healthcare, in collaboration with the K.U. Leuven Medical School, Belgium, have conducted a phase I clinical trial evaluating the feasibility of using **[^{18}F]-AH-110690** as a novel *in vivo* marker of AD-related brain amyloidosis. [^{18}F]-AH-110690 is a fluorinated derivative of the [^{11}C]-labeled Aβ amyloid ligand Pittsburgh Compound B (see above). Following evaluation in 6 healthy volunteers, [^{18}F]-AH-110690 was found to be safe, with a recommended dose of 185 MBq. Brain retention of [^{18}F]-AH-110690 was then assessed using PET, computerized tomography (CT) and MRI. After [^{18}F]-AH-110690 administration to 3 early-stage clinically probable AD patients and 3 healthy subjects, higher specific binding in neocortical regions (lateral and temporal cortex, posterior cingulate) in AD patients was found compared to in healthy subjects. Nonspecific binding of [^{18}F]-AH-110690 was predominantly seen in white matter. Time–activity curves demonstrated elevated retention of [^{18}F]-AH-110690 in known amyloid-containing regions of AD brains. These results suggest that [^{18}F]-AH-110690 may be a useful marker for the detection of early-stage AD (51).

Others

Pfizer has assesed the safety and tolerability of its orally available RAGE (Receptor for Advanced Glycation Endproducts) antagonist **PF-4494700** (formerly TTP-488) in patients with AD. In this 10-week, double-blind, parallel-group phase II study, patients (N = 67) with probable AD were randomized to receive either a high-dose (60 mg once daily for 6 days followed by 20 mg once daily for 9 weeks) or a low-dose schedule (30 mg once daily for 6 days followed by 10 mg once daily for 9 weeks) of PF-4494700 or placebo. The overall incidence of adverse events was similar across all groups (68%, 67% and 75%, respectively, for the high-dose, low-dose and placebo groups). The proportion of patients with adverse events assessed as treatment-related was 32% for the high-dose, 44% for the low-dose and 50% for the placebo groups. No deaths occurred during the study period.

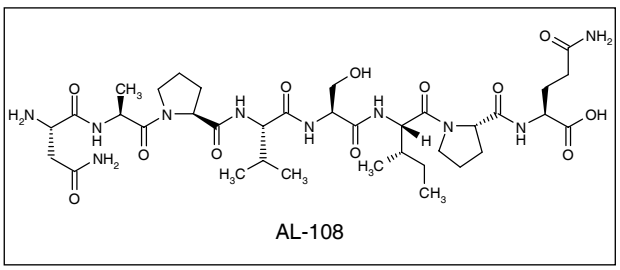


[^{18}F]-AH-110690

Moreover, no clinically significant or dose-dependent differences in clinical laboratory findings were observed in either of the PF-4494700-treated groups relative to placebo. Similarly, no dose-dependent differences in mean electrocardiographic parameters, including heart rate, mean P-R interval, QRS duration or Q-T_c segment were noted between treatment and placebo groups. PF-4494700 did not have any effect on plasma biomarkers, except for a dose-dependent increase in plasma $A\beta_{40}$ at weeks 4 and 10. Further studies are warranted to investigate its efficacy and safety as a potential long-term treatment for AD (52). In preclinical studies, PF-4494700 achieved high brain exposure and chronic treatment led to a reduction in Aβ buildup and cognitive deficits in a transgenic mouse model of AD (53). Pfizer is collaborating with TransTech Pharma to develop and commercialize RAGE modulators, including PF-4494700.

Results from a phase II proof-of-concept study assessing the intranasal NAPVSIPQ peptide formulation **AL-108** for the treatment of amnestic MCI (aMCI) have been reported by Allon Therapeutics researchers. In preclinical studies, AL-108 was previously found to reduce Aβ and tau phosphorylation in the triple transgenic mouse model of AD, hence affecting the pathology of neurofibrillary tangles. This 12-week, double-blind, randomized, placebo-controlled study was conducted in 144 patients with aMCI and assessed the safety, tolerability and effect of two doses of AL-108 (5 mg once daily or 15 mg b.i.d.) on cognitive domains relevant to aMCI and AD. At the highest dose, AL-108 showed a trend toward improvement on the global composite memory endpoint and significant effects on visual working memory (delayed match to sample of 12 s), which was improved compared to baseline values from 34.2% at week 4 to 46.8% at week 8 and 62.4% at week 16. At the same dose, verbal recall and working memory (digit span forward) tests became statistically significant from week 4 up to week 16. In contrast, AL-108 did not affect other cognitive domains that were not clinically impaired in this patient population. Moreover, treatment was well tolerated, with the incidence of reported adverse events being similar to that of placebo. The most commonly observed adverse events were headache, nasopharyngitis and nasal discomfort. The rates of serious adverse events and treatment withdrawals were similar between the two groups (54, 55).

Researchers at Schwabe have reported results from a study that investigated the effects of a once-daily formulation of the *Ginkgo biloba* extract **EGb-761** on AD and vascular dementia (VD) featuring neuropsychiatric symptoms. This 24-week study analyzed 404 patients with diagnosed mild to moderate dementia associated with AD (n = 333) and VD (n = 71) who were randomized to receive 240 mg of EGb-761 or placebo. Treatment was associated with improved total score on the Syndrom–Kurz Test (SKT) cognitive battery (–1.4 points) in both AD and VD patients, while those who received placebo deteriorated by +0.3 points or remained unchanged. In addition, the NPI composite score was also improved by –2.9 and –4.5 points in AD and VD patients, respectively, compared to placebo. Secondary measures such as NPI caregiver stress score, verbal fluency tests and Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) score, as well as patient quality of life and ability to perform activities of daily living were also significantly improved by EGb-761 treatment, with no major differences between AD and VD groups. The adverse event profile of EGb-761-treated patients was similar to that of the placebo group (56).



AL-108

Based on data from preclinical studies, researchers at the University of Massachusetts conducted three clinical trials with a novel **nutraceutical formulation** (NF) consisting of six vitamins and nutraceuticals that may potentially improve cognitive and behavioral symptoms in AD. First studied in an open-label trial in mild to moderate AD patients (N = 18) over 1 year, the NF improved scores of cognitive performance on the Dementia Rating Scale. Furthermore, caregivers reported that daily performance was maintained, with improvement in mood for at least up to 2 years. Results from another placebo-controlled trial in moderate to late-stage AD patients (N = 10) revealed a delay in cognitive decline and maintenance of daily activities for over 6 months. Finally, the formulation significantly improved executive function by 20% in the Trail Making Test after 6 months in a multisite trial in more than 90 dementia patients (57). The NF is scheduled to enter a 3-year phase II clinical trial funded by the Alzheimer's Association.

Mechanisms of disease

A study seeking to help explain the improvement in hippocampal-based cognitive tasks in patients with AD administered **insulin** found that it increased hippocampal activity in patients with early AD but not in nondemented controls. In the Memory and Insulin in Early Alzheimer's Disease (MAIN) study, 3 control and 3 nondiabetic early AD subjects aged over 60 underwent fMRI scanning after administration of 40 IU insulin aspart and after an equal volume of saline via nasal spray. During scanning, subjects were shown indoor/outdoor images and selected outdoor images by button press and insulin-related changes in BOLD responses were compared between groups. In the AD group, fMRI revealed greater hippocampal BOLD activity following the administration of insulin compared to saline, while no difference in hippocampal BOLD activity was seen in controls. Cognitive tests performed after fMRI revealed a mean performance increase on the Logical Memory II Test and the Selective

Reminding Test with insulin administration in the overall group (58).

A study conducted in 59 nondiabetic early AD patients showed a relationship between peripheral insulin and preservation of grey matter volume in specific areas related to memory function such as the hippocampus (59).

Further evidence from a post-mortem study in which 124 AD subjects with diabetes were matched to 124 nondiabetic AD subjects revealed that combining insulin administration with other diabetes medications reduced neuritic plaque burden (60).

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