Current research and development of treatments for Alzheimer’s disease

Alzheimer’s disease is a debilitating condition that causes enormous suffering. In this science article, Adam Todd, Adrian Moore, Mark Ashton and Son Van look at current research and development into new treatments for this disease.

**Alzheimer’s disease** is a neurodegenerative disorder that mostly affects the elderly, resulting in an individual’s gradual loss of cognitive function and, eventually, dementia. Studies have suggested that, with each five-year age group beyond 65, the risks of developing the disease double. Thus, with an ageing population (estimates suggest that, by 2050, 25 per cent of the UK population will be aged 65 or over while 10 per cent will be aged 80 or over3), there will be increased financial pressure on the NHS and social services.

The disease is characterised by the degeneration of areas of the brain primarily associated with cognitive function and memory, such as the hippocampus and cortex. The resulting damage can be divided into three categories: the formation of amyloid plaques, the generation of neurofibrillary tangles, and cell death, which is consistent with the amyloid cascade hypothesis.

The build up of amyloid β (Aβ) peptides in the brain, which aggregate to form amyloid plaques, are derived from the breakdown of amyloid precursor protein (APP), a process that is facilitated by a number of secretase enzymes: alpha secretase, β-site APP-cleaving enzyme and γ-secretase. The build-up of Aβ peptides precedes tau phosphorylation. The hyper-phosphorylated tau proteins form the neurofibrillary tangles (the tau protein provides support to the microtubules of the neuron) which, together with the Aβ peptide aggregates, ultimately lead to neuronal death.

Current treatments fall into two classes: cholinesterase inhibitors (eg, donepezil, rivastigmine and galantamine) and N-methyl-D-aspartate (NMDA) receptor antagonists (memantine). With both classes of treatment, an improvement in cognitive function is observed but, unfortunately, there is no halt to the progression of the disease.

Due to the limitations of current treatments and the expected increase in the incidence of the disease, there is a great deal of research into developing new treatments.

**Cholinesterase inhibitors**

**Phenserine** The selective cholinesterase inhibitor phenserine has been shown to inhibit the formation of Aβ in animal models. However, the results of two trials (phase III and phase IIb) have shown mixed results. In a phase III trial involving patients with mild to moderate disease, no significant difference was noted between the phenserine and placebo groups, and the trial was stopped. However, in a second study (phase IIb) involving patients with mild disease, phenserine treatment reduced both the level of Aβ in the cerebrospinal fluid and the formation of amyloid plaques.

**Dimebon** Dimebon is a cholinesterase inhibitor and NMDA-receptor antagonist that has been used extensively in Russia for over 20 years as an antihistamine. Following encouraging results from a phase II study in which patients receiving dimebon showed an improvement compared with the placebo group, there are currently six phase III trials investigating dimebon as a potential treatment listed on www.clinicaltrials.gov.

**Selective phosphodiesterase-4 inhibitors**

The process of memory formation in humans is characterised by at least two phases: short-term memory and long-term memory. Short-term memory does not require protein synthesis, whereas long-term memory requires both transcription and translation. Perhaps the most widely studied form of synaptic plasticity is long-term potentiation. Like long-term memory, it requires new protein synthesis, which results in cyclic adenosine monophosphate (cAMP) elevation and protein kinase A activation.

Various animal models have indicated that modulating the effect of phosphodiesterase-4 (PDE4) can affect the intracellular levels of cAMP, which, in turn, can have dramatic effects on long-term potentiation and long-term memory formation.

**Rolipram** The selective PDE4 inhibitor rolipram has been shown to have memory-enhancing effects in numerous studies. A further effect of rolipram and other PDE4 inhibitors is an anti-inflammatory effect in both *in vitro* and *in vivo* models. The significance of this additional effect is derived from.

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the important role that inflammation appears to have in the pathogenesis of AD. Because of the dual role that rolipram and other PDE4 inhibitors have demonstrated, there are a number of pharmaceutical companies trying to get a PDE4 inhibitor to market.

**γ-Secretase inhibitors**

The development of Aβ aggregates is a characteristic of Alzheimer’s and it is thought that the formation of these amyloid plaques is a trigger for further changes in the physiology of a neuron and, eventually, the death of it. The plaques are composed of Aβ peptides that result from the stepwise cleavage of APP by a number of enzymes, including γ-secretase. Of the various isoforms of Aβ produced (Aβ37 to Aβ43), it is the Aβ42 form that is most closely associated with the pathogenesis of the disease.

A number of groups have looked into the possibility of inhibiting γ-secretase as a means of treatment. Although initial work with compounds LY-411,575 and BMS-299897 looked promising in preclinical models, it was clear that, at the therapeutic dose, marked changes were observed to both lymphocyte development and the intestine. Despite problems with the early candidates, one compound, LY-450,139, is currently undergoing evaluation as part of a phase III trial.

An interesting alternative to the inhibition of γ-secretase is the development of γ-secretase modulators. These compounds are particularly attractive features of modulating the activity of γ-secretase is the resulting preferential formation of the lower molecular weight forms of Aβ and hence a reduction in the Aβ42 form. Much of the current research effort at developing γ-secretase modulators has focused on non-steroidal anti-inflammatory drugs. Following the initial work with ibuprofen, a number of studies in cell-based models and transgenic mouse models have shown that a number of NSAIDs have the ability to act as γ-secretase modulators.

**5-HT antagonists**

5-Hydroxytryptamine (5-HT) mediates a number of important biological functions, including increasing gastrointestinal motility (via the direct excitation of smooth muscle and an indirect mechanism mediated by the enteric neurons), excitation or inhibition of central nervous system neurons, platelet aggregation and the stimulation of vascular constriction (directly and via sympathetic innervation) and dilation. All of the effects of 5-HT are mediated via a family of receptors (5-HT1–5-HT7) which, with the exception of 5-HT7, belong to the G-protein-coupled receptor superfamily.

Lecozotan SR

Lecozotan SR was pursued by Wyeth Pharmaceuticals following initial work in animal models that showed the compound had cognition-enhancing properties by acting as a 5-HT1A receptor agonist. However, the development of the compound appears to have been terminated.

**Xaliproden**

Xaliproden is a 5-HT1A antagonist and nerve growth factor that facilitates glutamatergic and cholinergic neurotransmission. It was evaluated as a potential treatment in two phase III trials. However, due to a lack of efficacy, the programme was cancelled.11

**SB742,457**

Due to the exclusive distribution of the 5-HT6 receptor in the CNS, coupled with its unique pharmacology and extensive in vivo data from a number of rodent behavioural models showing that blocking the 5-HT6 receptor enhances cognition, there has been some evidence of development of 5-HT6 antagonists.12 A promising development candidate is SB742,457 (GSK), which is currently undergoing a phase II trial due for completion in December 2010.13

**Immunotherapies**

According to the leading theory of Alzheimer’s pathogenesis — the amyloid cascade hypothesis — the build up of Aβ peptides leads to aggregates, which in turn set off a cascade of events that ultimately lead to neuronal death. The process whereby Aβ peptides are able to aggregate and accumulate starts with the cleavage of APP into various isoforms of Aβ (Aβ37 to Aβ43). Work in various models has suggested that the aggregation of Aβ peptides may be halted by the use of monoclonal antibodies raised against the various isoforms of Aβ peptide. In one such study, the antibodies were able to penetrate the CNS where they either induced the removal of existing plaques or suppressed the formation of new plaques.14

**References**


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**Bapineuzumab**

A number of humanised monoclonal antibodies are undergoing development as potential treatments and, of these, bapineuzumab has been the most extensively studied. Originally developed by Elan and Wyeth, in early phase II studies a significant improvement was observed for one group of patients, although vasogenic oedema was noted in some (the condition was resolved in all cases). There are currently nine phase III trials involving bapineuzumab under way.

**Intravenous immunoglobulin treatment**

Studies in which APP-transgenic mice were treated with anti-Aβ peptide antibodies derived from intravenous immunoglobulin, leading to a decrease in the level of Aβ in the cerebrospinal fluid, have led to a number of clinical trials being run to evaluate the potential of the approach. Although the data from a number of trials have been encouraging, further trials are currently under way in order to try to evaluate the safety of the approach fully.15

**Conclusion**

Alzheimer’s disease is a debilitating condition that causes enormous suffering to individuals and their families and, with an ageing population, the prevalence of the disease is going to increase, placing an increasing burden on countries’ healthcare systems. Although the most recent treatment received approval in 2002, because of the high level of research activity, one can be hopeful that new treatments will emerge to tackle this challenging condition.