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## Tackling Toxics

*Proteins can misfold and aggregate during the process of ageing, and treatments for diseases resulting from the toxicity of these misfolded proteins require new approaches to drug discovery. A number of novel compounds are now in development that can inhibit the toxicity of soluble amyloid, as a potential disease-modifying treatment for Alzheimer's disease.*

A variety of seemingly unrelated chronic degenerative diseases, based on symptoms alone, have all been linked to a fundamental pathogenic process of protein aggregation of amyloid-like proteins (1). In each case, a specific protein or peptide aggregates to form toxic soluble oligomers and/or insoluble 'amyloid-like' fibres that can produce an inappropriate inflammatory response. Toxic soluble oligomers and inflammation are widely believed to cause the progressive degeneration of the cells associated with a number of these diseases. Table 1 lists some of the toxic proteins that underlie diseases resulting from amyloid-related toxicity.

Amyloid protein	Clinical syndrome
Amyloid- $\beta$ peptides (1-40, 1-42)	Alzheimer's disease Inclusion body myositis (IBM)
Amylin or islet amyloid polypeptide (IAPP)	Type 2 diabetes
$\beta$ 2-Microglobulin	Dialysis-related amyloidosis
$\alpha$ -Synuclein	Parkinson's disease
Prion protein	Transmissible spongiform encephalopathies (for example Creutzfeldt-Jakob disease [CJD])
Tau	Fronto-temporal dementia
Huntingtin (polyQ expansion)	Huntington disease
Superoxide dismutase	Amorphous lateral sclerosis
Transthyretin	Senile systemic amyloidosis Familial amyloidotic polyneuropathy
$\gamma$ -Crystallin	Cataract
Lyszyme	Lyszyme systemic amyloidosis
Ig light chains	Primary systemic amyloidosis
Serum amyloid A	Secondary systemic amyloidosis

Pre-eminent amongst ageing-related diseases associated with amyloid-related toxicity is Alzheimer's disease (AD), which affects nearly half of people over 85 and is projected to increase significantly. AD was first described by Alois Alzheimer in 1906 and is a progressive neurodegenerative disorder with characteristic clinical and neuropathological features. These degenerative effects result in the disruption of neurotransmitters carrying messages across synapses, which then leads to synaptic loss. The current treatments for mild-to-moderate AD include the use of acetylcholinesterase inhibitors to improve cognitive function and N-methyl-D-aspartate (NMDA) receptor antagonists for use in the moderate-to-severe stages of the disease. Such drugs are of relatively limited benefit to most patients because they have only modest symptomatic effects and have not yet been shown to have any significant disease-modifying properties. The effect of delaying disease onset on the prevalence of dementia are striking, and underline the enormous beneficial effect that even a modest treatment can have on the quality of life for sufferers and their carers, as well as the saving in costs. For example, it has been estimated that a two-year delay could result in a 20 per cent drop in prevalence.

### Targeting Amyloid as Disease- Modifying Alzheimer's Therapy

AD is categorised by the presence of a misfolded protein deposited as plaques in regions of the brain associated with memory. These plaques are mostly composed of amyloid-beta ( $A\beta$ ). Under normal circumstances there are essentially two forms of the protein, a shorter ( $A\beta_{1-40}$ ) and longer ( $A\beta_{1-42}$ ) version comprising 40 and 42 amino acids, respectively. In the brains of AD sufferers, the concentration of  $A\beta$  rises in the areas surrounding brain cells.  $A\beta_{1-40}$  and  $A\beta_{1-42}$  both occur naturally in the body, but at higher concentrations misfold and then aggregate to become neurotoxic – especially  $A\beta_{1-42}$ . These soluble oligomers of  $A\beta_{1-42}$  have been shown to be toxic species which can have subtle, detrimental effects on synaptic function. With time, the oligomers aggregate into  $A\beta$  fibrils and eventually plaques. In an overall process that is commonly referred to as the 'A $\beta$  cascade', the progressive accumulation of  $A\beta$  aggregates is believed to be fundamental to the initial development of neurodegenerative pathology and to trigger events such as neurotoxicity and synaptic loss that contribute to the progression of AD (2). The combination of  $A\beta$ 's damaging effects on the normal functioning of neurons and their eventual death causes a decline in cognition, most notably associated with memory deficits. The progressive damage caused by  $A\beta$  sets up a cycle of cell death that eventually leads to almost complete deterioration of mental function.

The amyloid cascade has been a valuable working hypothesis as the search for new treatments for AD has gathered pace. Over time our understanding of the pathological process has undergone an iterative process of modification and refinement as new evidence has been presented (2). This has spawned numerous drug discovery research programmes across a range of targets. For example, much effort has been expended on the discovery of  $\beta$ - and  $\gamma$ -secretase inhibitors to attenuate the generation of  $A\beta$ . However, some issues have surfaced regarding secretases as drug targets that can avoid mechanism-based toxicity, and it remains to be seen if this approach will provide new treatments for AD with an adequate therapeutic window. After more than a decade of research on secretases, no promising clinical data on cognition have yet emerged and trials have been stopped due to safety issues. The issue of selectivity has been raised regarding the wisdom of inhibiting  $\gamma$ -secretase activity and the likely consequences of also blocking a number of important physiological processes that are reliant on the function of this enzyme. A different practical challenge is presented by  $\beta$ -secretase which is a difficult molecular target for designing potent, brain penetrating small molecule inhibitors.

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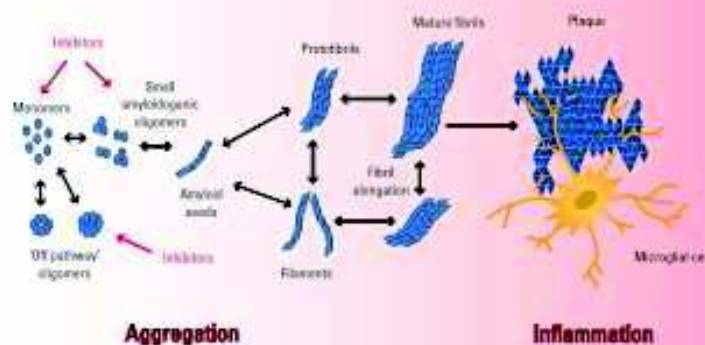
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By contrast, an alternative strategy that comes under the broad description of 'A $\beta$  aggregation inhibition' or 'antiaggregation therapies' has been to target A $\beta$  itself rather than its production. However, there have been relatively few good quality chemical starting points for this approach. Nonetheless, this is an area which could hold considerable promise, particularly with the rapid development in our scientific understanding of toxic amyloid assemblies that now provides further impetus for this alternative approach. Progressive accumulation of A $\beta$  assemblies is generally considered to be fundamental to the development of the neurodegenerative pathology and inflammation that contribute to AD.

Accumulating evidence increasingly supports a cogent argument that compounds preventing the generation of toxic A $\beta$  assemblies could provide successful new treatments for AD (3). Unlike current therapies, which only treat the symptoms of the disease, disease-modifying interventions that prevent the generation of toxic A $\beta$  assemblies may have the potential to slow or even halt AD progression.

The consensus is that AD severity correlates more closely with soluble forms of A $\beta$  rather than with fibrillar forms of the peptide, and suggests an important role for soluble oligomers of A $\beta$ . Therefore, strategies to block A $\beta$  aggregation at the initial stages of oligomerisation, for example small molecules that bind to and stabilise A $\beta$  monomer to prevent oligomerisation and allow neurophysiological clearance mechanisms to effect natural removal are particularly attractive (4,5). In addition, compounds that are capable of binding to toxic A $\beta$  assemblies/oligomers could neutralise their effects and facilitate their elimination (see Figure 1).

Figure 1: Formation of toxic amyloid species



AD is believed to result from initial synaptic failure, which precedes any significant neuronal degeneration, and this A $\beta$ -induced dysfunction of synaptic plasticity then appears to contribute to early memory loss (6). Long-term potentiation (LTP), a well-established electrophysiological model of synaptic plasticity, involves a sustained increase in excitatory synaptic transmission, and inhibition of LTP by A $\beta$  may mimic an early manifestation of AD. In normal adult rats and mice, A $\beta$  oligomers have been found to potentially inhibit hippocampal LTP *in vitro* and *in vivo*.

It has been established that low-n oligomers of A $\beta$  are composed of N- and C-terminally heterogeneous human A $\beta$  peptides, including the A $\beta_{1-40}$  and A $\beta_{1-42}$  species that occur in the human brain and extracellular fluids. Support for the role of low-n A $\beta$  oligomers as key toxic species has come from work by Cleary et al which demonstrated that defined molecular species of the A $\beta$  protein cause acute cognitive deficits in the rat (7). Specifically, Cleary et al and others have shown that soluble oligomeric forms of A $\beta$ , including dimers and trimers, are both necessary and sufficient to disrupt learned behavior. Furthermore, A $\beta$  dimers have been identified as the smallest synaptotoxic species in AD brains (8). Therefore, therapies based on directly targeting soluble A $\beta$  oligomers are an increasingly attractive approach for treating AD.

#### Antibodies or Small Molecules?

There are a number of antibody-based approaches that directly target A $\beta$ , but antibodies have significant limitations with regard to bioavailability in the brain, and may also have immunogenicity problems with chronic administration. A vaccine (AN-1792) did demonstrate some benefit in neuropsychological test battery tasks in a small number of patients in a Phase 2 trial (9). However, six per cent of the patients developed encephalitis and the trial was halted: this severe inflammation caused by the vaccine would, of course, preclude its therapeutic use. Passive immunisation strategies may hold more promise and bapineuzumab, a humanised monoclonal antibody against A $\beta$ , is now in Phase 3 trials and is the most advanced of a number of antibody products in the clinic. Like all antibody approaches, however, brain penetration issues may limit their therapeutic benefits.

Small molecule approaches, however, allow much better bioavailability in the brain to be achieved. Therefore, a number of compounds are in clinical development that interfere with the effects of A $\beta$ . For example, Tramiprosate, which is orally bioavailable, is thought to inhibit the binding of A $\beta$  to heparin sulfate, thereby blocking the formation of toxic A $\beta$  aggregates (10). A Phase 2 study with Alzhemed showed positive effects in attenuating the disease in patients with mild AD. However, Tramiprosate did not demonstrate significant cognitive benefit in Phase 3 trials. In spite of this early disappointment, a number of new candidate A $\beta$ -binding small molecules are emerging as potential diseasemodifying therapies.

Another small molecule, PBT2, is a copper/ zinc ionophore thought to bind to the A $\beta$ -Cu (or -Zn) complex and thus prevent or attenuate the subsequent oxidative damage to neurons and inflammation. It acts to reduce levels of A $\beta$  and neutralises its toxicity, as well as improving synaptic functioning by restoring copper/zinc sequestered by extraneuronal A $\beta$ . It promotes memory functions such as LTP, is effective in transgenic models for AD, and improves learning and memory and clearance of A $\beta$ . PBT2 improves cognition in animal models for AD and has shown positive initial results in Phase 2 clinical trials (11). Patients with early AD were treated with oral PBT2 in a double-blind, placebo-controlled clinical trial over 12 weeks. The drug induced a 12 per cent drop in cerebrospinal fluid (CSF) A $\beta_{1-42}$  levels and produced a significant improvement in executive function on a neuropsychological test battery (NTB).

A second small molecule in clinical development is ELND005 (also known as scyllo-inositol), a potential diseasemodifying treatment for AD (12). ELND005 is a small molecule compound that inhibits the aggregation and toxic effects of A $\beta$ ; it is also thought to act by breaking down larger A $\beta$  species. ELND005 has recently completed a Phase 2 trial. In this placebo-controlled study in 351 patients with

mild to moderate AD, the co-primary cognitive endpoints did not achieve statistical significance. However, a 250mg twice daily dose showed positive clinical trends on an NTB in mild patients and also demonstrated a biological effect on A $\beta$ <sub>1-42</sub> levels in the CSF in the subgroup of patients who provided CSF samples. Based on the evidence from these data, ELND005 is being advanced into Phase 3 clinical development. A summary of the leading amyloid-binding drugs in clinical trials for AD is summarised in Table 2.

Company	NCE	Class	Status
J&J/Pfizer	Bapineuzumab	Antibody	Phase 3
Eli Lilly	Solanezumab	Antibody	Phase 3
Baxter	Gantagard	Antibody	Phase 3
Han	ELND005	Small molecule	Phase 3
Prana	PBT2	Small molecule	Phase 2

Exebryl-1 (13) is a compound which is reported to prevent A $\alpha$  fibrillogenesis in a number of animal models and shown to prevent accumulation of soluble and insoluble forms of A $\beta$ . Exebryl-1 causes a reduction of A $\beta$  load in transgenic mice and improves short-term memory in the Morris water maze test. The compound shows good brain penetration following oral administration and is currently undergoing a Phase 1 trial to determine the safety of this compound for the treatment of mild to moderate stages of AD.

A further series of small molecules are also in pre-clinical development. However, alternative small molecule starting points for inhibitors of A $\beta$ <sub>1-42</sub> aggregation are relatively scarce, and the vast majority of compounds claimed to be inhibitors of A $\beta$ <sub>1-42</sub> aggregation are unsuitable in terms of their biological profile and have poor tractability for medicinal chemistry optimisation to provide orally bioavailable, CNS-penetrating compounds with a therapeutically useful half-life. RS-0406 is a small molecule which has been shown to be an inhibitor of A $\alpha$  toxicity and is also capable of significantly inhibiting A $\beta$ <sub>1-42</sub> aggregation (14). It also prevents A $\beta$ <sub>1-42</sub>-induced impairment of LTP and arrests A $\beta$ <sub>1-42</sub> oligomer-induced behavioural deterioration in the rat (15). Modifications to RS-0406 focused on improving its potency, introducing oral bioavailability and CNS penetrating properties of this molecule. To achieve this, selected structural changes were undertaken, which resulted in improvements in its drug-like nature. This has resulted in new analogues such as SEN1500 (16) and SEN1576 as promising compounds for clinical development. These compounds are more potent inhibitors of amyloid toxicity than RS-0406. They bind directly to A $\beta$ <sub>1-42</sub> monomer and oligomers, as demonstrated by surface plasmon resonance studies using a Biacore T100 instrument, they prevent the deficit in LTP caused by A $\beta$ <sub>1-42</sub> oligomers, and reverse A $\beta$ -induced memory deficit in an acute model of cognition. In addition they are orally bioavailable and have good CNS penetration. Consequently, SEN1500 and SEN1576 are thought to be the first small molecules with suitable bioavailability for further development that have been shown to directly bind to A $\beta$ <sub>1-42</sub>.

### Conclusion

Small molecule inhibitors of toxic A $\beta$  assemblies continue to be pursued as a viable anti-AD strategy. Several routes are being pursued, although the number of structural options remains limited. However, more structural types are likely to emerge as new screening approaches are applied. To date, results in the clinic have been mixed, but this is perhaps no more than might be expected for such a challenging disease and no small molecule drugs that have been shown to directly bind to A $\beta$  have been tested in the clinic. Furthermore, it is very likely that successful treatment of AD will require patients to take a combination of drugs, rather than rely upon monotherapy, and small molecule amyloidbinding drugs could potentially be co-administered with other medication.

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