EDITORIAL

Alzheimer’s disease (AD) is the most common age-related neurodegenerative disease and the most common cause of dementia. In Australia alone, the number of dementia sufferers is estimated at 270,000 and this figure is expected to reach 950,000 by 2050 if new and effective medications to treat AD are not developed [1]. Worldwide, 115 million people are predicted to be living with dementia by 2050 [2], representing a “dementia epidemic” of staggering proportions.

According to the “amyloid cascade” hypothesis [3], accumulation of toxic amyloid β (Aβ) peptide oligomers causes synapse loss early in the pathogenesis of Alzheimer’s disease, deposition of amyloid in plaques as the disease progresses, neuron death and dementia. Although insoluble amyloid plaques were originally thought to be the causative agent of neuron death, it is the extent of synapse loss rather than amyloid plaque load that correlates more strongly with the degree of dementia [4,5], suggesting that disruption of synapse function and synapse loss are early pathological events in AD. Furthermore, soluble Aβ oligomers have been shown to impair long-term potentiation (LTP), reduce dendritic spine density in hippocampal slices and impair memory in vivo [6]. These observations have provided additional imperative for pharmacological intervention as early as possible in order to prevent, or at least delay, the development of symptoms.

The Aβ peptide is produced from the amyloid precursor protein (APP) by proteolytic cleavage, firstly by BACE1 (β-site amyloid precursor protein cleaving enzyme 1 or β-secretase, [7]) and subsequently by the γ-secretase proteolytic complex [8]. Once the identities of these APP-processing enzymes were known, screening programs to develop specific inhibitors of each of these secretases were stepped up and some promising candidate molecules are in the pipeline. Unfortunately, the first Phase III clinical trial of a γ-secretase inhibitor had to be terminated due to adverse side-effects that were likely to be caused by mechanism-based toxicity rather than off-target effects. Described as a “promiscuous” enzyme, γ-secretase has been found to possess a broad range of substrates in addition to APP and at least some of the mechanism-based toxicity has been attributed to aberrant processing of another substrate, the Notch receptor.

After this experience, the focus has shifted to BACE1 as a key drug AD target in the hope that BACE1 inhibition will be a safer prospect than γ-secretase inhibition. Much of the early optimism was founded on the apparent lack of severe phenotypes in the BACE1 knockout mouse and the limited number of known BACE1 substrates. Over time, these issues have been investigated more thoroughly and there is a growing awareness of possible mechanism-based toxicity with BACE inhibitors. Nevertheless, the underlying rationale for using BACE inhibition to lower toxic Aβ levels recently was recently strengthened with the discovery of a rare mutation in APP near the BACE1 cleavage site that reduces Aβ levels and is protective against both AD and cognitive decline [9]. On the other hand, an increase in BACE1-mediated APP proteolysis similar to that seen in familial AD patients was shown to cause synaptic and memory deficits in a mouse model of dementia [10].

A major advantage of the BACE inhibition approach, given the ongoing debate about whether the main neurotoxic species in patients is the soluble oligomer or amyloid plaque form of Aβ, lies in the ability of BACE inhibitors to block the production of both these forms. Several BACE inhibitors are currently in clinical trials, including the Eisai inhibitor E-2069 and the Merck competitive BACE inhibitor MK-8931 which is in Phase II/III trials (NCT01739348 and NCT01953601, begun in November 2012 and November 2013, respectively). The aim of these trials is to determine whether BACE inhibition in prodromal and mild-to-moderate Alzheimer’s disease patients is able to block the amyloid cascade and slow the development of AD. Inherent difficulties in designing these types of studies exist, however, including deciding when to commence treatment, which patients to treat, how long the cohort should be followed so as to have the best chance of demonstrating efficacy. For the current trials, prodromal patients (those who exhibit amnestic mild cognitive impairment [aMCI] due to AD) are being recruited. Participants meet the “due to AD” criterion if they test positive for either of two AD ‘state’ biomarkers [11]: amyloid imaging positron emission tomography scan (PET, using the tracer [18F]-flutemetamol) or the CSF tau: amyloid-β42 (Aβ42) ratio screen. Selection of this subgroup of patients is a crux of the study design. For a BACE inhibitor to be hailed as an effective disease-modifying drug, the...
treatment groups would need to exhibit improved cognitive/activities of daily living scores. Mechanistically, according to the amyloid hypothesis, these improvements would be brought about by interfering with the amyloid cascade ergo evidence of amyloid deposition in the brains of these patients must be present initially in the AD trial cohort.

Provided the long-term safety/efficacy trials are successful, a BACE inhibitor could be administered to people considered ‘at risk’ of developing AD (i.e. carriers of genetic risk polymorphisms or ‘trait’ biomarkers) before they test positive for the AD ‘state’ biomarkers described above. By commencing BACE inhibitor treatment even earlier, it may even be possible to prevent the initiation of the amyloid cascade initiation altogether in ‘at risk’ individuals. This would be a huge advantage as there are major concerns that this process could be self-sustaining once initially triggered, rendering BACE1 inhibition at more advanced stages of the disease relatively ineffective [12]. In this context, it is crucial to establish the level of BACE1 inhibition that would be needed to block the cascade and/or reduce Aβ levels over the course of decades without causing mechanism-based toxicity by blocking the processing of other BACE1 substrates.

Thorough characterization of the BACE1 knockout mouse line has revealed a previously unappreciated spectrum of neurophysiological phenotypes typical of aberrant synaptic connectivity and myelination. These include memory deficits, morphological and electrophysiological deficits in neurons such as reduced spine density, altered excitability and seizures, poor motor co-ordination, defective axon guidance, schizophrenia-like endophenotypes and hypo-myelination [13]. These phenotypes of BACE1 KO mice result from the lack of processing of BACE1 substrates: for example, loss of processing of neuregulin-1 was linked to the hypomyelination phenotype however many aspects of the BACE1 KO phenotype could not be accounted for by the known BACE1 substrates. Additional important BACE1 substrates have since been identified [14] and certain proteins, such as members of the Seizure-related gene 6 (Sez6) family of proteases, are almost exclusively processed by BACE1. We showed previously that Sez6 is vital for proper excitatory synapse formation and maintenance [15], making it likely that the BACE1-shed ectodomains of Sez6 proteins are important mediators of these actions. As synapse loss in AD closely correlates with cognitive decline, loss of these forms of Sez6 and related proteins could make a major contribution to mechanism-based toxicity of BACE1 inhibition.

In conclusion, pre-clinical and clinical results for BACE inhibitors are highly promising and, so far, no prohibitive mechanism-based side effects have come to light. Careful characterization of the functions of newly discovered BACE1 substrates in the developing and mature brain will help inform current and future development of these drugs. Similarly, fine-tuning the level of BACE inhibition to achieve effective Aβ reduction while avoiding mechanism-based toxic side-effects will mean that the BACE inhibitor arsenal can be deployed in a preemptive strike against AD.

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REFERENCES