DEMENTIA

The challenge of dementia therapy

As a result of the unprecedented expansion in the global population aged over 60 years, the prevalence of dementia is expected to rise dramatically. According to the 2009 World Alzheimer Report, the number of people with dementia worldwide is set to increase from the current figure of 35.6 million to an estimated 115.4 million by 2050. The socioeconomic costs that accompany dementia will soar, unless therapies can be developed that prevent or slow the progression of dementia-causing diseases. This issue of *Nature Reviews Neurology* focuses on this therapeutic challenge, particularly in Alzheimer disease (AD)—the most common cause of dementia.

In the US, the FDA has licensed five drugs for the treatment of AD—four acetylcholinesterase inhibitors and the *N*-methyl-D-aspartic acid glutamate receptor antagonist memantine. These agents, however, only provide limited symptomatic relief from cognitive dysfunction and do not affect the underlying disease processes.

Various AD-modifying treatment strategies are being pursued, and many candidate drugs have entered clinical trials. Mostly, these therapies are designed to target amyloid-β (Aβ), a peptide that is the principal component of amyloid plaques. An elevation of Aβ levels in the brain, leading to subsequent aggregation of such peptides, is believed by many to be an early, and causative, event in AD pathogenesis. Two of the major anti-Aβ therapeutic approaches are reviewed in this issue, namely Aβ immunotherapy and secretase inhibition–modulation.

Aβ immunotherapy involves the use of anti-Aβ antibodies (delivered passively or generated following vaccination) to promote the removal and/or prevent aggregation of Aβ. This approach has proved effective in several AD animal models—reducing Aβ levels and improving cognition—and at least 13 candidate Aβ immunotherapies are now in clinical trials. How effective Aβ immunotherapy will prove to be in humans is hard to gauge, as few such drugs have completed late-stage trials. A similar story exists for agents that target the secretases—proteases involved in Aβ production. Preclinical studies have indicated that molecules that inhibit or modulate the secretases might lower human Aβ levels, but clinical data are sparse. The next 5 years should see a thorough examination of whether the Aβ immunotherapy and secretase-targeting strategies are of benefit in patients who already have AD, as multiple drugs in each class will complete phase II and/or phase III trials.

The effectiveness of AD-modifying drugs might largely depend on when they are administered. For example, studies in rodent AD models indicated that Aβ immunotherapies tended to be at their most effective in preventing cognitive decline and the build-up of neuropathology when delivered in the earliest stages of disease. Thus, targeting of Aβ could represent a good preventative strategy for AD but might be less effective for arresting or slowing the disease process once patients enter even a mild stage of dementia. Indeed, by this stage, the pathology downstream of Aβ might be acting independently to the effects of this peptide, and could require therapeutic intervention targeting other known pathogenic molecules in AD, such as tau. Should this scenario be correct, one might anticipate that current trials of anti-Aβ drugs are bound to disappoint, as these studies are being largely conducted in patients with mild to moderate AD.

The ability to reliably diagnose AD before dementia develops, during mild cognitive impairment (MCI) or even in advance of cognitive symptoms, might markedly enhance the success of anti-Aβ therapies (and other AD-modifying drugs). Encouraging developments have been made in the discovery of AD biomarkers that might facilitate early diagnsois and, hence, early administration of such drugs, when they become available. Biomarkers will also be highly valuable in AD clinical trials, enriching patient cohorts for the disease, stratifying subgroups of patients, offering a means of safety monitoring and, importantly, providing *in vivo* evidence of disease modification. These advancements might make trials of AD-modifying drugs feasible in patients with MCI or, possibly, presymptomatic individuals. Indeed, such studies might be the only way of determining whether targeting Aβ is a valid therapeutic strategy for AD. In recognition of the importance of biomarkers in AD, this issue includes Reviews on the use of structural MRI and PET in the detection and monitoring of this disease. A Review on progressive primary aphasias illustrates how the underlying cause of dementia might be revealed by using biomarkers in combination.

Dementia is becoming increasingly prevalent as the population grows old, posing a serious challenge for health-care systems in even the most developed countries—an alarming thought given that the largest rises in cases of dementia will take place in middle-income and low-income countries. Meeting the therapeutic challenge of dementia is, thus, of paramount importance. Achievement of this goal will entail development not only of novel compounds, but also of effective biomarkers for the underlying dementia-causing disease.

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Competing interests
The author declares no competing interests.