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As neurologists, we are surrounded by advances in our professional field, and we often find ourselves with more questions than answers. It is the remit of journals such as *US Neurology* to keep us informed. One particularly important question is 'are we at the dawn of rational disease modification in Alzheimer's disease?' Existing medications for treating dementia offer only modest, temporary, symptomatic relief to a subgroup of patients. Invariably, the onset of the disease is followed by about a decade of slow, steady decline from 'mild cognitive impairment' at the beginning to a persistent vegetative state at the end. In the mid-1980s, purification of cerebral amyloid and cloning of its parent, the amyloid precursor protein (APP), provided instant genetic insight into a plausible disease pathogenesis. APP was assigned to chromosome 21 in 1986 by Dimitry Goldgaber and Carleton Gajdusek, immediately causing 'aha!' moments among the dementia cognoscenti aware of Henryk Wisniewski's reports that patients with trisomy 21 invariably develop Alzheimer's disease before 50 years of age.

Thus, the race for anti-amyloid drugs began. Now, at least three classes of such compounds are in clinical trials. The first class, immunotherapy, was first investigated following Dale Schenk's discovery that vaccination of amyloid-laden Alzheimer mice could reverse or prevent amyloidosis. Rodents, dogs, monkeys, and 200 subjects in a phase I trial were inoculated, but the follow-up phase II trial was halted because 5% of the 300 subjects developed acute allergic encephalitis from the amyloid vaccine. The immunogen has since been studied and the encephalitogenic epitope separated from the epitope required to make the antibodies that are the actual 'drugs.' Now, vaccination and passive immunotherapy with synthetic humanized anti-amyloid immunoglobulin G (IgG) or Gammagard (intravenous immunoglobulin) are in trials. News from the trial of Elan and Wyeth is expected later in 2008.

Antiaggregants characterize the second class of anti-amyloids, and, as the name (or the nickname 'plaque busters') implies, these drugs maintain amyloid peptides in a dispersed state so that the brain's scavenging system can clear them away. The first to be tested, Alzhemed, failed last year. The next one in the pipeline, PBT2 from Prana, looks promising in mouse and early human studies.

The final class of drugs is the most internally heterogeneous. These are the 'secretase modulators,' which either block amyloid-forming proteases known as secretases or activate amyloid-destroying secretases. Hormone replacement therapies and statins are two alpha secretase activators that have failed to show benefit. A 5HT4 modulator with this property is in phase II trials. Inhibitors of the beta secretase have long been sought, but provide a challenge as the active site of the enzyme is large, effective, and non-toxic, and drugs that can penetrate the blood-brain barrier are hard to come by. The first of these is now in the clinic. An inhibitor of gamma secretase has recently begun trials, while the first gamma secretase modulator will complete phase III trials this year.

Moving hand in glove with drug development have been advances in amyloid imaging. Soon, anti-amyloid trials will include serial measurements of brain amyloid load. Hopefully, the ability to directly visualize the target will enable trials to become more efficient: clinical trials now require at least 12–18 months, but if brain amyloid scans show changes or progression in less time, that would be welcome indeed in terms of both identifying promising agents and discarding failing ones as soon as possible.

While I have sought to provide specific focus in this introduction, this edition of *US Neurology* includes numerous articles, each addressing areas of importance and interest. I hope it you find it a worthy read. ■