

# Harnessing the immune system to battle Alzheimer's

Some of the most promising approaches to fight Alzheimer's disease aim to develop vaccines

20th Century medicine can claim many victories against various maladies. Deadly diseases that plagued our ancestors only 100 years ago have become virtually unknown in the developed world. Smallpox has been eradicated and the World Health Organization is now striving towards the elimination of polio. Cases of mumps, rubella and measles are rare, while in an average winter, flu seems to be largely under control. And most of these outstanding and lasting achievements have been due to the use of effective vaccines.

At the same time, however, these advances have led to a burgeoning ageing population in developed countries, and other diseases, for which there are as yet no cures, are becoming more prevalent. Along with cancer, heart disease and diabetes, Alzheimer's disease has now become a major threat to the growing ageing population. In the USA, 4.5 million Americans are living with this debilitating and ultimately deadly disease, and that number is expected to grow to 14 million by the middle of the century, according to the Alzheimer's Association in Chicago, IL. In the EU member states, ~5% of people over 65 years suffer from the disease. As the risk of acquiring Alzheimer's grows with age—by age 65, one in 10 will have the disease, rising to five in 10 by age 85—it places a heavy burden on the social and medical infrastructure in our increasingly ageing societies. The annual cost of treating Alzheimer's disease in the USA is estimated to be ~\$100 billion—third only after heart disease and cancer, according to the philanthropic Institute for the Study of Aging in New York, NY.

While Alzheimer's disease has been studied extensively for many years, only four drugs are currently approved for treatment—all of which are acetylcholinesterase inhibitors with only limited efficacy. And although scores of other drugs are in development, the most recent and outstanding advances have unexpectedly arisen from research that aims at developing vaccines to prevent and treat the disease.

Although it is still unknown how and why the disease develops, it is clear that the degradation of neurons is accompanied by the formation of typical amyloid

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plaques and fibrils in the brains of ageing people that lead to dementia and eventually death. These insoluble aggregates outside of neurons are primarily composed of the amyloid- $\beta$  peptide ( $\alpha$ - $\beta$ ), a small fragment of amyloid precursor protein (APP) that is located in the cell membrane. In a normal brain, APP is degraded into several fragments, one of which is  $\alpha$ - $\beta$  that can exist in two different lengths of 40 or 42 amino acids. The shorter form is more soluble and aggregates slowly, whereas the longer form clumps into insoluble aggregates. In the late stage of the disease,  $\alpha$ - $\beta$ -42 forms long  $\beta$ -amyloid filaments outside the cell and dense insoluble plaques including fragments of dead and dying nerve endings. It is this central role that  $\alpha$ - $\beta$ -42 plays in the formation of plaques that has made

it a promising target for vaccine development.

'Vaccines are a new way to address the fundamental problem in Alzheimer's disease—the accumulation of amyloid plaques in the brain,' Bill Theis, vice president for medical and scientific affairs at the Alzheimer's Association, said. 'The development of vaccines to treat Alzheimer's disease is relatively new, and since the publication of the first paper by Elan scientists only 2 years ago, there has been a veritable explosion of vaccine research.' Indeed, many researchers think that the efforts to fight Alzheimer's disease are finally paying dividends. 'One reason that Alzheimer's disease is more amenable than other neurodegenerative diseases to an immunotherapy approach is its characteristic extracellular plaques [rather than intracellular abnormalities],' said Thomas Wisniewski, from New York University School of Medicine. A number of research groups are thus now working to find ways to prevent formation of these plaques.

Elan Pharmaceuticals in Dublin, Ireland, is leading the way with their vaccine AN-1792, a form of  $\alpha$ - $\beta$ -42 released from APP. Back in 1995, Elan tested it in mouse models of Alzheimer's and found that immunisation of young mice prevented them from developing amyloid plaques throughout their life. Similar immunisation of 1-year-old mice with substantial neuropathology prevented further deposition of the peptide or even reversed the process for 6 months. This is due, the company thinks, to antibodies against the vaccine that cross the blood-brain barrier and bind to  $\alpha$ - $\beta$  fibrils in amyloid deposits, thus promoting

## analysis

clearance of the plaques by microglia cells.

Originally developed by Elan scientist Dale Schenk, the vaccine is now jointly developed with American Home Products' Wyeth-Ayerst Laboratories (Madison, NJ) and recently completed a Phase I trial of 104 patients suffering from mild-to-moderate Alzheimer's in the USA and the UK. In July 2001, the company announced that the vaccine was well tolerated and produced the desired immune response in some participants.

In October 2001, Elan completed the enrolment of 375 new patients with moderate memory impairment and started Phase IIa clinical trials to measure patients' immune response, assess the drug's effectiveness and determine optimal dosage. But in mid-January 2002,

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Elan temporarily suspended the tests when four French patients developed symptoms of inflammation of the central nervous system. No further doses of the vaccine or placebo will be given until the clinical investigators determine the cause of the inflammation, the Alzheimer's Association stated on Elan's behalf. The company itself was not available for comment but reported through a press release that the exact cause of the inflammation was not determined at that time. The sponsors are now consulting with an independent safety monitoring committee and regulatory authorities before the trial is resumed.

Some scientists were not surprised at Elan's report of brain inflammation in test subjects. They had noted that using the entire peptide as a vaccine could itself stimulate an inflammatory response in the brain, and that administering an identical

protein could attract more amyloid to plaques, rather than breaking them down. This disagreed, however, noting that 'there is not enough information to make

side effects observed in the Elan trials. Last August, researchers from New York University published results in an animal model using a 30-amino-acid homologue

to a- $\beta$  with an additional six lysine residues at the N-terminus that had previously been shown to be highly soluble, non-amyloidogenic and non-toxic in human neuronal cell culture, according to lead researcher Wisniewski. 'Because a- $\beta$  crosses the blood-brain barrier in experimental animal models, forms toxic fibrils and can seed fibril formation, it is possible that in humans, a- $\beta$  1-42

can co-deposit on existing amyloid plaques leading to increased toxicity, and may actually promote plaque formation,' Wisniewski described the rationale for using a modified peptide.

The New York University team found that immunisation for 7 months with its compound reduced the amyloid burden in the brain of mice by >80% and a- $\beta$  1-42 levels in the blood by 57%. Inflammation of the brain was still detected, albeit at a reduced level. 'We are currently testing other peptide combinations with a number of adjuvants to see if it can improve on immune responses,' Wisniewski said about their current research and he added that he hopes to enter the clinic with a related compound within a year. However, it is still unclear what the exact mechanism of action is, whether the drug activates microglial cells to remove the plaques or whether the vaccine has a 'sink' effect, by removing a- $\beta$  from the blood, thus lowering its concentration in the brain.

The more similar an antigen is to the natural protein, the more difficult it is to generate an immune response, according to Daniel Chain, CEO of Mindset BioPharmaceuticals, an Israeli biotech company in Tel Aviv that is also working on vaccines against Alzheimer's. Mindset is therefore using modified peptides to trigger an immune response against a- $\beta$ -42. In addition, the company is developing a



After she got an overdose of the Alzheimer's drug, Muriel started remembering details of her former lives.

such a judgement at this time.' The vaccine will only show true efficacy in Alzheimer's patients, because the mouse model is just an approximation of the human disease, he added.

Indeed, Dennis Selkoe, Cynthia Lemere and Howard Wiener of Harvard University in Cambridge, MA, are also testing the full-length peptide using intranasal therapy with some success. Last November, Lemere reported results from experiments in mice similar to those that Elan achieved in its phase I trial. Their research showed that nasal administration of a- $\beta$ -42 induced antigen-specific and anti-inflammatory immune responses locally and systemically. 'Specifically, we found significant decreases in the cerebral a- $\beta$  plaque burden and a- $\beta$ -42 levels in mice treated intranasally with a- $\beta$  peptide,' said Weiner. He explained that the side effects—decreased local microglial and astrocytic activation, serum anti-a- $\beta$  antibodies, and mononuclear cells in the brain expressing anti-inflammatory cytokines—shows that the intranasal application works better than oral application. The team uses technology licensed from Autoimmune Inc. (Lexington, MA) developed by Weiner and others, and hopes to enter Phase I trials this year at Brigham and Women's Hospital at Harvard Medical School.

Other groups have modified the a- $\beta$ -42 peptide, or are using a small fragment derived from it, in order to diminish the

second, passive immunisation that uses antibodies directed only to the fibrillary form of the  $\alpha$ - $\beta$  peptide, not to the soluble, non-toxic precursor, which Chain believes could interfere with other activities in the body. 'The advantage of passive therapy is that it does not require immune activation or any adjuvants,' he said. One drawback, however, is that it must be given repeatedly because the body gradually removes the antibodies.

Neurochem in Saint-Laurent, Canada, is taking a different approach to overcome the problems of inflammatory reactions and an insufficient immune response. Their compound triggers a response to only a small portion of  $\alpha$ - $\beta$ -42, so antibodies will prevent the formation of amyloid fibrils while avoiding other, unwanted side effects, Francine Gervais, vice president of research and development, explained. 'Amyloid  $\beta$  is a protein that is normally present in the blood in soluble form,' Gervais said. 'However, we do not know its non-pathogenic function—only that it is important because it is conserved in many species.' What is not natural is when it deposits in the brain, so Neurochem's vaccine triggers the immune system to recognise only the soluble form of the protein and remove it before it forms fibrils. It should prevent plaque build-up, but is not expected to attack extant

plaques, Gervais said. She envisions that a single initial vaccination would be needed, and that patients would receive a 'booster' every few years.

Gervais does not believe, however, that one vaccine will necessarily work for all those at risk or with early-stage disease. 'Alzheimer's disease has a number of different risk factors besides age—notably, apo-E status and other genetic factors, and a history of head injury,' Serge Gautier, of the Center for Studies in Aging at McGill University in Montreal, Canada, and a member of Neurochem's advisory board, said. 'Therefore, a number of approaches besides vaccines are likely to be necessary to treat the range of patients.'

One approach is to lower the amount of  $\alpha$ - $\beta$ -42 in the brain rather than attacking plaques directly. This is simplified by the fact that  $\alpha$ - $\beta$  crosses the blood-brain barrier easily, especially in Alzheimer's patients where it is more permeable, according to Gautier. This could allow antibodies and other protein-binding molecules to act as a 'sink' for  $\alpha$ - $\beta$ -42 by removing it from the bloodstream, thus lowering its concentration and its ability to form plaques in the brain.

This was shown to be a promising approach last summer when David Holtzman from Washington University in

St Louis, MO, reported that a monoclonal antibody directed against the central domain of  $\alpha$ - $\beta$  caused a 1000-fold increase of the peptide in the blood of transgenic Alzheimer's mice and prevented further deposition in the brain. 'This "sink" effect is due in part to a change in  $\alpha$ - $\beta$  equilibrium between the central nervous system and plasma,' described Holtzman who is collaborating with Eli Lilly that produces the antibody. The goal of the study was to determine whether exogenous molecules could change this equilibrium, given that endogenous proteins, such as apoE and apoJ, can influence the transport of  $\alpha$ - $\beta$  between the brain and plasma, Holtzman said. He thinks that apart from antibodies, other proteins or molecules that bind  $\alpha$ - $\beta$  may serve to facilitate clearance of the soluble peptide from the brain.

Despite the drawback in Elan's clinical trials, most researchers are still optimistic that an immunotherapeutic approach will play an important role in treating and possibly preventing Alzheimer's disease. And the results from Elan's investigation should provide further knowledge of how to overcome this debilitating disease.

*Vicki Brower*

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## Will they throw the bath water out with the baby?

The US Congress is still debating whether to outlaw cloning humans

There appears to be no historical precedent for what a committee of the illustrious US National Academy of Sciences (NAS) did in January: it called for outlawing a certain kind of scientific endeavour. The reaction of US scientists to the promulgation of a ban was equally unprecedented: they went along with it—meekly.

The NAS committee recommended that cloning human embryos for procreation purposes should be prohibited by law and

that violations should be punished severely. In reality, this was a last-ditch attempt to salvage another kind of human cloning: embryo creation via somatic cell nuclear transfer with the aim of generating stem cells for disease research and, ultimately, therapy.

The report drew an emphatic distinction between two forms of cloning that are all too often lumped together: reproductive and therapeutic. Reproductive human

cloning, it said, should not now be practised because animal research shows that it is dangerous to the potential mother and baby—and likely to fail. But these strictures, it argued, did not apply to nuclear transfer for the production of stem cells, which should be allowed to proceed with no restrictions.

Science lobbyists such as the gigantic Federation of American Societies for Experimental Biology, representing 21 research