VACCINES

# Chasing the dream

*After a decade of disappointments, hopes for a successful Alzheimer's vaccine that ameliorates symptoms and ultimately prevents the disease are rising again.*

BY JIM SCHNABEL

Using the formidable powers of the immune system to attack one of the body's own proteins seems like a risky approach. But this is what nearly all vaccines, or immunotherapies, against Alzheimer's disease aim to do. Their target is amyloid-β, a tiny protein produced by neurons. Scientists do not know what function amyloid-β evolved to have in its ordinary, free-floating form. But they do know that it is unusually prone to sticking to copies of itself, and that this aggregation process seems to be the principal trigger for Alzheimer's disease.

The first vaccine against Alzheimer's disease — Dublin-based Elan Pharmaceuticals' AN-1792 — was based on a particularly aggregation-prone form of amyloid-β known as Aβ42. In mice that had Alzheimer's-like deposits, or 'plaques', of amyloid-β in their brains, it seemed enormously promising: it provoked a storm of anti-amyloid-β antibodies that dissolved the plaques in older mice and stopped plaques from forming in younger ones. But in humans, AN-1792 was a disaster. Elan halted its first large clinical trial in 2002, after patients developed meningoencephalitis, an inflammation of the brain and its membranes that was apparently caused by rogue immune cells[1].

Most subsequent efforts have fared little better. Milder, second-generation active vaccines against amyloid-β are still in clinical trials, but many researchers suspect that these will not be strong enough to provoke a sufficient antibody response in elderly patients with weak immune systems. Passive vaccine infusions of lab-grown anti-amyloid-β antibodies are meant to get round this problem, but they haven't performed well in clinical trials.

"We in the field have had to look back and say, what did we do wrong?" says Norman Relkin, a neurologist at Weill Cornell Medical College, part of Cornell University in New York.

But despite these disappointments, there are hints of clinical success from a surprising direction — one that could lead to a better understanding of Alzheimer's disease and to therapies and preventives that really work.

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vaccines against Alzheimer's disease
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The vaccine that has raised some researchers' hopes is a mix of antibodies pooled from donated human blood. Known as intravenous immunoglobulin (IVIg), it has long been marketed as a general booster for antibody-based immunity in people who lack it for genetic reasons, and as a moderator of some rare autoimmune conditions.

The idea of using IVIg to treat Alzheimer's disease occurred to Relkin and his colleague Marc Weksler after they found, in 2002, that people with Alzheimer's disease have lower levels of anti-amyloid-β antibodies in their blood than cognitively normal people of the same age. They decided to set up a small, 6-month study of IVIg in eight of Relkin's patients. "The concept simply was to give back these antibodies, since IVIg is derived from the plasma of young individuals who tend to have higher levels," Relkin says.

The results were surprisingly good: six patients improved their cognitive scores, and a seventh stabilized. In a larger trial of 24 patients, Relkin again found signs that IVIg was working: the eight-person placebo group worsened as expected, but nearly all the 16 treated patients improved moderately on both cognitive and quality-of-life measures over the first 6 months (ref. 2). Their improvements were roughly equivalent to turning back the clock by 6–18 months. What's more, they stayed at those levels for as long as the treatment continued — more than two years in some cases.

## INJECTION OF REALISM

The results of small trials often fail to hold up in larger trials. But Relkin's results have inspired some optimism — and some off-label prescribing of IVIg for Alzheimer's disease — because the improved cognitive and behavioural scores were dose dependent and have been backed up by changes in biological markers, including lower levels of amyloid-β in cerebrospinal fluid and reduced brain shrinkage. In fact, Relkin says, brain shrinkage is "towards the normal range in individuals who got the best dose, which is a very provocative finding".

The US National Institute on Aging, along with Baxter BioScience of Deerfield, Illinois, one of several producers of IVIg, is sponsoring a follow-up trial in 400 individuals with Alzheimer's disease. The results could be ready by the end of 2012. If the trial is successful, it could lead to the first Alzheimer's therapy approved by the US Food and Drug Administration that modifies the disease, rather than just treats the symptoms.

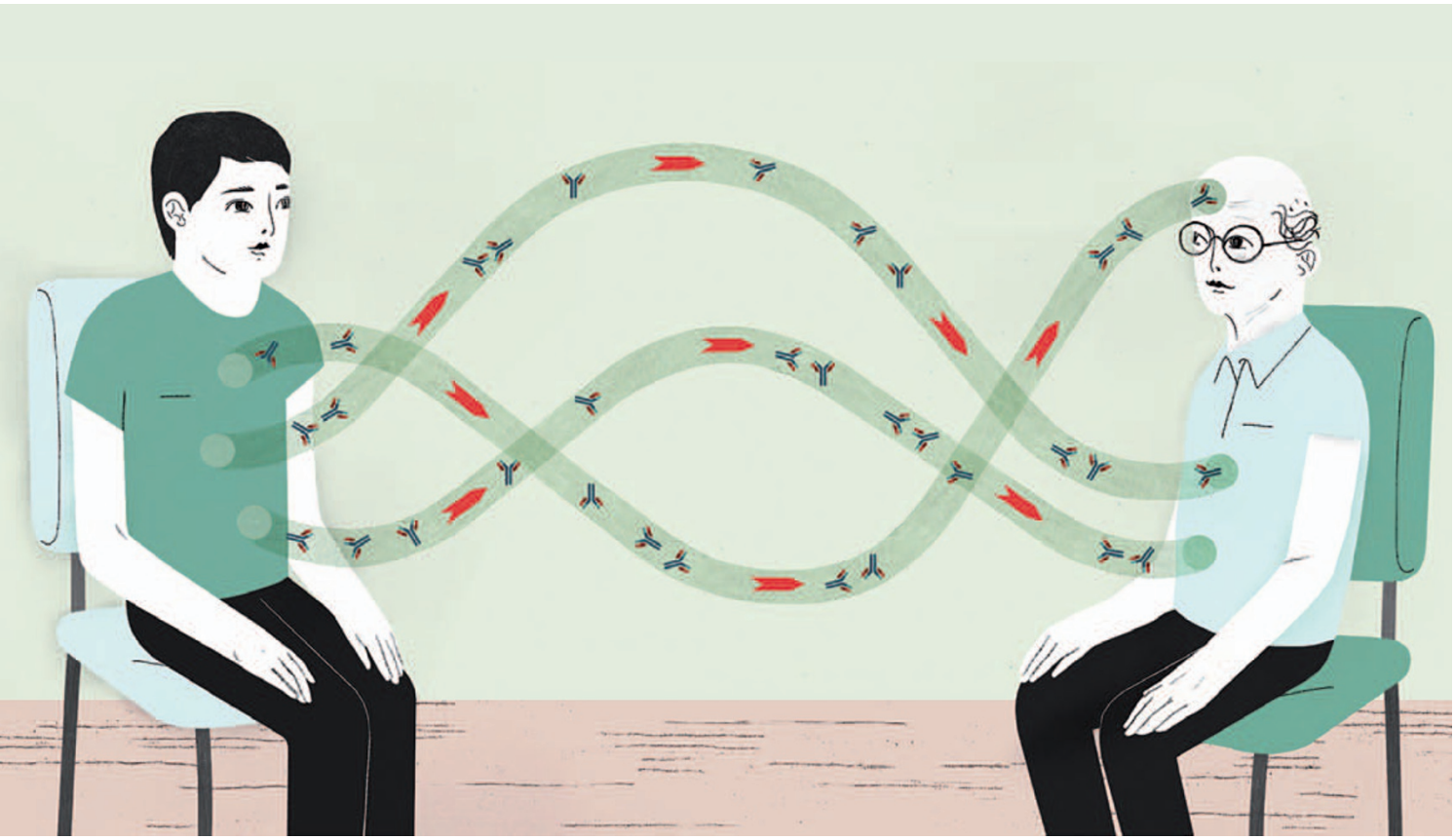
But this would not be the end of the Alzheimer's story, merely the end of the beginning. IVIg has several shortcomings. First, those who seemed to benefit from treatment had only modest gains. "I have not seen anyone re-enrol in adult education classes," says Weksler. Second, there seems to be a limited window of time when the therapy is effective. In the small trials carried out so far, the patients who started IVIg treatment later in the disease course seemed more likely to keep worsening.

There are also problems of cost and availability. IVIg is infused at high doses every two weeks in these studies, and patients might need them for the rest of their lives, at a cost of thousands of US dollars per infusion. Worse still, the production capacity for blood products from human donors is limited, and demand for IVIg from Alzheimer's patients and their families would swiftly outstrip supply. "We need next-generation products that are easier to produce and are based on IVIg's mechanisms of action," says Relkin.

Unlike most other Alzheimer's vaccines, IVIg has several plausible mechanisms. Although some of its antibodies may keep aggregates of amyloid-β in check, others may counter brain inflammation and reduce aggregates of tau protein, which also contribute to dementia. "You're talking about a complex disease that has many different pathological processes occurring either sequentially or in parallel," says Relkin. "So IVIg in this respect is ideally suited."

By contrast, AN-1792 and other big pharma Alzheimer's vaccines have aimed squarely at amyloid-β in its natural, single-copy form, as well as in fibrils — the long, insoluble, plaque-making aggregates that show up prominently in the brain and cerebral blood vessels of Alzheimer's patients. The lack of success with these vaccines suggests that single-copy and fibril amyloid-β might not be the best targets in patients who already have dementia.

So far, for all these vaccines, there has been only one published efficacy study: a phase II trial of bapineuzumab, Elan's passive anti-amyloid-β antibody infusion. The beneficial effects of bapineuzumab seemed weak to non-existent and, even worse, at high doses it caused brain swelling and associated



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microbleeds in some patients with heavy vascular amyloid-β deposits[3]. Autopsy and brain imaging studies of selected bapineuzumab and AN-1792 recipients suggest that these vaccines can fail to slow the progress of dementia even when they succeed in reducing plaques of amyloid-β in the brain[4].

One reason for these disappointing results may be that the vaccines address only amyloid-β and do nothing to counteract brain inflammation or tau aggregates. Another possibility is that they are less effective at clearing the small, soluble clusters of amyloid-β known as oligomers, which are now seen as far more toxic than fibrils and which seem to promote the appearance of tau aggregates[5] (see 'Little proteins, big clues', page S12).

The short-term effects of IVIg could be due to its ability to clear amyloid-β oligomers, Relkin says. "Studies have suggested that you can reverse signs of memory impairment in mouse models within 24 hours of giving anti-oligomer antibodies," he says. "It's wonderful that we have a potential therapeutic as well as something that is directing us towards new avenues, new mechanisms, in studying the problem."

## DREAM VACCINES

In the future, vaccines may also be used to treat people who have less advanced disease and so might get more benefit. "We're all moving towards the idea of treating patients with very mild dementia or even before they develop symptoms," says Dennis Selkoe, a neurologist at Harvard Medical School and long-time Alzheimer's researcher.

"The ultimate dream is to be able to give people a vaccine when they're still in their 20s or 30s, to prevent the disease process from even starting," says Cynthia Lemere, a Harvard neurobiologist who tests active anti-amyloid-β vaccines in monkeys.

Lemere, Selkoe and others believe that until dementia sets in, amyloid-β is the main driver of disease. Even the existing vaccine candidates might work well in this presymptomatic phase by keeping amyloid-β, in all its forms, within manageable levels.

Other researchers favour a universal Alzheimer's vaccine that leaves ordinary, single-copy amyloid-β alone and instead targets structures found only on amyloid-β aggregates, particularly oligomers and incipient fibrils. According to Relkin, the natural anti-amyloid-β antibodies found in IVIg seem to target these shapes, rather than single-copy amyloid-β.

"I see these as pathology-specific structures, so they're ideal targets," says Charles Glabe, an Alzheimer's vaccine researcher at the University of California, Irvine. "I think you'd have your best therapeutic effect this way, and the fewest side effects."

To elicit antibodies against these targets, Glabe and others have vaccinated animals with synthetic peptides that have the desired shapes but contain non-human amino-acid sequences, lowering the risk of autoimmune reactions. These vaccines reduce brain pathology and improve memory-related behaviours in mouse models of Alzheimer's disease, just as broader anti-amyloid-β vaccines do[6]. In principle, some of the aggregate-specific antibodies evoked by these vaccines would bind to aggregates of other disease-linked proteins, such as α-synuclein in Parkinson's disease or prion proteins in Creutzfeldt–Jakob disease (CJD), so the same approach could be used against all such diseases.

So far, none of these third-generation vaccines has had the corporate backing to reach clinical trials, but that could change quickly. "If one of the existing vaccines shows a strong effectiveness profile in clinical trials, then I think interest will go way up," says Glabe. He would particularly welcome a success for IVIg, because it is widely believed to work on the same principle as an oligomer vaccine. "But investors tend to lump all immunotherapies together," he says, "so they rise and fall together even though they may have very different targets." ■

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