in addition to Y_5-receptor antagonism that could be responsible for their effects on feeding behaviour. This conclusion is supported by the observation that such compounds inhibit feeding behaviour in mice that lack the Y_5 receptor, emphasizing the value of receptor knockout mice in defining the mode of action of drugs. Indeed, there is good evidence from studies in Y_1-receptor-deficient mice that the Y_1 receptor has a key role in NPY-induced feeding, and it seems likely that this is where efforts to target the activity of NPY will now be most concentrated. And in general, the study by Turnbull and colleagues serves as a warning that the effects of selective receptor activation might not necessarily be a good predictor of the importance of that receptor in more natural circumstances.

Peter Kirkpatrick

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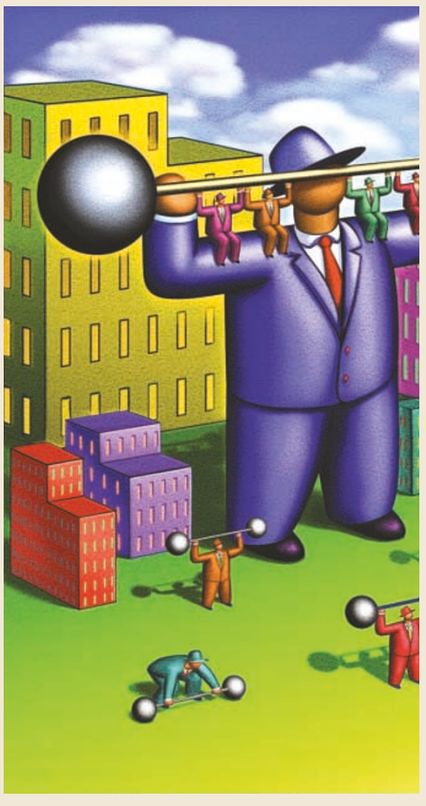

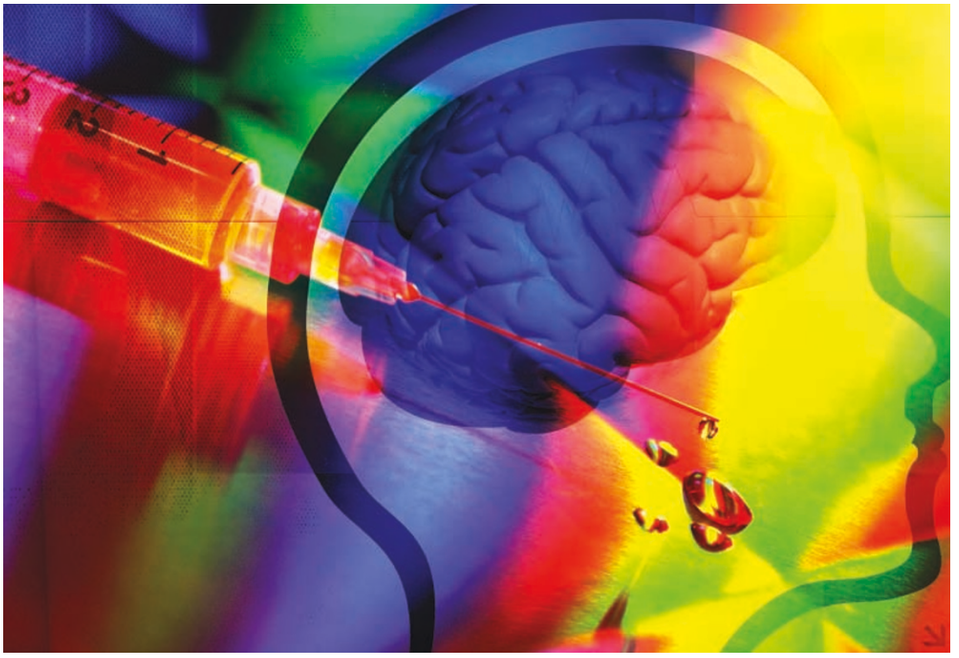

ALZHEIMER'S DISEASE

Vaccine revisited

Earlier this year, Elan Pharmaceuticals and Wyeth-Ayerst were forced to halt Phase II studies on their vaccine for Alzheimer's disease (called AN1792) after the discovery that 15 patients (out of 360) had developed severe brain inflammation. This was a huge blow, as the vaccine — a fragment of the β-amyloid precursor protein (APP) called $A\beta_{42}$ that targets the β-amyloid plaques that are a hallmark of the disease — had shown highly promising results in preclinical models and Phase I trials.

But two studies in *Nature Medicine* now reveal that there could still be hope for this strategy. Nitsch and colleagues report that they could detect a positive antibody response in patients who took part in the ill-fated trial. And McLaurin and colleagues show how refining the epitope could eliminate the harmful side effects.

In the first study, the researchers carried out immunohistochemical examinations from a subset of 30 patients who had taken part in the trial — 24 of whom received the vaccine plus booster, whereas the other 6 received placebo.

Nitsch and colleagues found that antibodies in the sera from most patients in the vaccine group recognized β-amyloid plaques, diffuse β-amyloid deposits and vascular β-amyloid in brain blood vessels from transgenic models bred to develop pronounced Alzheimer's-like β-amyloid deposits. Importantly, the antibodies did not cross-react with APP, which is found in the nerve cells of both healthy subjects and Alzheimer's sufferers. In other words, the vaccine selectively induced the desired immune response against disease-associated forms of β-amyloid — whether this mechanism can prevent cognitive decline will be the focus of future studies.

The second study assessed whether the beneficial effects of the vaccine could be separated from the inflammatory side effects. Mass spectrometry showed that the therapeutic antibodies that were raised against $A\beta_{42}$ recognized an epitope defined by residues 4 to 10 (termed $A\beta_{4-10}$). Incubating serum that contained antibodies raised against $A\beta_{42}$ with PC-12 cells showed that these antibodies could inhibit both the generation of fibrils (the long, thread-like aggregates of misfolded proteins that are associated with the formation of amyloid plaques) and cytotoxicity.

McLaurin and colleagues next investigated the immune response to $A\beta_{4-10}$. The immune system responds to antigens in two ways: it produces either T-helper type 1 (T_H1) cells, which stimulate a T-cell-based pro-inflammatory response (the response that many speculate was the cause of the side effects), or T_H2 cells, which stimulate a B-cell (antibody) response. They found that T_H2 cytokines were produced but there was no T-cell response.

Although these results will need to be tested in other models, they raise the possibility that a more refined vaccine, based on $A\beta_{4-10}$, could be effective and safe in humans. And, intriguingly, knowing the antibody–antigen interaction involved could also open the door to generating small-molecule drugs that mimic the effects of the vaccine.

Simon Frantz

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