

Can type 1 diabetes be prevented?

In this article, **Olwen Glynn Owen** reports on two clinical strategies that have the potential to make type 1 diabetes a disease of the past

Last month two researchers who believe type 1 diabetes (insulin-dependent diabetes mellitus) is preventable, were awarded the Pasteur-Weizmann/Servier prize for biomedical discoveries with therapeutic applications. The theme for these prizes was diabetes and autoimmunity. George Eisenbarth, executive director of the Barbara Davis Center for Childhood Diabetes, Colorado, US, won the senior prize while the junior prize went to Lucienne Chatenoud, professor of immunology, René Descartes University, Paris, France. Both scientists are prominent in a field where thousands are honing strategies that could see type 1 diabetes rendered avoidable for many at-risk individuals within a few years.

Professor Eisenbarth is credited with much of the groundwork that led to type 1 diabetes being recognised as a chronic autoimmune disease with a long prodromal interval, giving scope for intervention before symptoms emerge. The discovery of genetic susceptibilities and auto-antibodies associated with development of type 1 diabetes have led to assays that can identify a major proportion of individuals likely to develop the disease. Although type 1 diabetes is the commonest form of diabetes among children and adolescents, it also affects older people, who typically develop the disease in their 40s.

Type 1 diabetes is a complex disease to prevent because several auto-antigens have been identified, of which there are three major ones, including insulin. However, a number of clinical interventions are well into development, the two main strategies being vaccination against auto-antigens and therapy with monoclonal antibodies (MABs).

Immunologic vaccination

Up to 90 per cent of patients have circulating antibodies against their own islet cells or insulin. The Diabetes Prevention Trial, which studied both injectable and oral insulin as a vaccine in adults with newly-diagnosed disease, failed to arrest islet-cell destruction and work now in clinical trials is using more specific insulin peptides. The first of these to enter human trials is being studied in the UK. Two years ago, Mark Peakman, professor of clinical immunology at King's College, London and Colin Dayan, head of clinical research at Bristol University, announced a study (n=72) to evaluate the safety of an islet-cell derived insulin peptide produced by Clinalfa. Like all trials in the field to date, this one uses newly-diagnosed patients who could benefit from early intervention.

Professor Eisenbarth's laboratory has been working with a vaccine based on the insulin peptide B:9-23, which is also now ready for human trials. The vaccine prevented diabetes in a non-obese diabetic mouse model



Type 1 diabetes affects five million people worldwide, of whom 430,000 are children

but required modification to avoid risks of anaphylaxis.

Currently, the most advanced immunologic vaccine product, however, is DiaPep 277. This molecule, originally developed at the Weizmann Institute of Science in Israel, works against heat shock protein (hsp) 60, one of several auto-antigens in type 1 diabetes. It is now being developed by a German-based company, initially for the prevention of latent auto-immune diabetes in adults. The product began Phase III trials in September 2005, recruiting patients aged between 16 and 45 years with newly-diagnosed disease of less than three months. Phase II studies showed beneficial effects on beta cell preservation. Irun Cohen of the Weizmann Institute admits the team that discovered peptide 277 do not know how hsp 60 or peptide 277 produce their effects, nor how a single peptide vaccine could arrest auto-immune disease — only that it does.

“Curiously, vaccination with p277 or with hsp 60 induced a change in expression of auto-immunity not only to p277 and hsp 60 but also to other antigens in the diabetes collective, such as insulin and glutamic acid decarboxylase (GAD),” he wrote in a recent paper. Dr Cohen added that T-cell auto-immunity switched from a damaging to a protective response concerning the body's own beta cells but continued to function in damaging mode against foreign antigens.

Diamyd, a vaccine against GAD, has completed Phase II trials. It has also demonstrated beta cell preservation

Monoclonal antibodies

MABs are being used to redirect the immune system to prevent activity of T-cells that orchestrate the destruction of the insulin-secreting beta cells in the pancreas. Two principal MABs, hOKT3 gamma 1 (ala-ala) and CHAglyCD3, have been engineered to block the CD3 receptor on T-cells responsible for attacking pancreatic islets. ChAglyCD3, originally discovered in Oxford, is now being developed as TRX4 by a company in

Cambridge, Massachusetts. The product has been tested in the largest Phase II trial to date, led by Professor Chatenoud, where of 80 patients with newly-diagnosed diabetes half received the MAB for six days. “Results were impressive,” Professor Chatenoud said. “MAB-treated patients are continuing to produce their own insulin 18 months later, and required less exogenous insulin than the other patients.” The ideal would be to treat patients at a pre-diabetic stage. Once symptoms are apparent, up to 80 per cent of islet cells are already destroyed so diagnosed patients will continue to require lifelong insulin injections.

The other humanised MAB in Phase III development is being developed by the biotech firm MacroGenics. A pivotal Phase II/III trial is scheduled to end in 2009. A small Phase II trial published in 2002 tested the molecule in 24 newly-diagnosed patients. Nine of the 12 in the treatment group compared with 2 of the 12 controls had a sustained response lasting at least a year.

A third MAB, NI0401, has clinical trial approval to be studied for insulin-dependent diabetes, Crohn's disease, multiple sclerosis and rheumatoid arthritis. So far, its development has focused on patients with Crohn's disease.

Scientists at the La Jolla Institute for Allergy and Immunology, California, are pursuing a combined anti-CD3 antibody and a proinsulin immunomodulation approach. The MAB, along with an intranasal pro-insulin peptide vaccine, shows “strong synergy”, they claim. In mice the combination reversed recent onset type 1 diabetes in most animals, producing better efficacy, longer-lasting results and fewer side effects than either therapy has shown alone in human studies. “Diabetes never recurred in the lifespan of the mice,” a researcher commented. It is hoped that human clinical trials will begin this year.

MAB therapy produces flu-like symptoms, mild to moderate fever, pruritic urticarial rash and mild to moderate anaemia, all of which resolve within days.

Potential

Prevalence of type 1 diabetes is increasing by 3 per cent per year. With two clinical strategies for preventing type 1 diabetes advancing well, optimism is high that for many the disease will become avoidable. On receiving his award, Professor Eisenbarth said: “I am confident we will be able to predict and prevent type 1 diabetes in the near future”. The ultimate aim is to identify subjects at risk, from birth, by screening for genetic susceptibility and the emergence of auto-antibodies. Once the latter appear, interventions could, theoretically, induce tolerance to auto-antigens and restore the immune system's normal function before islet destruction gets under way.