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Tackling Type 1 Diabetes: New Immune-Modulating Drugs Attack the Root Cause

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A metabolic disorder caused by an autoimmune condition of genetic origin triggered by an external factor—this seems to describe some obscure disease, not one that strikes millions. Nonetheless, it is an apt description for one of the most common autoimmune disorders, type 1 diabetes, which claims more than 10 million patients worldwide, mostly children. Despite enduring an onerous regimen of daily insulin injections and blood glucose monitoring, these patients on average die 7–10 years early due to higher risk of heart disease, stroke, and kidney disease. But new hope comes from recent breakthroughs in immune modulation therapies. After encouraging preliminary results, several new drugs that promise to retard, arrest, or even reverse the course of this disease are poised for large-scale clinical trials. "The goal is to restore the immune system of a type 1 diabetes patient to look more like that of a healthy individual," says Richard Insel, executive vice president of research at the Juvenile Diabetes Research Foundation, a New York-based nonprofit that funds diabetes research worldwide.

The exact mechanism of type 1 diabetes is still something of a mystery, but a combination of genetic, immunologic, and environmental factors may be involved. A possible scenario is as follows: triggered by an external factor such as a virus or a toxin, the immune system in a genetically susceptible person begins to overreact to proteins secreted by the pancreatic β cells that make insulin and regulate the glucose response. Autoreactive T cells spring up and start attacking the β cells with cytokines. The humoral immune system then jumps into the fray with antibodies against insulin and other β cell-related proteins. The onslaught kills most of the β cells within a few years, bringing on the dreaded symptoms—weight loss, fatigue, excessive appetite, and frequent urination. By the time the condition is diagnosed, more than two-thirds of the β cell mass could be lost.

"You have to restore functional β cells and at the same time prevent the immune system from destroying them," says Insel. "That's what makes type 1 diabetes so hard to cure."

Until the 1920s, the diagnosis of type 1 diabetes was effectively a death sentence; few patients survived beyond a few years, despite near-starvation diets and other desperate measures. The discovery of insulin and its subsequent manufacture by recombinant technology have transformed the disease into one that can be "managed" with insulin therapy. Although patients can now lead fairly normal lives, they have to walk a metabolic tightrope, avoiding the twin dangers of too much or too little blood sugar. "No matter how diligent you are, insulin therapy is imperfect at preventing short-term and long-term complications," says Insel. "It can't replace the constant monitoring that goes on in the body with β cells."

To restore β cell function, some researchers are studying growth factors and similar molecules that stimulate β cells to regenerate. Others are testing methods to transplant β cells from pigs or cadavers to a diabetic patient's pancreas. Both strategies have shown promise in early studies. However, restoring β cells solves only part of the problem, since it doesn't fix the immune system defect that destroyed the cells in the first place. "You have to restore functional β cells and at the same time prevent the immune system from destroying them," says Insel. "That's what makes type 1 diabetes so hard to cure."

Serious attempts to tame the diabetic immune response started in the 1980s, with compounds such as cyclosporine that are used to prevent organ transplant rejection. In human trials, some of these immune suppressors did seem to help preserve insulin production in patients, but at the cost of unpleasant side effects such as kidney and liver toxicities. Researchers soon abandoned this brute-force approach for more nuanced strategies. In 1994, Lucienne Chatenoud and other researchers from the Hospital Necker in Paris showed that a monoclonal antibody targeting the CD3 protein on autoreactive T cells could induce immune tolerance in an adult nonobese diabetic (NOD) mouse model. Surprisingly, most of the mice went into complete remission and maintained normal glycemic levels even four months after the anti-CD3 treatment. However, the drug had a nasty side effect: it could trigger a massive release of TNFα and other cytokines, causing systemic toxicity.

To suppress autoreactive T cells without provoking an adverse immune reaction, researchers developed humanized anti-CD3 antibodies modified to reduce binding to Fc receptors. Two such compounds—otelixizumab from Tolerx and teplizumab from Macrogenics—have shown promise

in controlled human trials. A Phase II study with 80 subjects in 2005 showed that a single 6 day treatment of new-onset patients with otelixizumab helped reduce insulin needs for up to 18 months. According to one source, some of these benefits continue to the present day—nearly four years after the drug was given. "The most exciting thing is that we are targeting what causes the disorder," says Lou Vaickus, chief medical officer of Tolerx, contrasting that approach with insulin replacement therapy, where "the bottom line is, you are destroying an organ that is irreplaceable, and then you play catch up afterwards." Macrogenics's teplizumab had a similar success story in 2005, with the treatment group in trial of 42 new-onset patients showing a significant improvement in the insulin response two years after a 12–14 day course of treatment.

Studies suggest that anti-CD3 therapy has a dual effect: it not only destroys autoreactive T cells immediately, but also creates regulatory T cells that continue to keep the rogue cells in check for a long time. "What makes anti-CD3 attractive is that it is not continuous immune suppression," says Kevan Herold, who led the teplizumab clinical trial. "We give an immunomudulator for a brief period of time, with lasting effect—it is the first step in the direction of tolerance."

One of the drawbacks with systemic immune modulators such as anti-CD3 is the way they are administered: patients have to undergo an intravenous infusion of the drug for up to 2 weeks. Another potential drawback is the transient reactivation of existing infections, although neither trial reported any serious problems of this kind. Finally, the benefits of the treatment, though long lasting, are likely to diminish with time. "To be fair, it is not a cure," acknowledges Herold. "But the overall clinical experience is much better for the patients."

As an alternative to systemic interventions, a number of antigen-specific methods are being tried. Their goal is to retrain the autoreactive immune system with a vaccine based on antigens associated with β cells. In theory, such a targeted approach could fix the underlying problem in type 1 diabetes while having minimal impact on normal immune function. And as with any vaccine, the effect would be sustained. One vaccine that has shown clinical efficacy in type 1 diabetes is based on glutamic acid decarboxylase (GAD), a major autoantigen implicated in the disease. Tested in a placebo-controlled trial of 70 patients in 2006, the drug showed that it could help preserve insulin levels for up to 2 years without major side effects. In contrast to anti-CD3 therapy, the GAD vaccine, developed by a Swedish company, Diamyd Medical, is given in two or three simple injections. "And it seems to be just as effective, at least after 21 months of data," says Anders Essen-Moller, the company's CEO.

The antigen-specific approach has its own drawbacks. In theory, it could precipitate the very immune reaction that it is supposed to prevent, as has been observed with a similar treatment for multiple sclerosis. (However, no such adverse event has been reported with for GAD vaccine.) Further, since the pathophysiology of type 1 diabetes is still poorly understood, it is not entirely clear which antigen(s) would be the best to target. Other than Diamyd's GAD vaccine, most antigen-specific approaches tried so far have been clinically disappointing. Some experts fear that the antigens involved may vary between patients and with time, and present a moving target for immunotherapy.

Could systemic and antigen-specific agents be combined? In 2006, Matthias von Herrath and other researchers from the La Jolla Institute for Allergy and Immunology in San Diego showed that an insulin-related peptide vaccine could work in synergy with an anti-CD3 compound to cure type 1 diabetes in mouse models. For their experiments, the researchers used molecules developed specifically for mice. "We need to develop this kind of therapy for humans," says Herrath. "In order to do this, we need flexibility on the part of companies to share their Phase 3 products for combination trials." However, this is unlikely to happen very soon, says Vaickus. He points out that it took decades for drugs in oncology to be used in combination. "You can't just throw in two or three agents together when they are in development," he says. "You need to first find out what each does singly."

Both types of therapies share one major limitation: neither succeeds in inducing normoglycemia, or normal blood sugar levels, without insulin. In contrast, by some estimates more than 200 therapies have succeeded in producing a complete remission of type 1 diabetes in the NOD and other rodent models. Some experts attribute this to the differences between the rodent immune system, which is well characterized, and the human immune system, which is still something of a mystery. "Our knowledge of immunology is a drop in the bucket compared to the complexity of the human immune system," says Vaickus. Others point out that it is much harder to study type 1 diabetes in humans, since the β cells that are key to the disease lie hidden in the pancreas. "We know a lot about the mouse, but we lack a good understanding of human type 1 diabetes," says Insel.

Despite these challenges, a massive worldwide effort is underway to find more effective therapies for the disease. Besides nearly a dozen company-sponsored trials, several studies are being coordinated by TrialNet, an international clinical trial network for type 1 diabetes. Some of these studies are looking at nutritional interventions. Others are testing drugs that have already been approved for other autoimmune conditions such as rheumatoid arthritis. Cellular approaches based on dendritic cells could also emerge in the near future, according to TrialNet study chairman Jay Skyler. "We may see a whole variety of treatments blossoming in the next few years," he says.

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