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Authors and Disclosures

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Search for Diabetes "Cure" Focuses on Beta-Cell Regeneration

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Editor's Note:

The Sanford Project is an ambitious study that began in June 2008 with the goal of finding a cure for type 1 diabetes through beta-cell regeneration. The Sanford Project is a joint effort of Sanford Health, founded by philanthropist Denny Sanford, and the University of South Dakota. Beta-cell regeneration is a relatively new and very promising area of diabetes research. Scientists hope that the body's ability to generate new beta cells can be exploited to reduce or even eliminate insulin dependency in type 1 diabetes. Alexander Rabinovitch, MD, is Associate Director of the Sanford Project. He is an expert in beta-cell regeneration and was recruited from the University of Alberta in Canada. Dr. Rabinovitch spoke to Medscape recently about the project and the tremendous possibilities offered by this research.

Medscape: Can you fill us in on recent developments in the type 1 diabetes project?

Dr. Rabinovitch: Our goal has been to find a treatment that will work in type 1 diabetes: to achieve normoglycemia and hopefully reduce the need for insulin.

We have spent at least 5 years in the laboratory determining which 2 medications we'd like to test in people who have developed type 1 diabetes. We've discovered in our basic research, using nonobese diabetic (NOD) mice with type 1 diabetes, that we could restore them to normoglycemia with a combination of 2 drugs: sitagliptin (Januvia®) and a proton-pump inhibitor (PPI).

Sitagliptin, a dipeptidyl peptidase-4 inhibitor, raises endogenous glucagon-like peptide-1 levels (GLP-1), and the PPI, lansoprazole, raises endogenous gastrin. The combination of GLP-1 and gastrin produced by these 2 drugs protected existing beta cells in the mice, regenerated new beta cells from the pancreatic exocrine duct cells, and at the same time stopped the autoimmune reaction against the new beta cells.

Medscape: How did you arrive at using these 2 medications?

Dr. Rabinovitch: Both of these medications are currently used for other indications. Sitagliptin is an oral anti-hyperglycemic currently used to treat type 2 diabetes in adults. Sitagliptin potentiates the secretion of insulin by the pancreatic beta cells. Now, we have found that it does more than that. When we treated type 1 diabetic NOD mice with sitagliptin, it not only stimulated the remaining insulin-producing cells to secrete insulin but, along with lansoprazole, it also generated new insulin-producing beta cells.

Gastrin complements sitagliptin, and the 2 drugs work synergistically to encourage the beta cells to regenerate, at least in mice. This potential benefit of gastrin was reported back in

1993 in a publication by a group at Harvard. Dr. Stephen Brand published a study showing that if you could get cells in the pancreas to make gastrin, then the pancreatic exocrine duct cells could transform into islet beta cells.

Medscape: What prevents the immune system from attacking the newly formed beta cells, the way it does in type 1 diabetes, to stop them from producing insulin?

Dr. Rabinovitch: That's a very good question. We were surprised to find that we didn't have to use any drugs to suppress the immune system to prevent it from reacting against the new beta cells. It turned out that GLP-1, induced by sitagliptin, and gastrin, induced by the PPI, acted together against the immune system. So we are doing 2 things: We are generating new insulin-producing cells and we are preventing the autoimmune reaction without using conventional immunosuppressive agents.

These are very exciting developments. I am confident that we will see some new possibilities from this trial. I am not saying that these 2 agents will get type 1 diabetics off of their insulin entirely, but I am confident that they'll need less insulin, have better glucose control, and avoid harmful swings in blood glucose.

Medscape: Where do you go from here?

Dr. Rabinovitch: We are planning to study sitagliptin and lansoprazole in combination therapy for new-onset type 1 diabetes. Our inclusion criteria are subjects ages 11-45 within 6 months of a diagnosis of diabetes and confirmed to be type 1 by the presence of autoantibodies for type 1 diabetes.

The reason for restricting the trial to patients with recent-onset type 1 diabetes is that we know we can count on protecting preexisting beta cells and possibly regenerating new beta cells. If it works in recent-onset type 1 diabetics, we will expand the study to those with longer-existing type 1 diabetes.

We will enroll 54 patients, randomly assigned in a 2:1 ratio to active agents or placebo. The therapy is 2 capsules a day, along with insulin, for 1 year. The follow-up is at 1 year and the primary outcome is the C-peptide response to a mixed meal-tolerance test. Secondary outcomes are A1c and blood glucose levels. At the end of 1 year, patients will be taken off therapy to see if the hoped-for effects on lowering glucose, lowering insulin requirements, and improving pancreatic C-peptide secretion (insulin partner) persist.

If there is an effect (needing less insulin, improved glucose control, and improved pancreatic beta-cell function), then we will conduct a much larger study. We may possibly be allowed to do a study in patients younger than 11 years of age or in patients with long-standing type 1 diabetes.

Medscape: How does this research fit into the search for a cure for type 1 diabetes?

Dr. Rabinovitch: Most of the emphasis in type 1 diabetes research has been on addressing the autoimmune response. In most trials, investigators have tested a variety of antibodies that block one or another limb of the immune response.

What is different about this project is that we are focusing more on regenerating beta cells. We are counting on these agents to not only regenerate but also stop the autoimmune attack. The advantage of that, if it works, is avoiding serious immunosuppression.

Medscape: Is there a chance that this therapy could work for type 2 diabetes?

Dr. Rabinovitch: Yes. Sitagliptin is already used in type 2 diabetes. A significant percentage of people with type 2 diabetes fail to have good control with oral agents, and we now accept that they may need insulin. It's evident that not only are their beta cells malfunctioning but they have also lost a number of insulin-producing beta cells. Perhaps not as much loss as in type 1 diabetes, and the loss is unrelated to an autoimmune process; nevertheless, for reasons unknown, their beta cells are not functioning adequately. We envision that

regeneration of the beta cells might work for patients with type 2 diabetes who otherwise would need insulin.

Medscape: Are any other new therapies showing promise for type 1 diabetes?

Dr. Rabinovitch: When it comes to restoring the ability of the pancreatic beta cells to make insulin in patients with type 1 diabetes, there are a few different approaches. One method of replacing beta cells, at present, is achieved by transplantation.

My surgical colleagues at the University of Alberta in Edmonton developed the so-called "Edmonton Protocol" for islet transplantation. That approach has certain limitations. The material used as human donor tissue to replace the insulin-producing beta cells is very limited because it is obtained from deceased pancreas donors.

It takes a lot of work in the lab to prepare those donor cells for transplantation, and it takes perhaps 3 or so different donors to provide enough insulin-producing cells for 1 recipient. Moreover, the recipient must take immunosuppressives to prevent immune system rejection of the transplanted islets.

For these reasons, we typically reserve that treatment for adult patients who have had type 1 diabetes for many years, who are in and out of hypoglycemic unawareness, and who might be at risk for dying at the wheel of their car, for example. It is not a procedure that could be applied to the vast majority of type 1 diabetics who are not in that condition.

One possible way to get away from immunosuppressive agents for those patients would be to encapsulate the islets from the donor pancreas and protect them from immune rejection. Insulin from the transplanted encapsulated islet tissue would still be able to permeate through the membrane of the capsule, and glucose could permeate into the encapsulated islets. However, engineering of capsules that would be permeable to both insulin and glucose is still being perfected. Another area that is being investigated is the use of porcine islets, but with these sources, the immune barrier may be even stronger.

Therefore, we would prefer to treat type 1 diabetes by stimulating the patient's own pancreatic cells as the precursors of new insulin-producing cells, using drugs that are safe and effective.

Medscape: Denny Sanford wants to cure type 1 diabetes in his lifetime. Do you think we are going to make that goal?

Dr. Rabinovitch: The ultimate question of *when* we will cure diabetes is one that I am asked often by the families of my patients with type 1 diabetes. It is a very difficult question to answer. If you ask me again a year from now, I hope to be able to tell you at that time that we are having an effect and that we can then expand this treatment out to many other patients.

Medscape: What impact has Mr. Sanford's philanthropy had?

Dr. Rabinovitch: In the area of type 1 diabetes, what he has offered in terms of support for this trial (and others to come) has really made a tremendous impact. It has given us at least a few years' jump-start on this research for type 1 diabetes. When we were beginning our work at the University of Alberta in Canada, working in the lab with the mice, the Juvenile Diabetes Research Foundation (JDRF) was working with us to fund the clinical trial. Sanford invited me to consider carrying out the trial here. There is no doubt that in partnership with JDRF and major support from Sanford Health we've had the opportunity to move this trial forward.

Over the past 6 weeks since our clinical trial began, we have enrolled 9 young patients who were recently diagnosed with type 1 diabetes. At this rate, we should have completed enrollment of all 54 subjects by spring 2011, with final results 1 year later.