Stem cell therapy for diabetes still a long way off

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Ever since scientists started talking about the potential of embryonic stem cells, curing Type 1 diabetes has been a dear dream.

When researchers announced in 1998 that they had derived stem cells from human embryos, their landmark report flagged Type 1 as a disease that might be treated by stem cell transplants.

In the run-up to the 2004 vote on California's Proposition 71, diabetes was repeatedly mentioned as a target by scientists campaigning for a state-backed stem cell agency.

Years later, the promise remains. But success has been elusive. Scientists are still studying how embryonic stem cells, which can become any type of body cell, can be turned into cells that make insulin at the right time, in the right amounts, and transplanted into patients to cure diabetes. The effort has been challenging.

"It's maddeningly simple as a concept," says Dr. Gordon C. Weir, a diabetes researcher at the Joslin Diabetes Center in Boston. "It's been incredibly frustrating that we can't bring this to the clinic more quickly."

Type 1 diabetes, once known as juvenile diabetes, is an autoimmune disorder that is usually diagnosed when patients are children or young adults. As many as 3 million Americans have the disease. They face a lifetime of vigilance, blood monitoring and insulin injections to keep the condition in check.

One reason why Type 1 diabetes seemed to be such a great fit for stem cell therapies was how motivated patients and advocates were to find a cure, says Meri Firpo, a stem cell scientist at the University of Minnesota, Twin Cities. Groups such as the Juvenile Research Diabetes Foundation were willing to fund research using human embryonic stem cells - controversial, because it involves destroying embryos - before other organizations were.

There were technical reasons too that made the disorder an attractive target.

In Type 1 diabetes, for reasons not fully understood, a combination of genetic and environmental factors triggers a patient's immune system to kill off beta cells, the insulin-producing factories that group together in the pancreas into clusters known as the islets of Langerhans.

Healthy people have about a million functioning islets in the pancreas, each composed of about 1,000 beta cells. In Type 1 diabetes, those islets are destroyed. Restoring the islet cells would cure the disease - and researchers already know that they can do that. Scientists made the first successful islet cell transplant in 1989, placing beta cells from a cadaver into a diabetic patient.

The treatment, still experimental, isn't perfect. Islet recipients must take anti-rejection drugs to prevent the body from attacking the foreign cells, and these have serious side effects. But in the last two decades the transplants have improved recipients' diabetes to the point where some no longer require insulin, at least until their new beta cells peter out and a new transplant is needed.

The problem is that there are not enough cadaver pancreases to go around. About 35,000 people in the U.S. are diagnosed with Type 1 diabetes each year and only around 2,000 cadaver pancreases become

available for transplantation, says Weir of the Joslin Center. Only people with especially poor glucose control are candidates.

But if scientists can figure out how to turn embryonic cells (or alternatively, adult cells that have been transformed back to a versatile, embryonic state) into functioning beta cells, they'll have a possibly endless supply.

Researchers at a company called ViaCyte Inc. of San Diego have successfully nudged human embryonic stem cells to become precursors to beta cells. When implanted into mice, the cells developed into beta cells and reversed diabetes in the animals.

But fine-tuning the cells to make them safe and effective for human use will take time. For example, beta cells do more than just produce insulin; they also respond to body cues to produce just the right amount of insulin when it's needed and thus regulate glucose levels with great precision. If you make beta cells that produce too much insulin, the level of glucose can drop dangerously low - and people can pass out, lapse into a coma or even die.

"We have not regenerated the intricate mechanisms that regulate the levels of secretions," says Matthias Hebrok, director of the UC San Francisco Diabetes Center. "Beta cells are like a Porsche - an amazing, calibrated machine. What we've made is more like a Volkswagen Beetle."

Another major problem is the issue of autoimmunity - the problem that causes Type 1 diabetes in the first place. "Even if we are able to generate beta cells from stem cells, if you put them into a patient with Type 1 diabetes, they'll be eliminated quickly, because the immune system is primed to destroy those cells," Hebrok says.

Physicians combat autoimmune responses with anti-rejection drugs. In the future, immunologists hope to figure out ways to specifically interfere with the immune system's attack on beta cells.

ViaCyte is working on a different potential solution: an embryonic stem cell-based therapy that encloses beta-cell precursors inside a membrane envelope, then implants them under a patient's skin. The pouch will allow insulin to flow out of it, into a patient's bloodstream, but won't allow cells of the immune system to get in and attack the implant (or allow rogue cancers from the transplant, should they arise, to escape into the body).

Finally, diabetes researchers face the same challenges as any other scientists working with stem cells: They need to learn how to produce large numbers of beta cells and make sure they're safe and stable.

Over the long term, the best solution would probably be to figure out how to teach a patient's body to regrow islets for itself from stem cells, and possibly even other types of cells, that are already in the body, Firpo says.

Weir, Firpo and Hebrok say they can't predict when stem cell therapies for diabetes might finally arrive - even though, Hebrok says, "What we've learned in the past decade and a half is truly amazing."

The soonest ViaCyte's technology would begin human trials would be 2013. Other strategies won't be ready for testing until even further in the future.

"There was too much hype for this type of technology. There are no shortcuts in this kind of research," says Dr. Camillo Ricordi, an islet cell transplantation expert at the University of Miami Diabetes Research Institute.

"Next century, when you look back at it, two decades won't seem like much. But for those affected right now, every month is too long."