Diabetes dilemma

Fluorescence image of mouse pancreatic islets. The live islets are green; the dead ones are red. The islets are seeded on a microporous polymer scaffold prior to transplantation. Image from the lab of Lonnie Shea.
For many of those with type 2 diabetes, the disease often can be managed with diet and exercise. For type 1 diabetics, the disease can be managed with daily injections of insulin.

But there are complications related to manual monitoring of blood glucose — some as severe as blindness, kidney damage, and lower-limb amputation. And there are people whose bodies cannot handle daily injections of insulin. Annual medical costs for diabetes are estimated to be $116 billion, and according to the National Institutes of Health, more than 1.5 million new cases of diabetes are diagnosed each year.

So researchers continue to search for alternatives for managing blood glucose. Within the past decade, a new option has emerged: islet transplantation. Islets are clusters of cells from the pancreas that include beta cells, which regulate blood glucose levels. Though the cause of type 1 diabetes is unknown, researchers do know that a diabetic’s own immune system mistakenly destroys the islet cells in the pancreas. Researchers also know that it’s possible to take working beta cells from a donor and transplant them into a diabetic. Attempts have shown that this procedure essentially cures the diabetes; injections of insulin are no longer needed.

There are drawbacks, however. The patient must take immunosuppressant drugs to prevent the body from rejecting the cells, and the beta cells tend to stop working after only a couple of years.

Yet there is hope. Several Northwestern researchers are working on different ways to make islet transplantation more effective. What if, for example, new materials could help protect the islets and integrate them into the body? Under the umbrella of the Institute for Bionanotechnology in Medicine (IBNAM), three McCormick faculty members are working with professors and surgeons at the Feinberg School of Medicine on three different approaches to the islet transplantation dilemma.

**How to make islets survive**

Islet transplantation has been around only for about a decade, and only a handful of hospitals across the country perform the procedure. The most popular location for transplanting the cells is the liver because it has many blood vessels that give the islets the nutrients they need to grow.

In 2006 the Collaborative Islet Transplant Registry reported that two-thirds of the 225 patients who received islet transplants between 1999 and 2005 achieved “insulin independence” after transplantation. But six months after receiving the last islets, only half of recipients no
longer needed insulin, and at the two-year mark it dropped to a third.

No one really knows why the islets fail; maybe they aren’t getting enough nutrients, or maybe they are attacked by the recipient’s immune system. So researchers are trying several methods to try to improve the success of the transplanted islets. One approach involves using an adhesive to stick the islets to the liver.

Enter Phil Messersmith, who knows how to get things to stick together. Several years ago Messersmith, professor of biomedical engineering and of materials science and engineering, and his group created a nanoadhesive called Geckel that fused a gecko’s dry adhesion with a mussel’s wet adhesive properties. He and his group also have developed synthetic polymers that mimic the composition and properties of the adhesive proteins that mussels use. “It’s a very good glue to use in wet conditions,” he says.

About five years ago Messersmith began to collaborate with Lonnie Shea, professor of chemical and biological engineering; Samuel I. Stupp, the Board of Trustees Professor of Materials Science and Engineering; and Dixon Kaufman, professor of surgery, director of the Pancreas and Islet Transplantation Programs of Northwestern Memorial Hospital, and a key collaborator at Feinberg. “We all got together with the intent of offering a unified, multifaceted approach to the treatment of diabetes,” Messersmith says.

Messersmith thought he could use his mussel-inspired adhesive to stick islets to a layer of fat. That way surgeons wouldn’t have to cut an organ, avoiding a blood inflammatory response that can contribute to islet failure. “It’s an easier approach to transplanting,” he says.

Messersmith tested his adhesive in mice in a procedure using syringes to place the islets on the tissue and then to apply the adhesive. The adhesive bonded within a minute and held the islets in place for up to four months. He found that the mice’s blood glucose dropped to a normal range within a week after implantation. The group published a paper on the results earlier this year, and Messersmith would like to continue testing the procedure in mice to better understand the immune response to the islets.

Though it’s just one of several areas of research pursued in his lab, Messersmith hopes to continue this study to understand the immune response to his adhesive. “Increasing the options available for islet transplants would be a significant accomplishment,” he says.

Building a sponge-like home for islets

Lonnie Shea takes a different approach. He is trying to create a tiny home for islets as they become part of their new body. “Typically researchers have tried to isolate islets from the immune system to help them survive,” he says. “Islets occupy 1 percent of the mass of the pancreas but get 10 to 15 percent of the blood supply. If you’re isolating islets from the immune system, you’re not allowing blood vessels to access them.”

Shea’s group creates tiny structures called scaffolds out of a biodegradable polymer — the same material from which biodegradable sutures are made — and shapes them into a sponge. Each pore in the sponge is about 250 to 400 microns across and holds one or two islets, resulting in about 75 islets per sponge (normal mice pancreases have about 200 islets). Surgeons can then implant this sponge into the body. This technique, Shea says, gives surgeons an easy-to-use material, keeps the islets from aggregating (so they don’t compete for nutrients), and allows blood vessels to grow through the scaffold and into the islets. Shea also puts a coating of extracellular matrix proteins around the scaffold that makes the islets easier to graft onto an organ; islets in the pancreas are normally surrounded by a fibrous matrix. “We’re trying to deliver a minimal mass of islets and have them engrafted for a long time,” he says.

Shea and his group have tested the scaffold in the fat pad of a mouse — the equivalent of the omentum (a layer of fat around the stomach) in humans. The results showed that blood vessels grow through the scaffold, and the scaffold itself degrades in 100 days. The islets continued working in the mouse for 300 days. “That’s a large portion of the lifespan of the mouse,” Shea says. “We’re optimistic.” Shea and his group have begun testing the scaffolds in pigs and primates. Early results from these ongoing studies
have been encouraging. Immune response to the islets is still an issue. Shea has been collaborating with Steve Miller, professor of microbiology-immunology at Feinberg, to develop strategies for inducing tolerance by coupling antigens from donor cells with islets, reducing attacks from the recipient’s immune system. Shea hopes to create synthetic particles that would mimic these strategies to induce tolerance from the immune system.

Shea also collaborates with Feinberg’s Dixon Kaufman and Bill Lowe, an associate professor of medicine, an expert on the genetics of diabetes and islet cells and another collaborator of many engineers. “I think the collaboration is great,” Shea says. “No one person has solutions to all aspects of this problem. The materials we have are platforms for targeting the various barriers to engraftment and function.”

Shea eventually hopes to be able to test his scaffold in diabetic humans who cannot have islets transplanted into their livers. “I’m hoping it can be a cure for type 1 diabetes,” he says. “I am fortunate to have three healthy children. I hope our research can one day end the need for any children and their parents to be burdened by the constant strain of insulin regulation and the associated impact to the quality of life.”

“Diabetes is clearly one of the main targets of regenerative medicine.”

SAM STUPP

Nanostructures that grow blood vessels

Sam Stupp is well known for his research on molecular self-assembly strategies for regenerative medicine. Molecular self-assembly is the assembly of molecules without guidance or management from an outside source. This occurs naturally in many biological systems, and researchers have begun to imitate the process to create tiny nanostructures that are programmed for certain functions. Stupp has used this technique to develop novel materials to promote regeneration in the central nervous system, which could impact therapies for spinal cord injury and Parkinson’s disease, and he has developed new materials for the regeneration of bone, cartilage, and blood vessels.

The growth of blood vessels is a major component of Stupp’s work, since regenerating tissue requires new blood vessels to provide nutrients to the cells. In 2004 Stupp led the charge to create a National Institutes of Health–funded bioengineering research partnership with Shea, Messersmith, Kaufman, and others to explore new solutions for regeneration of the central nervous system and cell-replacement therapies for diabetic patients. “Diabetes is clearly one of the main targets of regenerative medicine,” Stupp says. “We reasoned that growth of blood vessels should be a major focus.”

Stupp is working to improve the outcome of islet transplantation by using materials that promote the formation of blood vessels in transplant sites. He and his group have created self-assembling bioactive nanofibers that are formed by an interaction between heparin and peptide molecules. The proteins that signal cells to make new blood vessels grow have a specific affinity for heparin.

“Our nanofibers interact with those proteins, capture them, and even position them in the right orientation so that they can signal the cells and start the process of making new blood vessels,” Stupp says. When endothelial cells (the cells on the interior of blood vessels) get the signal from the proteins, they begin to proliferate and create tube-shaped structures — the genesis of blood vessels.

The researchers found that, when tested in mice, the nanostructures indeed promoted blood vessel growth around the transplanted islets in vivo and enhanced the cure rate of diabetic mice that received the islets. That spurred Stupp to go a step further and actually introduce the nanostructure inside the islets themselves after they had been isolated and before they were implanted. “That way blood vessels can sprout from the islets themselves,” he says.

Though this technique has just been tested in vitro, the positive results already have Stupp planning for the next step of testing these pretreated islets in transplantation models. “The McCormick-Feinberg axis is critical to
this work,” Stupp says. “It would have been impossible to do this work at McCormick in isolation. One of the missions of IBNAM is to promote research collaborations, and this collaboration has been very successful.”

Bringing the lab to the bedside
When describing their research and their approaches, all McCormick researchers say none of it would be possible without their Feinberg collaborator Dixon Kaufman. Kaufman arrived at Northwestern 18 years ago from the University of Minnesota, where islet transplantation was pioneered. “I was recruited to start a pancreas and islet transplant program here,” he says. “I was the first and only one at the time working in that area.”

In 2001 one of Kaufman’s students attended presentations of Stupp’s IBNAM incubator awards program. “He said, ‘I met someone new, Sam Stupp, and he’s got some interesting materials in nanotechnology,’” Kaufman recalls. IBNAM played an important role in helping integrate new collaborations and supported Kaufman with an incubator award in 2002. Later, Kaufman and Lowe, another collaborator, found out about Shea’s work with microporous scaffolds and started working on a new project.

“We all have very similar personalities,” Kaufman says. “Surgeons make things happen. We’re pretty decisive. And when these guys are in their element, they make things happen, too. Our personalities mesh. The success of our collaboration really has to do with our collegiality and the innovation that everybody can bring to a focused area.”

Grants were received, meetings commenced, and the engineers used Kaufman’s mouse lab for testing. “It was fresh and exciting,” Kaufman says. “It really expanded the intellectual input in this field. I think we were one of the first medical school and engineering groups to start working together on a very clinically relevant area of islet transplantation.”

These days there are still only about 10 islet transplantation programs in the United States. The one at Northwestern performs about one procedure a month and, like every program, faces donor shortages. Although organs from about 7,000 deceased donors become available each year, according to the NIH fewer than half of the donated pancreases are suitable for harvesting islets. Still, Kaufman believes the procedure can one day be a cure for diabetes. “We want to transform lives,” he says. “We want to get people who were diabetic insulin-free.”

“We want to get people who were diabetic insulin-free.”

DIXON KAUFMAN

Other treatments possible
While stem cell–derived islets are now more science fiction than reality, Stupp is beginning to work on another possible cure for diabetes: nanostructures designed to turn faulty islets back on.

“Our vision is to produce a type 2 diabetes therapy that we could introduce systemically,” Stupp says. “People would get an injection of these nanostructures, which would navigate through the blood stream to the pancreas and give insulin-producing cells within islets signals to survive and produce insulin.”

Such a therapy would affect a large number of patients, but the lab is just beginning to create the nanostructures and test them in vitro with cells. “Diabetes is a growing problem,” Stupp says. “But this research has implications beyond the disease. That is what makes this specific idea such a good target.”

Emily Ayshford