Regenerating islet cells may lead to a cure for diabetes—which is why it’s a priority for the University’s Stem Cell Institute

For decades, researchers have focused much of their energy on minimizing the impact of diabetes. Because people with diabetes do not have functioning pancreas islet cells—essential for producing the insulin our bodies need—physicians and scientists have found ways to help them manage their blood sugar levels through lifestyle changes, medications, and insulin injections.

But Jakub Tolar, M.D., Ph.D., director of the University of Minnesota’s Stem Cell Institute, wants to think much bigger. He doesn’t just want to make it easier for patients to live with their diabetes; he wants to cure them of it. And that means replacing not insulin, but the nonfunctioning islet cells themselves.

“It’s not that different from replacing a part on a broken engine,” he explains. “If we can replace islet cells in high enough numbers, in high enough quality, [patients] will be cured of diabetes.”

Tolar’s goal is bold, and he’s putting the full weight of his organization behind it: he’s made diabetes a top-three priority of the Stem Cell Institute, where scientists are currently working on key projects to regenerate islet cells—and perhaps cure diabetes once and for all.

Assistant professors James Dutton, Ph.D., and Anannya Banga, Ph.D., for example, are working to convert stem cells in the liver into insulin-producing cells. Over the past five years, they have learned how to directly reprogram liver cells by using vectors that deliver genetic material into cells to “overexpress” specific genes in liver cells. If the process is done right, these reprogrammed cells can produce significant amounts of insulin.

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The most recent combination vector these researchers have created, known as Ad-PNM, has proved to be the most potent ever produced. While scientists in the past have been encouraged when their work resulted in a cell that produced even one ten-thousandth of the amount of insulin a typical islet cell produces, the cells generated by Dutton and Banga produce about one-fifth of what’s made by a typical islet cell.

“It’s a bit like Goldilocks,” Dutton says of the process. “The levels of gene expression provided by the vector are ‘just right.’”

More important, the resulting cells are having an impact. When the vector was injected into diabetic mice, the reprogrammed cells essentially restored the rodents’ normal glycemic levels. While the researchers are hesitant to call the mice cured—only further long-term studies can help make that claim—they say early results are promising: “Our research now is focused on why this works so well and how we can translate it to patients.”

Meanwhile, researcher Meri Firpo, Ph.D., is teaming up with other scientists on two stem cell–linked projects. With researcher Anindya Bagchi, Ph.D., she is applying the lessons of cancer cells, which seem to defy death, to regenerating islet cells that have been destroyed or have failed.

Firpo and Bagchi are currently working to unravel the mechanisms of cell growth and death by studying the cellular pathways of healthy and dying islet cells in mice. They’re hopeful that they can eventually manipulate these cells to prevent their deaths. “We want to take advantage of those regulatory mechanisms in islets to get them to survive—or even regenerate,” Firpo explains.

Firpo is also working with Melanie Graham, Ph.D., M.P.H., on projects that use stem cell–derived islets in new transplantation technologies.

Islet transplantation can reverse some cases of diabetes, but the “containers” that hold the islet cells during and after transplantation have flaws. The pair is working closely with engineers to create a small device made from silicone that allows stem cell–derived islets to more effectively “read” how much glucose is in the blood and then secrete insulin in proportion to that reading.

Firpo’s team is one of three U groups working to develop and perfect the “containers” that would potentially hold transplanted or regenerated human, pig, or stem cell–derived islets.

For Tolar, groundbreaking projects like these give the University an edge in diabetes research. “Our goal,” he says, “is to contribute in a unique way to this collective knowledge and collective effort to cure diabetes.”

Seaquist named to ADA leadership role

University of Minnesota professor and endocrinologist Elizabeth Seaquist, M.D., in January was named President of Medicine and Science for the American Diabetes Association, the nation’s largest voluntary health organization leading the fight against diabetes. Seaquist has been a member of the organization since 1987.
Join us for a special event: *Diabetes Spotlight*

Learn about how the U of M’s trailblazing scientists are shaping the future of diabetes treatment at the first-ever Diabetes Spotlight, to be held from 5:30 to 8 p.m. on Thursday, May 29, at the McNamara Alumni Center.

Guests will have the chance to attend two of four 20-minute presentations by top U of M researchers, including:

- Jakub Tolar, M.D., Ph.D.: Diabetes-focused stem cell research
- Bernhard Hering, M.D.: Islet cell transplantation
- Sayeed Ikramuddin, M.D.: Gastrointestinal/bariatric surgery as it relates to diabetes
- Brian Fife, Ph.D.: The role of the immune system in diabetes

A reception will follow.

**Teddy bear delivers funding to researchers around the world, including one Minnesota expert in cystic fibrosis-related diabetes**

He has toured 47 states and 23 countries to increase awareness of cystic fibrosis (CF)—a genetic disorder that causes mucus to build up and clog some organs of the body, primarily the lungs—and he gets hugs everywhere he goes. This furry advocate is Burke P. Bear, a cuddly teddy bear named in honor of Burke P. Derr, who died two days before his 19th birthday in 1997 from complications of CF.

Today Burke’s memory lives on through the work of his father, Bob Derr, for Pennsylvania Cystic Fibrosis, Inc. (PACFI), and the CF researchers it supports, including Antoinette Moran, M.D., a renowned pediatric endocrinologist in the University of Minnesota Medical School’s Department of Pediatrics.

Burke was a pretty typical kid in most regards, but his CF landed him in the hospital about three times a year for weeks at a time. Some of his friends, on top of their CF, also had cystic fibrosis-related diabetes (CFRD), which affects about 20 percent of adolescents and 40 to 50 percent of adults who have CF.

In the past, people with CF who developed diabetes faced a much higher mortality rate than those without diabetes. Gradually, as doctors have become more aggressive about screening for diabetes, the number of deaths stemming from CFRD has decreased.

Much of that progress is thanks to Moran’s work. She pioneered CFRD research during her residency at the University of Minnesota in the 1980s when she noticed that a surprisingly high number of CF patients were developing diabetes. And much of Moran’s progress was made possible by PACFI, which has supported her CFRD studies for the last decade.

Moran has used the PACFI funding to get fledgling research ideas off the ground. Currently, she’s putting the organization’s money toward a study focused on updating mortality rate trends in CFRD patients.

The progress holds special meaning for Bob Derr and for everyone who knew Burke. “To lose someone you love and to have something like this come out of it is remarkable,” Derr says.

Register by May 21 at www.rsvp.umn.edu/SpotlightOnDiabetes or by contacting Kerry Lengeling at kerryl@umn.edu or 612-624-6128.

As a special gift for Burke Derr, a lifelong teddy bear collector, his friends asked a teddy bear company to create a bear for Burke. Today Burke P. Bear is the world-traveling mascot for PACFI.
The University of Minnesota and Harvard University will partner on a multicenter clinical study evaluating a potential treatment for kidney disease in people who have type 1 diabetes. The study will be funded by a $24.3 million grant from the National Institutes of Health.

Part of the Preventing Early Renal Function Loss in Diabetes Consortium, the study is designed to assess the possible benefits of using the FDA-approved drug allopurinol to slow the decline of kidney function in people who have type 1 diabetes. Allopurinol is meant to lower levels of uric acid, which has been linked to a risk of kidney complications in people who have diabetes. What the researchers don’t know is whether the uric acid in itself or another related culprit is responsible for predisposing diabetics to kidney disease.

Michael Mauer, M.D., a professor of pediatrics and medicine at the University of Minnesota Medical School, is coleading the trial. Luiza Caramori, M.D., Ph.D., an assistant professor of medicine and pediatrics at the University, is directing the study.

“If we see a significant benefit of allopurinol on slowing progression of diabetic kidney disease, this will become a standard addition to the treatment of diabetic kidney complications, especially given that allopurinol is relatively inexpensive and safe,” Caramori says.

Kidney disease is burdensome for people who have type 1 diabetes; an estimated 10 to 15 percent develop end-stage renal disease and require hemodialysis or a kidney transplant to survive.

“This study has large human suffering, public health, and health cost implications,” says Mauer.