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Discoveries *in Diabetes*

A publication for those who support diabetes research, education, and care at the University of Minnesota

Can bacteria help defeat diabetes?

A study on fecal transplants may lead to a new treatment for diabetes

The trillions of tiny bacteria in our guts that help break down food may turn out to play more than just a critical role in digestion—they could also be important for fighting diabetes. A clinical study launched recently by University of Minnesota researchers will test a novel approach to helping prediabetes patients by boosting the diversity of the microbial mix in their intestines. This procedure could improve patients' insulin sensitivity, which lies at the heart of type 2 diabetes.

Studies have shown that diabetic patients typically have a less diverse microbial community in their guts than other people do. This diversity is essential not only for aiding digestion but also for helping the body produce the short-chain fatty acids that regulate glucose levels.

As part of a study designed to help patients regain this rich microbial diversity, U of M gastroenterologist Alexander Khoruts, M.D., will introduce trillions of beneficial bacteria into a prediabetes patient through a fecal transplant. This approach to correcting a person's microbiome isn't actually new; it was first documented some 1,700 years ago. More recently, scientists have rediscovered the procedure's potential benefits, and Khoruts has used it successfully to fight *Clostridium difficile*, a type of bacteria that can cause life-threatening infections.

"We believe a diverse microbial community will have the best capacity to produce the right signals to regulate glucose in prediabetes patients," says Khoruts.

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Photo by Richard G. Anderson

Gastroenterologist Alexander Khoruts, M.D., is testing a novel approach to improving glucose regulation in prediabetes patients by boosting the diversity of microbes in their guts.

Can bacteria help defeat diabetes? *(continued from cover)*

A jump start to better health

The tiny microbes in our gut that feast on the food we eat as it moves through the digestion process have a powerful influence on our bodies. "Microbes have the capacity to communicate to the brain and influence behavior," Khoruts explains. For example, they send the signal for hunger and thus nudge us to eat more.

A microbial 'organ'

In the healthy human body, microbial cells outnumber human cells by nearly 10 to 1. Up to 100 trillion microbes live in each of us. The large intestine alone is home to an enormous bacterial ecosystem estimated to encompass 33,000 species. Alexander Khoruts, M.D., and colleague Michael Sadowsky, Ph.D., director of the University's BioTechnology Institute, say this gut collective plays such an important role in human physiology they think of it as a microbial "organ." Khoruts and Sadowsky successfully developed fecal transplants to treat life-threatening infection of the intestine caused by the bacterium *Clostridium difficile*.

However, in people with prediabetes and type 2 diabetes, these microbes may have lost some of their ability to process certain foods. This could be due to larger societal shifts, in particular our use of antibiotics, which can kill some of the "good" bacteria and leave the remaining bacteria less able to do their work. Or, it may be that the food reaching our intestines doesn't need the final digestive action of these microbes because it is highly processed. In either scenario, the microbes continue to send hunger signals to the brain. This, in turn, may lead to overeating, obesity, and, eventually, type 2 diabetes.

By restoring a normal balance of bacteria in a patient's gastrointestinal tract, a fecal transplant may help prevent these false hunger signals. For the clinical trial Khoruts is leading, physicians will use fecal matter collected from a "champion" donor who has normal blood sugar levels and an ideal mix of gut microbes. This stool is then mixed with a saline solution and placed in the patient's intestine during a colonoscopy. After the procedure, participants receive 10 weeks of healthy meals developed by a dietician. Khoruts and his team believe the transplant and closely monitored diet will jump-start healthy processes in the guts of study participants and lead to better glucose regulation.

A powerful option for a complex disease

The transplant and meals are just one part of the larger study. To learn more about what and how these microbes tell our brains what to do, Khoruts will work closely with researchers across campus, including psychiatrist Kelvin Lim, M.D., and David Bernlohr, Ph.D., Distinguished McKnight Professor and Cargill Chair in Systems Biology of Human Metabolism. The team will perform MRI scans of the study participants' brains while they view images of food, both before and after the transplants.

"We want to see how people respond to food stimuli," says Khoruts. The scans should help the investigators to better understand how microbial balance affects communication between the gut and the brain.

If successful, the small-scale study could lead to larger trials with type 2 diabetes patients. Eventually, Khoruts believes, fecal transplants could become a powerful option in a doctor's arsenal to treat this complex disease.

"There may be no magic bullet to cure type 2 diabetes, but I do think multiple approaches, combined, will make a difference," he says. "This can be one more element to help patients."

Designing the ideal donor

Islet transplantation with no need for immune suppression is seen as the Holy Grail for curing type 1 diabetes. The U's Schulze Diabetes Institute is leading the way

Immunologist Christopher Burlak, Ph.D., is on a mission to make islet transplantation widely available to cure type 1 diabetes and knows he's at the best place in the world to achieve it: the Schulze Diabetes Institute (SDI) at the University of Minnesota. "There's only one group in the world that can do this work, and that's SDI," says Burlak, the institute's new scientific program director.

"I joined a winning team."

Building on what he's already accomplished, Burlak appears well positioned to achieve what he came here to do—genetically engineer pigs to create the ideal islet donor. He's driven by his passion for science. And he's also greatly inspired by his son Jack, who was diagnosed with type 1 diabetes on his second birthday.

Stealth transplants

Islet cells produce insulin, which is essential for controlling glucose levels in the blood. In type 1 diabetes—an autoimmune disorder—the immune system attacks and destroys islet cells. If left unchecked, this disease is fatal.

The transplantation of islets from a donor to a patient to treat type 1 diabetes was pioneered at the U in the 1970s, and tremendous progress has been made in recent years. However, the need for human donor islets far exceeds the supply, so access to this treatment is limited.

Early attempts at developing pig islet transplants for humans have been problematic due in part to the need for lifetime use of heavy immunosuppressive drugs to prevent rejection of the transplanted cells. To avoid this problem, Burlak aims to genetically modify donor pigs to make their islets look more like human islets.

"I like the word stealth; we're making a donor pig that will have stealth islets," Burlak says. "If we can engineer pigs to produce islets that will go unrecognized by the recipient immune system and produce insulin to control blood sugar, that will be fantastic."

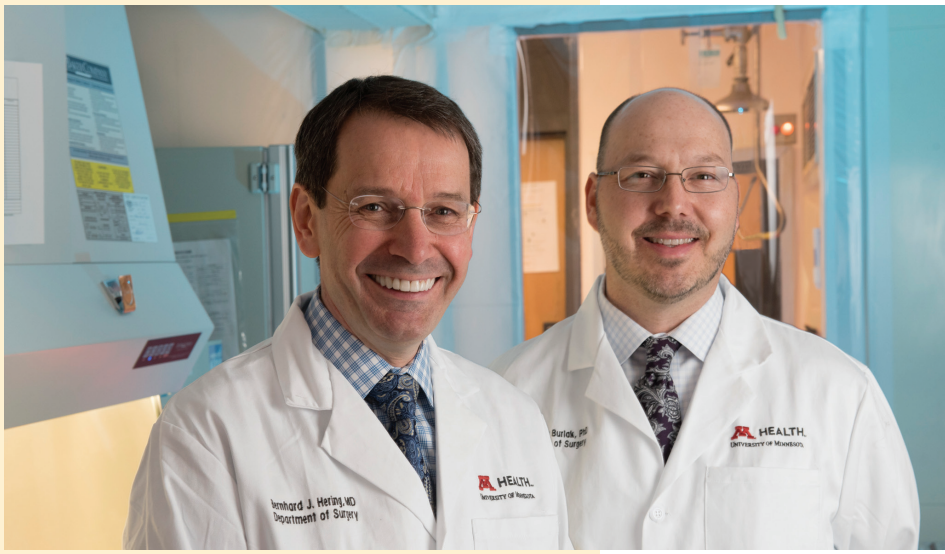
Bacterial scissors

To do this, Burlak will identify and, using bacterial "scissors," snip out pig genes that are most likely to be offensive to the human immune system. The pigs' DNA then repairs itself, resulting in a mutation that makes the pig cells appear less offensive to the patient's immune system.

"In our hands, this is easily accomplished," says Burlak, who's already had success with this newer approach. Before coming to the U, he used this technology at Indiana University to genetically modify pigs to be better liver and kidney donors. "Experience suggests that if we modify just a few genes that will be enough to make pig islets look like human cells," he says.

Bernhard Hering, M.D. (left), scientific director of the Schulze Diabetes Institute at the U of M, and researcher Christopher Burlak, Ph.D., are collaborating to make islet transplantation safe, effective, and widely available to cure type 1 diabetes.

Photo by Scott Streble



Burlak's confidence also stems from his collaboration with Bernhard Hering, Ph.D., scientific director of SDI and a world-renowned expert in islet transplantation.

"It's a lock-and-key fit," Burlak says in describing their partnership. "Bernhard has already been hugely successful with human-to-human islet transplants. If I can perfect pig cells and we can optimize the recipient immune system to tolerate those cells, this could result in long-term graft survival with little or no immune suppression. That's the goal."

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Jeff Passolt's Golf Classic "Fore" Diabetes Research

Join the fun on June 15

Join us for a day of golf, food, and fun at the 19th annual Golf Classic "Fore" Diabetes Research. The event benefits work at the University of Minnesota's Schulze Diabetes Institute and its research partners at Spring Point Project to advance a cure for diabetes.

The Golf Classic is Monday, June 15. New this year, it will be held at the Meadows at Mystic Lake in Prior Lake, Minnesota.

The tournament includes morning and afternoon rounds, lunch and dinner programs, and an auction. Join the fun and help support a great event that has raised nearly $6 million for diabetes research.

To register, please visit **DiabetesGolfClassic.org** today!

You're invited to a lunch briefing with our faculty

Attend one, two, or all three

Please join us for lunch and an exclusive opportunity to hear from faculty researchers about their pioneering efforts to develop better treatments for diabetes.

- **April 10** – Building an artificial pancreas
- **May 6** – The role nutrition and exercise play in diabetes
- **May 15** – Diabetic eye disease

All events will be held in the McNamara Alumni Center on the East Bank Campus.

To register, please visit **www.rsvp.umn.edu/DiabetesLunch** or contact Amanda DeLisi at adelisi@umnj.edu or 612-625-6973 at least two weeks before to the event(s) you would like to attend.

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