Leading Diabetes Breakthroughs

Researchers at Mount Sinai Are Developing New Treatments Designed to Optimize Care

BY BARBARA BRODY

Courtney Constantino, a participant in the artificial pancreas clinical trial, in which pregnant women with type 1 diabetes tested the device in 48-hour outpatient sessions and then went home using the system

For more than 100 years, Mount Sinai has served as a leading center for the care of patients living with diabetes. Mount Sinai has also been at the forefront of research in the field since the 1950s, when Rosalyn Yalow, PhD, and Solomon Berson, MD, developed radioimmunoassay (RIA), a method for measuring small concentrations of substances in the blood, such as insulin. This landmark discovery transformed our understanding of the causes of diabetes.

"Our faculty live up to this distinguished legacy through cutting-edge basic and translational research focused on improving the lives of our patients and ultimately curing diabetes," says Andrea Dunaif, MD, Chief of the Hilda and J. Lester Gabrilove Division of Endocrinology, Diabetes and Bone Disease for the Mount Sinai Health System, the Lillian and Henry M. Stratton Professor of Molecular Medicine, and Professor of Medicine (Endocrinology, Diabetes and Bone Disease) at the Icahn School of Medicine.

Pioneering Type 1 Diabetes Research for Pregnant Women

A Mount Sinai team led by Carol J. Levy, MD, Clinical Director of the Mount Sinai Diabetes Center, and Professor of Medicine (Endocrinology, Diabetes and Bone Disease), is making great strides toward developing an "artificial pancreas" that is customized for use by pregnant women with type 1 diabetes. Although a few artificial pancreas systems are now available—Mount Sinai played a key role in the research that enabled some of them to reach the market—none are devised to meet the specific blood glucose targets needed for pregnant women with diabetes.

The artificial pancreas, also known as a hybrid closed-loop system, integrates and analyzes data from a continuous glucose monitor (CGM) and an insulin pump. The system carefully delivers insulin to keep a patient's blood sugar within the target zone of 70-180 mg/dL around the clock. But such glucose targets become far tighter during pregnancy, as patients are generally advised to stay within the range of 63-140mg/dL.

"During pregnancy, the targets become markedly narrowed, because the risk to the developing fetus of hyperglycemia is so pronounced," Dr. Levy explains. Potential dangers include congenital anomalies in the newborn, preeclampsia in the mother, delayed fetal lung maturity, and an increased risk of fetal death. Yet hypoglycemia also carries serious risks to the mother.

"For people with [type 1] diabetes, managing blood sugars is often like walking a tightrope," Dr. Levy says. Constantly trying to avoid highs and lows puts an undue burden and stress on patients, she notes—one that only becomes more challenging when pregnancy is added to the mix. A customized closed-loop system would relieve some of the pressure by automatically adjusting insulin in response to glucose sensor readings. It has the potential to yield better patient outcomes by keeping glucose levels in the target range longer while decreasing the risk of dangerous hypoglycemic episodes.

Developing an artificial pancreas that is safe and effective in pregnant women is no easy feat, but Dr. Levy and her colleagues are well on their way. About two years ago, the U.S. Food and Drug Administration (FDA) granted them permission to test a novel closed-loop system that employs a Tandem insulin pump, a Dexcom G6 CGM, and an algorithm that was designed for pregnant women by the Doyle Group at Harvard.

Conducted during the early days of the COVID-19 pandemic, the research evaluated 11 women in their second or third trimester. Patients wore the closed-loop system while being carefully monitored for 48-hour periods. This pilot study, which was recently published in *Diabetes Technology & Therapeutics*, demonstrated that the system was safe.

With basic safety data in hand and funding from the National Institutes of Health (NIH), women were approved to test and use the system at home for one week while being monitored remotely. The Mount Sinai team is now also supported by a grant from the Helmsley Foundation to continue the study until delivery and collect even longer-term data, and research is ongoing. Dr. Levy, who serves as principal investigator for this study, is working in conjunction with colleagues at Mount Sinai, the Harvard John A. Paulson School of Engineering and Applied Sciences, the Mayo Clinic, and the Sansum Diabetes Research Institute.

If this current phase of research is successful, the project will continue progressing to larger, multi-site studies and eventually develop a version of the closed-loop system that would be suitable for commercial distribution. Dr. Levy, who has type 1 diabetes and gave birth to two children before this technology was available, is hopeful that pregnant women with diabetes will benefit from this advancement within several years.

"The passion of our team, as well as that of the patients who are participating in these studies, is really evident," Dr. Levy says, adding that collaboration between academia and industry has also been key. "Academia often has the ideas, but industry is going to eventually put these products out. Working together is the only way we can do it."

Reversing Type 1 and Type 2 Diabetes Through Beta Cell Regeneration

Elsewhere at Mount Sinai, researchers led by Andrew F. Stewart, MD, Professor of Medicine (Endocrinology, Diabetes and Bone Disease), and Director of the Diabetes, Obesity and Metabolism Institute (DOMI) at Icahn Mount Sinai, are making progress in developing a brand-new way to treat and potentially reverse type 1 and type 2 diabetes by stimulating the replication of beta cells.

Although type 1 diabetes is well known for being insulin dependent, people with type 2 also lack adequate insulin as a result of having too few insulin-producing beta cells, Dr. Stewart says. While he acknowledges that genetics and lifestyle factors play a significant role in type 2 diabetes, scientists agree that insulin deficiency is of equal importance.

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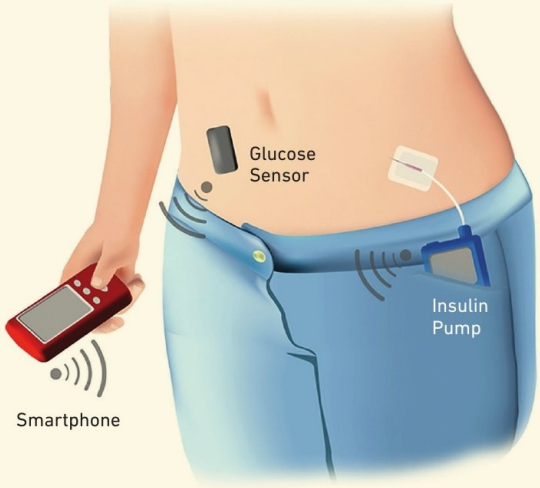
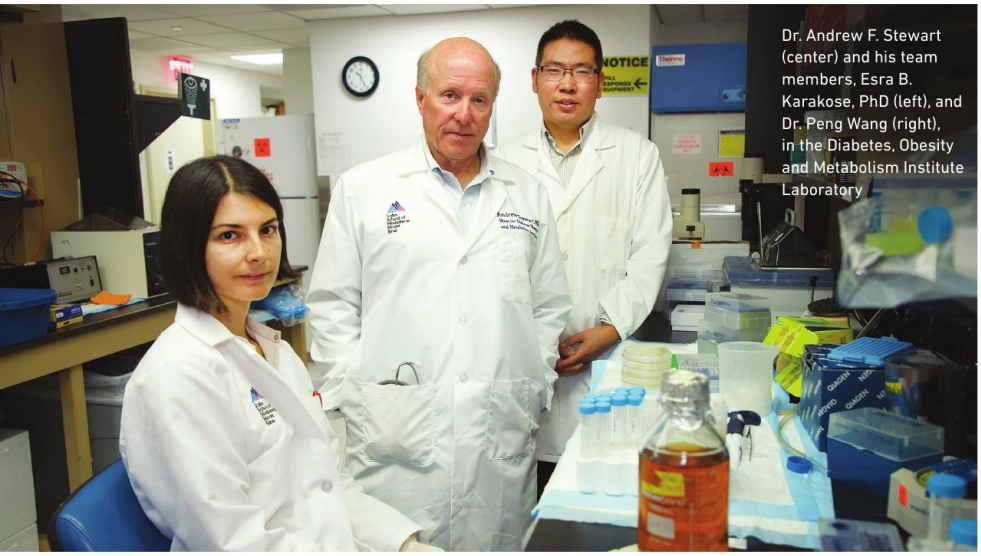
Dr. Carol Levy (center) with members of the clinical trials team at the Mount Sinai Diabetes Center

How Does an Artificial Pancreas Work?

In the artificial pancreas, or closed-loop system, a controller—consisting of a software algorithm on a smartphone—receives readings from a continuous glucose sensor and prompts doses from an insulin pump, with reduced input from the patient.





Dr. Andrew F. Stewart (center) and his team members, Esra B. Karakose, PhD (left), and Dr. Peng Wang (right), in the Diabetes, Obesity and Metabolism Institute Laboratory

"It's not uncommon for people who are thin to get type 2 diabetes, and they're absolutely insulin resistant," he explains. "Also, if you look at people with type 2 diabetes at autopsy, they have lower beta cell mass compared to BMI-, age-, and gender-matched controls." Meanwhile, obese individuals who avoid type 2 diabetes have a greater than average supply of beta cells.

So how do you get more beta cells? Pancreas transplants are one option, though they carry a host of risks, and donor organs are in short supply. It is also possible to grow new beta cells from stem cells, but this technique is unlikely to benefit many patients given how expensive it is, Dr. Stewart says. His solution is to instead get patients to regenerate the remaining beta cells in their own bodies.

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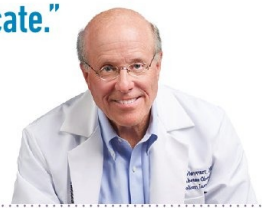

Treating Diabetes with a Novel Two-Drug Approach

People with type 2 diabetes have about half the ideal number of beta cells; those with type 1 have about 10 percent. In either case, Dr. Stewart believes he has found a way to treat any existing beta cells so that they proliferate until a patient has an adequate beta cell mass. The key: a two-drug combo that pairs a GLP-1 agonist—which stimulates the secretion of more insulin—with a novel compound called harmine.

Harmine was identified by Dr. Stewart's collaborator, Peng Wang, PhD, Professor of Medicine (Endocrinology, Diabetes and Bone Disease) at Icahn Mount Sinai. Harmine has the ability to make both rodent and human beta cells regenerate in laboratory animals. So far, Dr. Stewart and his colleagues have demonstrated that mice treated with harmine have a 2 percent proliferation in beta cells. When mice are treated with harmine plus a GLP-1 agonist—his team used exenatide (Byetta or Bydureon)—beta cell replication, mass, and insulin production increase exponentially.

Using brand-new imaging techniques involving microscopy, the team demonstrated that they could increase beta cell mass in the mice by sevenfold over a period of just three months. If this two-drug regimen proves equally effective in humans, it could be a game changer. "If you make someone's beta cells proliferate enough, you could reverse their diabetes," Dr. Stewart says.

GLP-1 agonists have already been well tested, but pure harmine has never been studied in humans. Before Dr. Stewart and his colleagues test harmine on people with diabetes, they need to determine the highest tolerable dose in healthy subjects. This year, they obtained FDA approval to conduct a phase 1 study of a synthetic version of harmine in healthy people for this purpose. James Murrough, MD, PhD, Associate Professor of Psychiatry and Neuroscience, and Director of the Depression and Anxiety Center for Discovery and Treatment at Icahn Mount Sinai, is the lead investigator of this ongoing trial.

Pending the success of the trial, researchers will advance to studying the harmine/GLP-1 treatment in people with type 2 diabetes and then type 1. Those with type 1 would also require some type of immune-suppressive treatment to prevent destruction of the newly proliferated beta cells.

Lastly, Robert J. DeVita, PhD, Professor of Pharmacological Sciences, and his team in Mount Sinai's Drug Discovery Institute have synthesized a plethora of next-generation DYRK1A inhibitors and harmine analogs that are far more potent than harmine: These may be the ultimate DYRK1A inhibitors used in people with diabetes. Other Icahn Mount Sinai collaborators on this project include Adolfo Garcia Ocaña, PhD, Professor of Medicine (Endocrinology, Diabetes and Bone Disease); Sarah A. Stanley, MBBCh, PhD, Associate Professor of Medicine (Endocrinology, Diabetes and Bone Disease) and Neuroscience; and Kunal Kumar, PhD, Postdoctoral Fellow, Pharmacological Sciences.

"Anyone with diabetes needs more beta cells, and years ago we set our sights on finding drugs that could help beta cells replicate," Dr. Stewart says. "Our work at the DOMI is truly revolutionary, and our novel discoveries will lead to better outcomes for diabetes patients."