SPECIALTY REPORT | WINTER 2018

Mount Sinai

Hilda and J. Lester Gabrilove

Division of Endocrinology, Diabetes and Bone Disease

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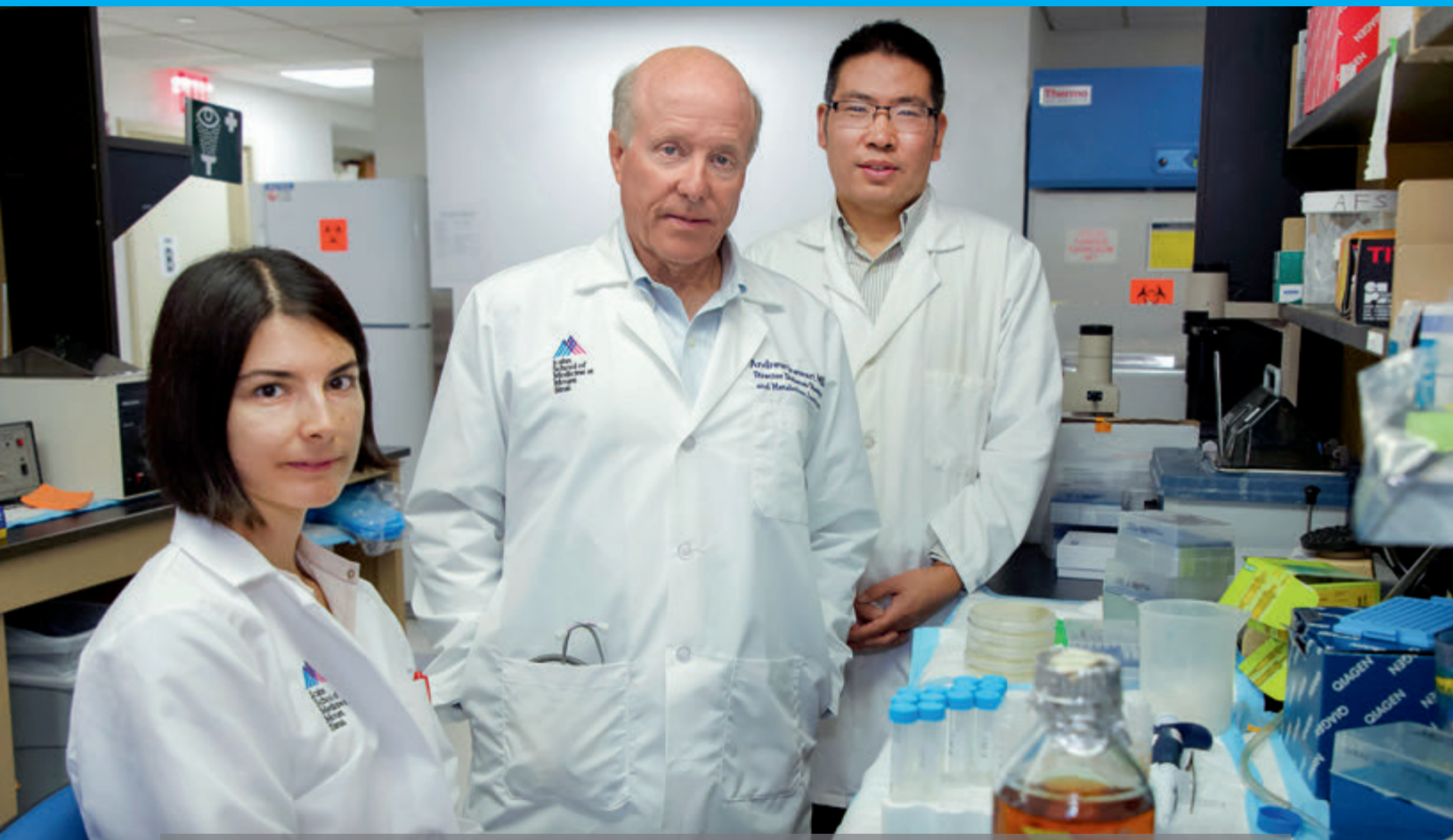

In Benign Tumors, Discovering Pathways to Beta Cell Regeneration

In the largest genomic study of insulinomas, researchers at the Icahn School of Medicine at Mount Sinai have uncovered multiple pathways to human beta cell proliferation, long seen as a holy grail in treating and possibly curing diabetes. Insulinomas—rare and usually benign pancreatic beta cell tumors that overproduce insulin—have now become an invaluable tool in the search for diabetes therapies.

"We've sequenced 38 human insulinomas with 30,000 genes each, and now know all the genes that are mutated and misregulated," says Andrew F. Stewart, MD, Director of the Diabetes, Obesity and Metabolism Institute and the Irene and Dr. Arthur M. Fishberg Professor of Medicine at the Icahn School of Medicine at Mount Sinai. "For the first time, we have a genomic recipe—an actual wiring diagram in molecular terms—that demonstrates how beta cells replicate."

Andrew F. Stewart, MD, center, with team members Esra Karakose, PhD, and Peng Wang, PhD

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Leader in PCOS Research Is New Chief of Endocrinology, Diabetes and Bone Disease

Andrea E. Dunaif, a renowned physician-scientist in diabetes and women's health, joined the Mount Sinai Health System as Chief of the Hilda and J. Lester Gabrilove Division of Endocrinology, Diabetes and Bone Disease in May 2017. In her new role, Dr. Dunaif seeks to build on Mount Sinai's strengths in research on diabetes, metabolism, and endocrine disorders.

Dr. Dunaif is a leader in the research of polycystic ovary syndrome (PCOS), which affects about seven percent of reproductive-age women and causes hyperandrogenism and ovulatory disturbances. Research led by Dr. Dunaif has shown that PCOS is associated with insulin resistance and is a leading risk factor for type 2 diabetes in young women. She has also shown that the male and female relatives of affected women are at increased risk for metabolic syndrome, type 2 diabetes, and reproductive problems. "I am transferring my research program here," Dr. Dunaif says, "so Mount Sinai will become a major center for the genetics of PCOS."

In a continuation of her work, funded by a $2.5 million National Institutes of Health (NIH) grant, Dr. Dunaif is mapping chromosomal regions that have a high likelihood of containing genes causing PCOS. The ultimate goal is to identify novel therapeutic targets and genetic markers that could be used for PCOS prediction and prevention.

Dr. Dunaif will hold an endowed chair as the Lillian and Henry M. Stratton Professor of Molecular Medicine. She began her career at The Mount Sinai Hospital in the early 1980s and most recently served at Northwestern University's Feinberg School of Medicine in Chicago as Chief of Endocrinology, Metabolism, and Molecular Medicine; Vice Chair for Research in the Department of Medicine; and Director of the Specialized Center of Research on Sex Differences, supported by the NIH.

She plans to take advantage of the "phenomenal expertise in genetics at Mount Sinai" by working closely with the Department of Genetics and Genomic Sciences and The Charles Bronfman Institute for Personalized Medicine at the Icahn School of Medicine at Mount Sinai. She also seeks to expand on her Division's strengths across the Health System, including the study of diabetes and metabolism as well as population health at Mount Sinai St. Luke's; the new Thyroid Center at Mount Sinai Union Square; and the groundbreaking research on artificial pancreas systems and pancreatic beta cells at the Icahn School of Medicine.

"Returning to Mount Sinai is very much like coming home," Dr. Dunaif says. "And it is exciting to see the extraordinary growth of the Icahn School of Medicine, which celebrates its 50th anniversary in 2018, and the Health System. It was always excellent, but now it is one of the premier academic health centers in the country." ■

Study Traces the Links Between Alzheimer's and Diabetes

A Mount Sinai study involving Alzheimer's disease and metabolism suggests that therapies that enhance insulin signaling in the brain might significantly benefit both Alzheimer's and diabetes patients.

Led by Christoph Buettner, MD, PhD, Professor of Medicine (Endocrinology, Diabetes and Bone Disease), and Neuroscience, Icahn School of Medicine at Mount Sinai, the study suggests that patients who have Alzheimer's disease have an increased risk of developing diabetes because of impaired brain insulin signaling.

"Researchers have known for years that there is an association between Alzheimer's disease and diabetes, meaning that if you have one, you have an increased risk of developing the other," Dr. Buettner says. "Commonly, it's believed that diabetes makes the Alzheimer's worse, but since the brain controls metabolism, Alzheimer's per se may cause prediabetes or diabetes. That was the rationale for this study." Published in the August 2016 issue of the journal *Alzheimer's & Dementia*, the study focused on transgenic APP/PS1 mice. These mice are genetically

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IN THIS ISSUE

Mount Sinai Study Finds That FSH Could Hold the Key to Bone Loss and Weight Gain at Menopause

A study in mice indicates that follicle-stimulating hormone (FSH), whose levels rise at menopause, could be responsible for a characteristic gain in belly fat and loss of bone. It also found that blocking the hormone could help reverse those effects. The strong clinical potential of these results was noted in *The New England Journal of Medicine*, and in *Nature Medicine*, which named the study one of the eight "notable advances of 2017."

The work began about 10 years ago when Mone Zaidi, MD, PhD, Professor of Medicine (Endocrinology, Diabetes and Bone Disease), Icahn School of Medicine at Mount Sinai, challenged endocrinology's long-held notion that the pituitary hormone FSH controlled only reproductive targets: the production of estrogen in women and sperm in men. Using animal models, Dr. Zaidi showed that FSH had direct effects in conserving bone.

That groundbreaking discovery further piqued Dr. Zaidi's curiosity. Could FSH also play a role in the sharp increase in visceral fat that occurs in women during late perimenopause?

To answer the question, his group conducted a study that included injecting a polyclonal antibody that blocked FSH signaling into several groups of laboratory mice: females that had their ovaries removed and were fed a normal diet; male and female mice that were fed a high-fat diet; and female mice on a normal diet. "What we found was that by targeting FSH and blocking its action, we could not only prevent bone loss but also reduce body fat and improve energy homeostasis," he observes. "We thought to ourselves, 'This is really a weird finding.'"

Dr. Zaidi then enlisted the support of Clifford J. Rosen, MD, a bone and fat expert who is Director of the Center for Clinical and Translational Research at Maine Medical Center Research Institute. For the next two and a half years, the scientists replicated each other's work in their own laboratories, culminating in the publication of their comprehensive study in the June 2017 issue of the journal *Nature*. Their findings confirmed that blocking access of FSH to its receptor, using an epitope-specific polyclonal

A leading journal calls the study one of the "notable advances of 2017."

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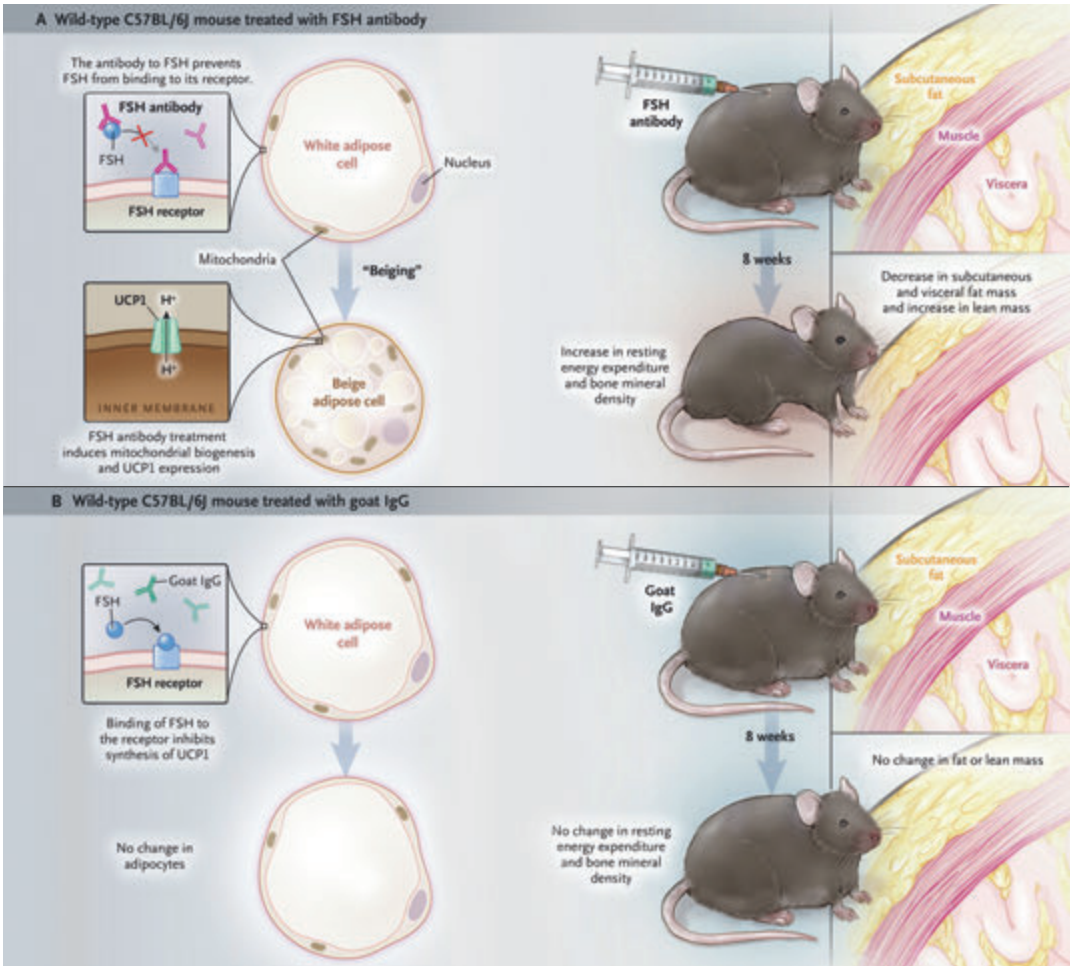

A. *The FSH antibody treatment induced the expression of uncoupling protein 1 (UCP1) and mitochondrial biogenesis in white adipocytes (a process called "beiging," through which they become more like brown fat cells).* ***B.*** *In the control condition, mice were treated with an IgG antibody. The binding of FSH to the receptor inhibited the synthesis of UCP1 (inset), and there was no change in the fat cells.*

Carol J. Levy, MD, with her patient Lisa, who has participated in four artificial pancreas trials.

Clinical Trials Are Advancing the Artificial Pancreas

Seeking to ease the burden of care for type 1 diabetes patients

Clinical trials at the Icahn School of Medicine at Mount Sinai are pushing the boundaries of technology to allow patients with type 1 diabetes to limit the time-consuming monitoring of their blood-sugar levels that makes the disease so difficult to manage.

The first artificial pancreas (AP) system was approved in September 2016 by the U.S. Food and Drug Administration. Since then, a team led by Carol J. Levy, MD, Associate Professor of Medicine (Endocrinology, Diabetes and Bone Disease), Icahn School of Medicine, has been making significant progress in advancing that technology.

"The Artificial Pancreas Research Program at Mount Sinai holds the promise of freeing the patient from the burdens involved in self-care on a minute-to-minute basis, including frequent finger-stick testing, careful monitoring of glucose sensor data, and regularly making insulin dose adjustments to reduce the risk of both high and low blood-sugar levels," Dr. Levy says.

The devices used for the studies consist of a software algorithm that runs on a smartphone, which communicates with the patient's insulin pump and glucose sensor. Mount Sinai has been performing research on many types of these systems since 2014.

In November 2017, an important milestone was reached with the start of Protocol 1 of the International Diabetes Closed Loop Trial, whose objective is to assess the efficacy and safety of home use of a closed-loop control (CLC) system compared with sensor-augmented pump (SAP) therapy. The three-month multicenter randomized trial involves 126 subjects with type 1 diabetes. Subjects were still being recruited as of December 2017, but the first participants had already begun the trial. Some are using the inControl platform, a commercial-grade model of the Diabetes Assistant (DiAs) system developed by the University of Virginia and TypeZero Technologies. A control group will continue with SAP therapy—using their personal insulin pumps with a continuous glucose monitor and a glucometer. The trial, sponsored by the National Institutes of Health, will compare the participants' ability to control their blood sugar, keeping it within a target range of 70 mg/dL to 180 mg/dL. Data collection is to be completed in June 2018, with the intention of providing evidence to the U.S. Food and Drug Administration for marketing approval.

Encouraging results on a version of the DiAs system were reported in an earlier study, published in June 2017 in *The Journal of Clinical Endocrinology & Metabolism*. That multicenter five-day study compared 44 participants with type 1 diabetes, some using a CLC system from 11 pm to 7 am, and others using their own SAP systems day and night at home. It found that using the closed-loop system overnight increased participants' time in the target range over 24 hours, and decreased their time in the hypoglycemic range. In a psychosocial analysis, the study also found that subjects who used the system overnight slept better due to reduced nocturnal hypoglycemia, and possibly because they were experiencing less stress.

As AP systems are developed for widespread use, the main obstacles concern the reliability of the glucose sensors, Dr. Levy says. Other barriers include the cost: the artificial pancreas now on the market costs $6,000 to $7,000, with insurance companies often covering a significant portion. And systems for children under age 14 are still being developed. Still, the AP technology shows great promise, Dr. Levy says, and she anticipates that people with diabetes will have more options as soon as 2019: "In short, these devices have the potential to result in better quality of life for people with type 1 diabetes." ■

Artificial Pancreas Systems Give A Patient Peace of Mind

Lisa, a type 1 diabetes patient, has participated in four artificial pancreas studies led by Carol J. Levy, MD, Associate Professor of Medicine (Endocrinology, Diabetes and Bone Disease), Icahn School of Medicine at Mount Sinai. There is one part of each study that she finds especially hard: the end.

"It is so painful to have this device for only a short time, when it improves my life so much," she says. "It's traumatic every time I have to give the thing back."

Lisa, a stay-at-home mother of two young daughters, was diagnosed with type 1 diabetes when she was 12 years old. Since then, her life has been a "marathon" of checking her blood sugar and figuring out her insulin dosage based on how much exercise she gets, what she eats, and when she eats. But despite her best efforts, sometimes she miscalculates and suffers from hypoglycemia.

Lisa says that Dr. Levy has helped her manage her condition and has supported her through two pregnancies complicated by the hormonal fluctuations that come with diabetes. "Very few people get the kind of care I have received," Lisa says. "Dr. Levy—and the team at Mount Sinai—are very unique in their knowledge, kindness, and dedication."

In Lisa's first study, she joined a group of participants who stayed at a Manhattan hotel, using the Diabetes Assistant (DiAs) platform for five nights. In the second study, participants spent three days in a hotel, using the DiAs system day and night with a different algorithm and with no meal announcements. In the third study, Lisa took home an updated version of the DiAs system, called inControl, for a training study to test its use with a different model insulin pump. In the latest trial, which began in November 2017, she took home an inControl system to use for three months.

"When I took the device home for the training study I did not have a single episode of hypoglycemia," Lisa says, "and with amazingly tight control of my glucose levels, which is unheard of."

The artificial pancreas systems are "brilliant," she says, because "you are not trying to create an insulin-producing cell, or fight the immune system; you are just using math to take out human error in controlling the devices that patients already use." Lisa says the artificial pancreas provides a tremendous relief from the burden of decision-making, even if it is just overnight. And it gives her the same advice about adjusting her insulin that she might get from her doctor, an international leader in diabetes treatment.

"Basically, with this device," she says, "everybody has a Dr. Levy with them all the time." ■

An artificial pancreas algorithm refines the dosage administered through an insulin pump, above, with the tightest possible glucose control and the least hypoglycemia and hyperglycemia.

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STUDY TRACES THE LINKS BETWEEN ALZHEIMER'S AND DIABETES

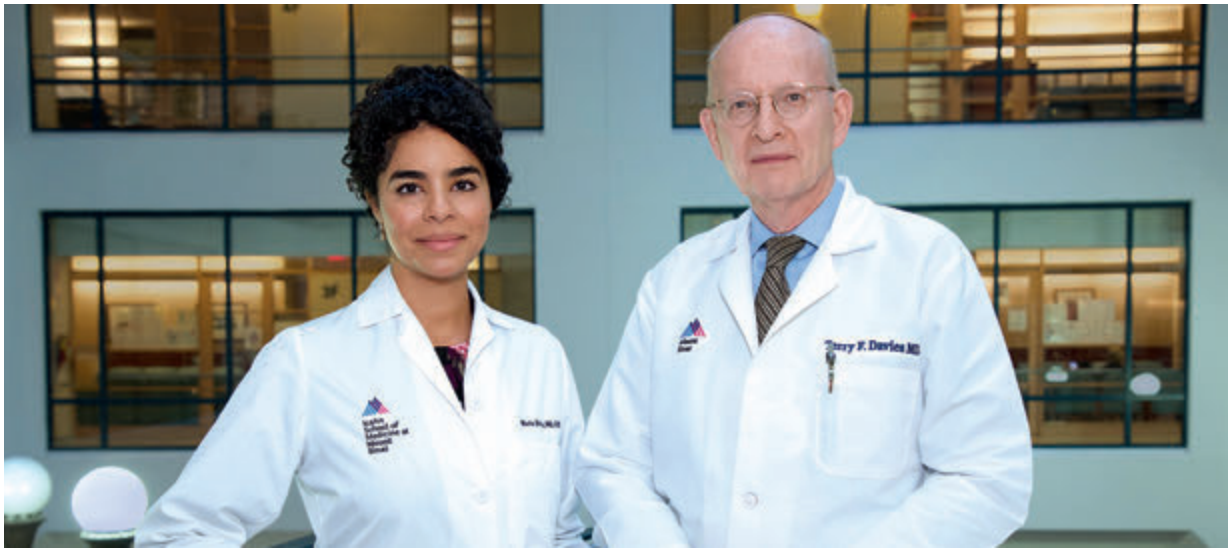
engineered to model the pathology of Alzheimer's disease, with high levels of the amyloid precursor protein (APP)/presenilin-1 (PS1). Dr. Buettner sought to determine whether these mice were more susceptible to a high-fat diet and aging-induced metabolic dysregulation.

Using two age cohorts—5-month-old mice to approximate 30-year-old humans and 11-month-old mice to approximate 55-year-old humans—Dr. Buettner administered a high-fat diet (with 60 percent of calories provided in the form of fat) to the APP/PS1 mice and then monitored their hypothalamic insulin signaling and their glucose, lipid, and branched-chain amino acid (BCAA) levels. He discovered considerable worsening of metabolic control among the APP/PS1 mice that consumed a high-fat diet when compared with their wild-type littermates, with a more pronounced decline in the older cohort of mice.

"Our findings suggest that patients with Alzheimer's disease are more susceptible to diabetes, possibly because Alzheimer's impairs brain insulin signaling, a mechanism that may underlie the link between this disease and diabetes."

Furthermore, Dr. Buettner observed that the mice that consumed the high-fat diet exhibited significantly higher circulating plasma BCAA levels. "Previous studies have demonstrated that obese patients tend to have elevated BCAA levels long in advance of developing diabetes, suggesting that these are biomarkers of diabetes risk," Dr. Buettner says. "Given that these levels were higher in the APP/PS1 mice, and we had previously shown that insulin signaling in the brain regulates BCAA breakdown, the results suggest BCAA may be a biomarker, or reflection, of brain insulin resistance in patients with Alzheimer's disease."

Dr. Buettner says his findings provide a rationale to develop therapies that enhance brain insulin signaling, which would benefit both Alzheimer's disease and diabetes patients. "For Alzheimer's disease patients, there are studies involving intranasal insulin and its impact on cognition defects, but a therapy that enhances or restores insulin receptor signaling would probably be more beneficial," he says. ■



Maria Brito, MD, Director of the Mount Sinai Thyroid Center at Union Square, and Terry F. Davies, Co-Director

New Thyroid Center Offers Cohesive Care and Expert Referrals

Patients with thyroid disorders, as well as physicians seeking referrals for complex thyroid cases, have a valuable new resource in the Mount Sinai Thyroid Center at Union Square. The Center gathers a wide array of services in one ambulatory facility in Manhattan.

At a single site, specialists in endocrinology and surgery, and a wide range of lab services

"This is a multispecialty, collaborative center that includes Endocrinology, Endocrine Surgery, Head and Neck Surgery, Pathology, and Radiology," says Director Maria Brito, MD, Assistant Professor of Medicine (Endocrinology, Diabetes and Bone Disease) at the Icahn School of Medicine at Mount Sinai. "I don't think there is another thyroid center in Manhattan that has all of these services in one single building." The Center is still expanding and will be joined by a Diabetes and Endocrine Center in a combined space at Mount Sinai Union Square in late 2018.

One goal of the Thyroid Center is to simplify care. "It is one-stop shopping, which is what we all want when we go to the doctor," says the Center's Co-Director, Terry F. Davies, the Florence and Theodore Baumritter Professor of Medicine (Endocrinology, Diabetes and Bone Disease). "If your physician says you need to see another specialist, it's nice if he or she is in the next room. You can have your interview with the specialist and the surgeon; you can have a biopsy; you can have a sonogram; and you can have your blood tests, all in the same visit."

New patients will be seen within 72 hours, Dr. Davies says, addressing a frequent complaint in medical care—having to wait weeks for an appointment.

Five endocrinologists and five surgeons are active in the Center, including "household names" in their fields, Dr. Davies says, such as William B. Inabnet III, MD, and Mark L. Urken, MD. For appropriate patients, surgeons offer scarless thyroidectomy, often robotic, in which the thyroid is removed through incisions in the axilla or the mouth. For certain patients with recurrent cysts, nodules, and some thyroid cancer recurrences, Dr. Brito and her colleague Michael A. Via, MD, specialize in a minimally invasive option, ethanol ablation, in which an alcohol solution is injected into these lesions, causing reabsorption or destruction.

The Center's physicians work closely with peers across the Mount Sinai Health System. For example, "we meet twice a month for the thyroid tumor board, in which surgeons and physicians discuss difficult cases," says Dr. Davies, a leading physician-scientist in autoimmune thyroid disease who has been funded continuously for 35 years by the National Institutes of Health.

In addition to providing expert, cohesive care, the Center is the national headquarters of the Thyroid, Head & Neck Cancer (THANC) Foundation, founded by Dr. Urken. The nation's largest private funder of research for these cancers, THANC administers the Thyroid Cancer Care Collaborative, a data registry in which physicians can record important data about their thyroid cancer patients, enabling them to share clinical information with their patients as well as de-identified data with other physicians and researchers.

Sharing knowledge among peers is a top priority of the Center, which is an important referral destination for primary care doctors seeking to consult with endocrinologists, and for endocrinologists seeking to collaborate with surgeons. "We think this is definitely an appropriate place for second, third, or fourth opinions," Dr. Brito says. "But it is very important for both primary care doctors and specialists to know that we expect to collaborate with them. They will not lose their patient to the Center; instead, they will gain a colleague." ■

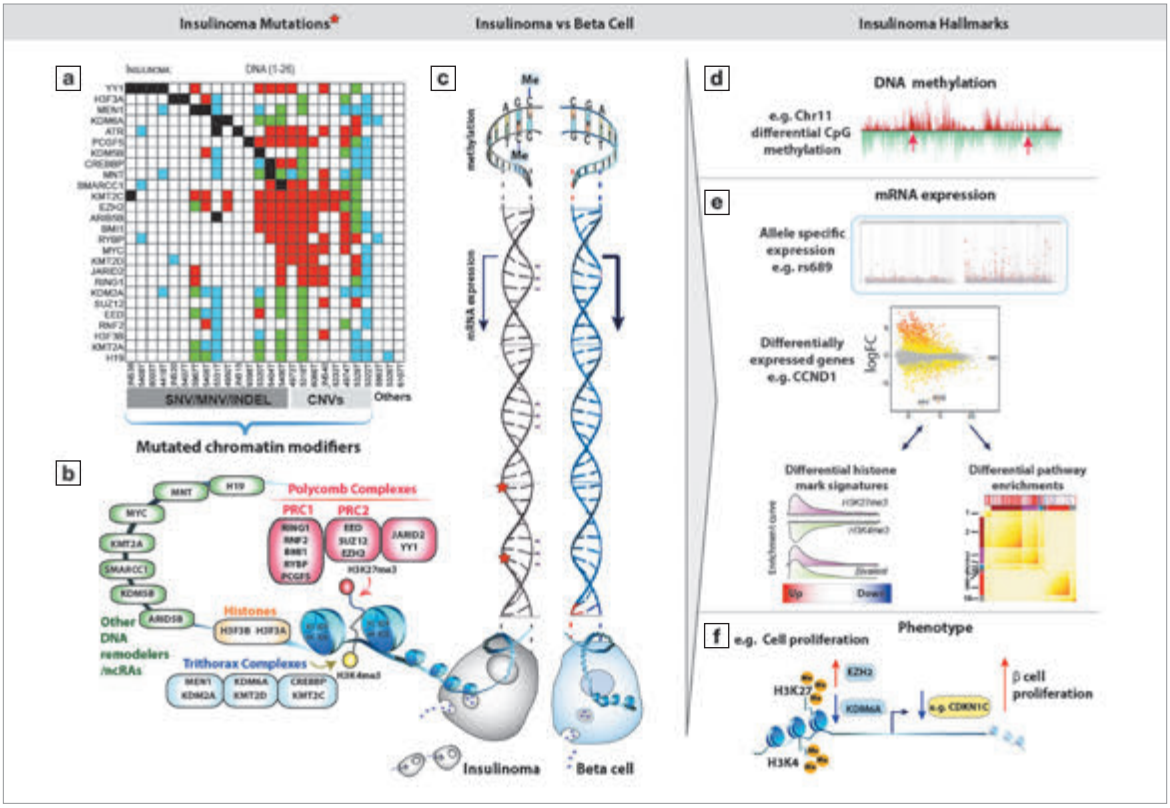
The results of that research were reported in the journal *Nature Communications* in October 2017. The study showed how an integrative analysis of exome and RNA sequencing led to an extensive map of the genomic and molecular landscape of insulinomas.

Dr. Stewart says that one of the reasons he joined Mount Sinai five years ago was that its strong Genomics and Bioinformatics programs offered him the potential to assess the insulinomas he had been collecting. "I wanted to do genome sequencing and RNA expression as part of comprehensive studies to figure out which genes were turned on and which weren't in insulinomas," he says. Eric Schadt, PhD, Dean for Precision Medicine and Jean C. and James W. Crystal Professor of Genetics and Genomic Sciences, Icahn School of Medicine, assigned a team of bioinformatics specialists to work closely with Dr. Stewart, led by Carmen Argmann, PhD, Associate Professor of Genetics and Genomic Sciences, Icahn School of Medicine. "We are now further expanding our sequencing to 100 insulinomas. We already have found many pathways that are clearly druggable," Dr. Stewart observes.

Over the past decade, Dr. Stewart's work has repeatedly undercut the argument that human beta cells were impossible to reproduce. In 2009, while Chief of the Division of Endocrinology and Metabolism at the University of Pittsburgh School of Medicine, he showed that beta cells could be induced to replicate at high rates using gene therapy techniques to activate cell cycle progression. The next advance came when Dr. Stewart's lab at Mount Sinai reported in the March 2015 issue of *Nature Medicine* the discovery of the first drug that can trigger human beta cell regeneration: harmine. In that study, Dr. Stewart's team used high-throughput screening to assess which of 100,000 chemical compounds might hold the key to making beta cells grow. They identified 86 potential candidates, and eventually winnowed the field to harmine, which is derived from the flowering plant harmal, or ayahuasca.

Harmine, however, has psychoactive properties that act not only on beta cells but on the brain and other tissues throughout the body. That complication has touched off the search within the research community to find other small molecules that target only beta cells. "We're making considerable progress in making the next-generation versions of harmine in combination with other drugs that will afford us much higher proliferation of human beta cells," Dr. Stewart says. "With the insulinoma project, we have acquired a road map to even more effective beta cell regenerative drugs." ■

Rare tumors that overproduce insulin are providing crucial clues for diabetes treatment.



A road map to beta cell proliferation in insulinomas: ***(a)*** *A waterfall plot summarizing cumulative coding mis-sense variants (black), loss of copy number variants (blue), copy-neutral loss of heterozygosity (green), or copy number gain (red) among polycomb, trithorax, and related chromatin-modifying genes. In the grid, each vertical column represents the DNA landscape of each of the 26 insulinomas. Collectively, these observations highlight the frequency of genomic and transcriptomic abnormalities in polycomb, trithorax, and other epigenetic modifying genes across the majority of human insulinomas, the marked heterogeneity among insulinomas, and the frequent mutation of multiple chromatin modifiers in almost all insulinomas.* ***(b)*** *An illustration emphasizing the relationship between polycomb, trithorax genes, and H3K27me3 and H3K4me3 marks in human beta cells and insulinomas.* ***(c)*** *An extension of illustration b, highlighting mutations (red stars), and abnormal CpG methylation. Subsequent panels highlight altered DNA methylation and imprinting abnormalities* ***(d)*** *and asymmetrical gene expression from imprinted loci and abnormal chromatin marking patterns* ***(e)****, all of which may lead to differential expression patterns of cell cycle genes* ***(f)****, and to increased beta cell proliferation.*
Andrew F. Stewart, MD, et al.

›continued from page 3 **FSH COULD HOLD KEY TO BONE LOSS AND WEIGHT GAIN AT MENOPAUSE**

Mone Zaidi, MD, PhD

antibody, resulted in increased bone mass and a marked reduction in adiposity in ovariectomized mice. As for the possible mechanism behind these changes, Dr. Zaidi found that the antibody reduced white adipose tissue—where fat is stored—and, importantly, converted it to brown (or beige) adipose tissue, the type of fat that is burned to provide energy.

Dr. Zaidi, founding director of the internationally recognized Mount Sinai Bone Program, is now focused on the clinical applications of these findings. In humans, a version of the antibody used in his study might be able to simultaneously treat bone loss and fat accumulation in women, offering a new approach to associated medical conditions, such as osteoporosis, cardiovascular disease, cancer, and diabetes. And because the antibody was found to be effective in both male and female mice, the benefits could extend to both genders in humans, particularly in controlling obesity.

Dr. Zaidi points out that there are two classes of obesity drugs on the market today: those that suppress appetite and those that reduce the absorption of fat from the gut. Both classes, however, come with significant side effects. The FSH antibody, Dr. Zaidi says, "works on neither of these sites, but instead acts directly on fat cells by converting white to brown fat tissue. This is truly a new game." In collaboration with Mount Sinai Innovation Partners, Dr. Zaidi is exploring opportunities to realize the potential of this research through commercial partnerships. ■