In 2008, Fajun Yang, Ph.D., was invited to join the Einstein Diabetes Research Center—even though the word “diabetes” appeared nowhere on his CV. His specialty was lipid (fat) metabolism, yet the appointment made perfect sense: Diabetes is increasingly recognized as a disease in which glitches in the body’s regulation of lipids play a major role.

Dr. Yang’s journey to diabetes research—and to Einstein—was a long and winding one. While in college, he envisioned a career in applied chemistry, switched to biophysics in graduate school and then became fascinated by nutrition. China offered few doctoral programs in nutrition at the time, so Dr. Yang headed to the University of Kentucky.

“I did research into links between nutrition and inflammation there,” he explains. “People were always asking, ‘What’s the underlying mechanism?’ I realized I needed to learn more molecular biology and biochemistry.”

So he pursued two postdoctoral fellowships, in cancer biology at Stanford and cell biology at Harvard. Along the
May you live in interesting times” is a well-known Chinese curse that is especially apt today. Consider the many exciting scientific discoveries that are poised to be translated into new therapeutic interventions—coupled with our current state of poor healthcare delivery and dwindling investment in medical research.

Funding for R01 grants—the main source of research money given out by the National Institutes of Health—is at an all-time low in terms of the number of grants funded (only 10 percent of applications) and dollar amounts spent. This occurs at a time when money for research could make a world of difference, particularly when it comes to diabetes.

Recent findings by Einstein researchers are revealing novel approaches to treat diabetes and obesity. For example, Dr. Fajun Yang has identified a mechanism responsible for nonalcoholic fatty liver disease, which is a serious complication of diabetes, insulin resistance and obesity. Dr. Preeti Kishore, in collaboration with Dr. Meredith Hawkins, has shown that the sugar analogue xylitol decreases blood lipid levels (a major contributor to both insulin resistance and cardiovascular disease) while improving carbohydrate metabolism.

These and other important new findings highlighted in this newsletter hold great potential as future treatments or even cures for diabetes. Despite today’s dire fiscal situation, we must find a way to translate these important findings into improved therapies to benefit patients.

**The Accidental Diabetes Researcher (continued)**

way, he mastered techniques for deciphering the regulation of gene expression, with a focus on genes involved in lipid metabolism. He was now an ideal candidate for diabetes research.

“It’s no coincidence that the prevalence of diabetes is directly proportional to the prevalence of obesity,” says Dr. Yang, now an assistant professor of medicine (endocrinology) and of developmental and molecular biology at Einstein. “Lipid metabolism has intimate relationships with insulin resistance, where insulin can’t do its normal job of lowering blood sugar levels. We also know that dysregulation of lipid balance can cause obesity and lead to the cardiovascular complications of diabetes. So it’s important to understand the molecular mechanisms involved in regulating fat metabolism.”

Dr. Yang is investigating those mechanisms in his study of a protein called SREBP-1c. This protein controls key genes involved in making fat. Previous studies have found that abnormally high levels of SREBP-1c are linked to overweight and to type 2 diabetes, but just how is poorly understood.

To better understand that link, Dr. Yang is investigating SREBP-1c’s interaction with CDK8, an enzyme that curbs fat production by keeping active SREBP-1c levels in check. With funds from the American Diabetes Association, Dr. Yang is trying to learn more about how these two proteins are related, with the long-term goal of seeing whether influencing their molecular interaction could help prevent or treat type 2 diabetes.

In a second study, funded by the National Institute of Diabetes and Digestive and Kidney Diseases, Dr. Yang is focusing on another SREBP-1c regulator called SIRT1, a so-called longevity gene. “As we age, active SREBP-1c becomes more abundant in cells, causing nonalcoholic fatty liver disease, in which the liver accumulates fat,” says Dr. Yang. One reason for this is that SIRT1—which normally puts the brakes on active SREBP-1c—gets less expressed in old age, he explains. “This led me to ask, what upstream signals regulate SIRT1?” One such signal, Dr. Yang has found, is an enzyme called LSD1. His next step is to gain a fuller understanding of how SIRT1 and LSD1 interact to regulate SREBP-1c, which in turn regulates lipid metabolism.

If diabetes can be cured by figuring out these molecular pathways, then Dr. Yang is the man for the job. After all, he’s traveled an impressively eventful path already.

**Q: Type 2 diabetes is on the rise. What about type 1?**

**A:** Both types are becoming more common, says DRC director Dr. Pessin. The obesity epidemic is known to be fueling type 2 diabetes, but type 1 is different: It’s an autoimmune disease in which the body forms antibodies that destroy insulin-secreting cells in the pancreas. Theories for why type 1 diabetes is on the rise include too little childhood exposure to viruses or bacteria; less breastfeeding; solid foods at an early age; endocrine disruptors and other environmental factors; cold temperatures or winter viruses—and better diagnosis.

“Just as we’re now finding more type 2 diabetes in children,” says Dr. Pessin, “we’re finding more type 1 in adults.”

**To learn more about the Diabetes Research Center, please visit www.einstein.yu.edu/diabetes**
**Sweet News About a Sweetener**

**Preeti Kishore, M.B.B.S.**
Assistant Professor of Medicine (Endocrinology)
Albert Einstein College of Medicine
Assistant Attending Physician, Endocrinology
Montefiore Medical Center

Many people with diabetes use the lower-calorie sweetener xylitol (derived from the fibers of plants and vegetables), since it doesn’t boost blood sugar levels. But whether it affects sugar metabolism has been unclear till now.

People with type 2 diabetes have high blood levels of nonesterified free fatty acids (NEFA), which aren’t desirable. High NEFA levels cause insulin resistance—a condition in which the pancreas makes insulin but the body’s cells can’t effectively use it to absorb glucose from the bloodstream. This results in a rise in glucose levels in the blood, which can lead to type 2 diabetes or prediabetes. Dr. Kishore and her team theorized that xylitol might prevent NEFA from causing insulin resistance.

The researchers first increased NEFA levels in test animals and then administered xylitol along with NEFA. They found that xylitol did indeed prevent NEFA-induced insulin resistance and therefore was likely to prevent the boost in blood sugar levels that NEFA ordinarily causes. The study was published in a 2012 issue of *Diabetologia*.

**Obesity: A Neurodegenerative Disease?**

**Dongsheng Cai, M.D., Ph.D.**
Professor of Molecular Pharmacology
Albert Einstein College of Medicine

Researchers recently identified specialized stem cells called hTNSCs that are active in adults (they give rise to new neurons and other brain cells) and are located in the brain’s hypothalamus—the control center for releasing many different chemicals.

Dr. Cai and his colleagues investigated these stem cells and found that they become partially depleted in mice on a long-term high-fat diet. The researchers also found a link between the loss of hTNSCs (neurodegeneration) and increased activity of IKKβ and NF-κB. These two proteins are responsible for the inflammation of the hypothalamus resulting from a high-fat diet; the inflammation can lead to metabolic syndrome, a group of risk factors (including extra weight gain and insulin resistance) that increase the chance for developing diabetes and cardiovascular disease.

Dr. Cai and his colleagues conclude that dietary obesity is partly a neurodegenerative disease that could potentially be treated with therapies to regenerate certain nerve cells. Their findings appeared in a 2012 *Nature Cell Biology* article.

**New Facts About Brown Fat**

**Gary J. Schwartz, Ph.D.**
Professor of Medicine (Endocrinology)
Professor, Dominick P. Purpura Department of Neuroscience
Albert Einstein College of Medicine

Brown adipose tissue (commonly known as “brown fat”) is a good-guy body fat that actually burns itself and other fats—along with calories—to produce heat. What fires up the fat? Dr. Schwartz and postdoctoral fellow Clemence Blouet, Ph.D., have found evidence that brown fat gets ignited by the same gut-to-brain nerve pathways that signal us to stop eating.

Working with rats, the researchers administered dietary fat into the upper part of the small intestine (where nutrient absorption begins). They then observed that the brown fat’s temperature had risen, meaning it was being burned.

Drs. Schwartz and Blouet will now look for ways to manipulate the gut-brain neurocircuits with drugs or nutrients to burn brown fat—and control the obesity that can lead to type 2 diabetes and other metabolic diseases. The findings appeared in a 2012 issue of *PLOS ONE*.

**Why Moses Was Diabetes Free**

This year’s Rifkin lecturer is a leading Einstein researcher: **Nir Barzilai, M.D.**, the Ingeborg and Ira Leon Rennert Chair in Aging Research. Dr. Barzilai directs Einstein’s Institute for Aging Research and is a professor of medicine (endocrinology) and of genetics. His topic on April 19 was “Why Did Moses Live to 120 Years Without Diabetes?”

The DRC sponsors the annual two-day Rifkin lecture series in memory of **Harold Rifkin, M.D.**, a clinical professor associated for nearly 50 years with Einstein and Montefiore, the University Hospital and academic medical center for Einstein. Dr. Rifkin served as president of the American Diabetes Association and the International Diabetes Federation and as editor of *Diabetes Mellitus: Theory and Practice*. His extraordinary intellect, charismatic teaching and advocacy for patient care and research were widely recognized.
The DRC welcomes four new members:

- **Kathryn Anastos, M.D.**, has many research interests, among them how HIV affects diabetes. Dr. Anastos is professor of medicine (general internal medicine), of epidemiology & population health and of obstetrics & gynecology and women’s health, co-director of the Einstein Global Health Center and attending physician in medicine at Montefiore.

- **Deepa Rastogi, M.B.B.S.**, studies overweight and obesity in children, which often lead to asthma and diabetes. She is assistant professor of pediatrics (respiratory medicine), the Joseph S. Blume Faculty Scholar in Pediatric Development and director of the Pediatric Asthma Center at the Children’s Hospital at Montefiore.

- **Andrew F. Stewart, M.D.**, is the newest member of the executive committee of the Diabetes Research and Training Center (DRTC). (Under the DRC umbrella, the DRTC supports basic, clinical, behavioral and translational research and includes the Global Diabetes Initiative.) Dr. Stewart, director of the Mount Sinai Diabetes, Obesity and Metabolism Institute, is a DRC “outside member.”

- **Ling Qi, Ph.D.**, assistant professor in nutritional sciences at Cornell University College of Human Ecology, is also a DRC “outside member.” Dr. Qi researches inflammation in obesity and the role of unfolded proteins in obesity and diabetes.

The Leon Lowenstein Foundation, Inc., has given two grants, totaling $100,000, to Einstein for diabetes prevention research. One $50,000 grant supports the work of **Alison Karasz, Ph.D.**, associate professor of family and social medicine; the other $50,000 was awarded to **Elizabeth A. Walker, Ph.D., R.N.**, professor of medicine (endocrinology) and of epidemiology & population health and director of the DRC’s Prevention and Control Core.

The funds will enable Dr. Karasz to expand an already well-established program called APPLE (Activating People to Pursue Lifestyle Change Through Empowerment). This community-based research project is aimed at preventing diabetes by addressing obesity in New York City’s South Asian immigrant community, specifically among women. The Lowenstein Foundation’s support will allow Dr. Karasz and her team to bring the APPLE program to two additional communities in Queens.

Dr. Walker, working with her community partners, will use the $50,000 grant to build on the Family Health Challenge (FHC), a project launched in 2009 by the South Bronx–based Mary Mitchell Family and Youth Center. The FHC is an interactive program targeting children ages 7 to 12 in after-school community programs. It focuses on developing healthy lifestyles to prevent and control obesity.

Dr. Walker and her colleagues will evaluate and modify the FHC and add a family-centered component. The goal is to incorporate the FHC into many New York City after-school programs over the next few years. Dr. Walker’s partners in the new project are the Mary Mitchell Center, the Committee of Interns and Residents and the Bronx borough initiative Bronx CAN.

The Lowenstein Foundation previously funded Dr. Walker’s work on two projects in diabetes prevention and control among adult Bronx residents.

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To learn more about supporting the work of the DRC, please contact:

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