In 2018 our researchers made several vital molecular discoveries that deepen our understanding of the conditions we treat, while our clinicians enhanced care to improve quality of life for all of our patients.

In the pages that follow, you’ll read about several collaborations, both within NYU Langone and with colleagues at other prominent institutions, that have yielded promising results—from new diagnostic imaging tools for hard-to-detect pituitary tumors, to the identification of a key pathway that could be a therapeutic target for both diabetes and heart disease. The labs of Ann Marie Schmidt, MD, and José O. Alemán, MD, PhD, have continued to prolifically publish findings on the links between inflammation, obesity, and diabetes, whereas a team at NYU Winthrop is uncovering how diabetes impacts brain function as we age. Among our other accomplishments: a program of enhanced support for diabetic teens transitioning to adult care, as well as expanded services for transgender patients seeking gender-affirming care.
Tracking the Metabolic Path from Diabetes to Cardiovascular Disease

In a long-running collaboration between NYU Langone endocrinology and cardiology, researchers are shedding light on the molecular factors that prevent atherosclerosis regression in patients with diabetes, closing a major gap in the study of diabetic vascular pathology.

THE IMPACT OF DIABETES ON ARTERIAL SELF-REPAIR

Two-thirds of people with diabetes die from cardiovascular disease or stroke, and strategies that typically lower LDL and reduce atherosclerosis in patients are much less effective in individuals with diabetes. While most of the available research has focused on understanding the underlying mechanisms driving the progression of atherosclerosis in patients, a multidisciplinary team of NYU Langone researchers has taken a different approach.

“We are trying to understand the factors that affect atherosclerosis regression,” says Ira J. Goldberg, MD, the Clarissa and Edgar Bronfman, Jr. Professor of Endocrinology and director of the Division of Endocrinology, Diabetes, and Metabolism. By regression, Dr. Goldberg and his colleagues mean the reduction in cholesterol and inflammatory cells in the artery that accompanies cholesterol reduction in the blood. These changes are thought to make the artery more stable and less likely to cause a blood clot leading to a heart attack.

Atherosclerosis, caused by lipoprotein retention within the arterial wall and inflammation associated with macrophage accumulation, is accelerated in people with type 1 and type 2 diabetes, likely due to multiple metabolic abnormalities, including dyslipidemia and hyperglycemia.

We are trying to understand the factors that affect atherosclerosis regression.”
—Ira J. Goldberg, MD

A New Leader for the Center for Diabetes and Metabolic Health

In September 2018, Lauren H. Golden, MD, joined NYU Langone as clinical associate professor of medicine to serve as the new director of the Center for Diabetes and Metabolic Health. She leads a multidisciplinary team dedicated to helping people with type 1 and type 2 diabetes manage their condition, prevent complications, and integrate diabetes management into their daily lives.

Prior to joining the center, Dr. Golden served as an assistant professor of medicine and head of professional education at the Naomi Berrie Diabetes Center at Columbia University Medical Center. With her vast expertise, Dr. Golden will work to advance care standards, build interdisciplinary clinical collaborations, and broaden research efforts, in addition to improving patient access to care, preventive services, and telemedicine.
For several years, Dr. Goldberg has been working with Edward A. Fisher, MD, PhD, MPH, the Leon H. Charney Professor of Cardiovascular Medicine, to understand how diabetes impairs the blood vessels’ capacity for self-repair after cholesterol has been reduced to normal levels.

“We are seeking to understand how the abnormal factors in people with diabetes prevent circulating blood cells in blood vessels from becoming reparative,” says Dr. Goldberg. The studies will help elucidate the link between diabetes and cardiovascular disease.

Tracking Atherosclerosis at the Molecular Level

At the center of the team’s research is the glucose-metabolizing enzyme aldose reductase, which is thought to fuel diabetes complications by directing glucose into pathways producing inflammatory metabolites. Previous animal models provided little insight into the role that aldose reductase plays in plaque buildup and regression because mice naturally express very low levels relative to humans. Drs. Goldberg and Fisher, along with Ravichandran Ramasamy, PhD, professor of medicine and biochemistry and molecular pharmacology, are homing in on the enzyme’s actions under hyperglycemic conditions.

In earlier studies of diabetic mice, the research team demonstrated that hyperglycemia impairs atherosclerosis regression even in the context of aggressive lipid management. They reported that under hyperglycemic conditions in the body, the number of monocytes drawn to arterial plaques increases in response to lipid lowering, as did the levels of inflammation-promoting macrophages derived from these monocytes. Under hyperglycemic conditions, glucose is not always targeted to energy metabolism, but instead metabolized into harmful metabolites via aldose reductase and, likely, other enzymes.

The NYU Langone team created a mouse model that is both diabetic and expresses aldose reductase at human levels, to determine if this exacerbated the negative effects observed in the previous studies. “Indeed, we found that if you overexpress aldose reductase in hyperglycemic mice, it totally prevents regression. ‘This suggests that if sugar is aberrantly modified, repair cannot occur,’ says Dr. Goldberg. In fact, the researchers saw continued progression of plaque buildup, despite normal lipid levels, as well as greater macrophage inflammation. These studies also suggest a generalized defect in repair that might underlie other complications of diabetes.

If these mouse models are confirmed to reflect the same metabolic phenomena in humans, investigators expect that the new generation of high-potency aldose reductase (AR) inhibitors currently undergoing preclinical testing will show cardiovascular benefits. “Because statins are not as efficacious in people with diabetes, AR inhibitors could serve as an adjunct therapy, blocking the glucose-specific mechanism that amplifies cardiovascular disease in this population,” says Dr. Ramasamy.

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—Ravichandran Ramasamy, PhD

How Type 1 Diabetes Impacts Brain Function

With a $4.2 million, five-year grant from the National Institutes of Health (NIH), researchers at our affiliate, NYU Winthrop Hospital, are trying to uncover the connection between diabetes and neurocognitive function and decline, an area of research for which there is little definitive information available to clinicians and patients. Alan M. Jacobson, MD, chief research officer at NYU Winthrop Hospital, is leading a consortium of medical centers throughout the United States and Canada to study the effects of type 1 diabetes on brain structure, cognition, and memory, especially among the growing population of older patients who are at greatest risk for potential neurocognitive complications.

Dr. Jacobson’s latest brain function studies are an extension of the more than three-decades-long Epidemiology of Diabetes Interventions and Complications (EDIC) study, for which he was a principal investigator. EDIC relies on the well-characterized cohort of more than 1,200 of the original 1,400 patients who participated in the landmark Diabetes Control and Complications Trial (DCCT), which changed the way type 1 diabetes patients are treated. Participants have been followed for more than three decades through the studies, with serial cognitive testing and ongoing assessment of their biomedical status.

The team is now using MRI on 400 patients with type 1 diabetes selected from this cohort to represent a broad range of medical outcomes. “By leveraging the DCCT/EDIC cohort, we can use longitudinal biomedical data gathered over 35 years to examine risk factors for alterations in brain structure, chemistry, and function,” says Dr. Jacobson. “We can then link these changes in the brain elucidated through MRI to cognitive outcomes over the course of follow-up.”

“Patients have increasing concerns about the extent to which diabetes can influence cognitive ability as they enter the age of greatest risk for impairment,” says Dr. Jacobson. “This study can help determine whether these effects occur and identify modifiable risk factors that can be addressed with proper treatment.”

The Cortical Thickness Maps

Comparison of adults with and without type 1 diabetes (T1DM), showing thinner cortex in brain regions that regulate cognition.

Tracking the Metabolic Path from Diabetes to Cardiovascular Disease

At the 17th annual Dean’s Honors Day Ceremony last October, NYU Langone faculty, administration, and trustees honored Ann Marie Schmidt, MD, the Dr. Iven Young Professor of Endocrinology, with the prestigious Master Scientist Award for her lifetime achievements in diabetes and metabolic disorders research.

Nearly three decades ago, Dr. Schmidt discovered the multi-ligand receptor for advanced glycation end products (RAGE), a cell-surface receptor involved in virtually all inflammatory responses and linked to diabetic complications in the heart, eyes, and kidneys. Her work has illustrated that blocking or genetically deleting RAGE in mice protected them from developing both diabetes complications and insulin resistance.

Dr. Schmidt’s team is now focused on understanding how molecules associated with obesity and diabetes bind to RAGE and signal adverse metabolic and inflammatory effects. Most recently, Dr. Schmidt has focused on the development of small molecules that inhibit interaction between RAGE and intracellular effector DIAPH1, a key signaling pathway partner implicated in this process. These small molecule inhibitors may provide a foundation for a novel class of RAGE inhibitors to treat macro- and micro-vascular diabetes complications and other related disorders. “If we’re successful, we may also improve metabolic responses in weight loss to mitigate—or even prevent—obesity,” says Dr. Schmidt.

Researchers at NYU Langone have discovered that peroxisome proliferator-activated receptor gamma (PPARγ), a key regulator of adipogenesis, shifts its function as we age, suggesting that targeting it could have an impact on metabolic function and longevity.

MECHANISMS OF ADIPOSE BIOLoGY

In midlife, white fat accumulates, thermogenic function diminishes, and the likelihood of obesity and metabolic disease increases. To uncover the mechanisms driving these changes, Elisabetta Mueller, PhD, associate professor in the Department of Medicine at NYU Langone, is zeroing in on signature factors that regulate adipose biology at different life stages. Her mouse-model findings are revealing possible pathways that, if activated, could reverse age-related metabolic decline.

THE EVOLVING VARIEGATION OF FAT

Two discoveries in the past decade—that both brown fat and newly identified beige adipocytes persist in adulthood—have led to a deeper understanding of fat tissue biology. This, in turn, has opened promising avenues of research that could have huge implications for aging. Dr. Mueller and her team are at the forefront of this research, studying the cascade of molecular events that determines adipogenesis and calorie utilization throughout life.

Adipose tissue is critical for energy homeostasis at any age. White fat stores energy, brown fat burns it, and beige fat switches back and forth from burning to storing depending on conditions in the body. But in older populations, researchers see decreased brown and beige fat cell function, while white adipocytes accumulate in the visceral cavity. The combined effect is metabolic dysfunction that often leads to obesity, diabetes, and other diseases.
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THE MASTER FAT REGULATOR

One of the key regulators of adipocyte differentiation, and a focus of the Mueller lab, is the nuclear receptor PPARγ, which is required for the development of all types of fat cells and functions as a regulator of both white and brown gene programs in adipocytes. “Given the importance of PPARγ in fat tissue biology, we sought to determine this receptor’s role in aging-associated metabolic decline,” says Dr. Mueller. In a recent study, her team found that, compared with controls, middle-aged mice with ablation of PPARγ in subcutaneous fat tissue had more white fat composed of larger adipocytes, increased insulin resistance, decreased thermogenesis, reduced levels of brown fat genes, and disadvantageous changes to several other metabolic indicators.

Conversely, PPARγ suppression in young mice yielded much different results, namely an abnormal decrease in the amount of fat that was associated with a lipoatrophic phenotype. Along with the findings of other comparative studies, the data suggests that in young mice PPARγ’s main role is to maintain lipogenic functions, whereas in aging mice PPARγ’s job appears to shift to managing energy expenditure with the lipogenic functions taken over by related transcription factors. These results provide a new rationale for targeting PPARγ in aging.

“This is the first evidence that, during aging, PPARγ function in subcutaneous adipose tissue may be primarily to control energy expenditure,” says Dr. Mueller. “This receptor has an important role in aging, and its activation could lead to beneficial effects in age-associated metabolic disease.” The team is now looking for compounds that activate PPARγ and testing their impact on health span and longevity. Dr. Mueller expects that the first findings from this research will be published early next year.

Helping Teens with Diabetes Prepare for Adult Care

Research shows that when young people with diabetes are supported throughout their transition from pediatric to adult care, they are more engaged in their healthcare, better adhere to treatment regimens, and experience decreased hospitalization and improved health outcomes. “Changing your doctor is never easy, and when you are an adolescent with diabetes it can be even harder to make the transition,” says Mary Pat Gallagher, MD, assistant professor of pediatrics and director of the Robert I. Grossman, MD, and Elisabeth J. Cohen, MD, Pediatric Diabetes Center. In a new program, Dr. Gallagher will work closely with Lauren H. Golden, MD, clinical associate professor of medicine and director of the Center for Diabetes and Metabolic Health, to ensure that teens and their families are transition-ready by focusing on proactive communication and early engagement.

To further facilitate a smooth transition, the center is working to develop comprehensive transition guidelines in conjunction with patients and their families. The new policy will include a transition registry to track the progress of each patient, assessments to determine the readiness and timing of the transition, and a portable health summary that will accompany the patient into adult care.

New Treatment for Cushing’s Syndrome

NYU Langone patients with endogenous Cushing’s syndrome and concurrent uncontrolled blood pressure or impaired glucose tolerance/type 2 diabetes are participating in a phase-two, open-label study of orphan drug CORT125134, a glucocorticoid receptor antagonist. CORT125134 modulates the effects of the stress hormone cortisol and treats the hyperglycemia secondary to hypercortisolism in adult patients with Cushing’s syndrome.

“The mechanism of action is similar to that of mifepristone, with the exception that it does not bind to progesterone receptors, so it circumvents unwanted anti-progestin side effects,” says Nidhi Agrawal, MD, clinical assistant professor of endocrinology, diabetes, and metabolism, and an investigator in the trial.
How Unhealthy Fat Gets from Blood to Tissue

As researchers explore the links between the fatty acid transport system and conditions such as insulin resistance, type 2 diabetes, and heart failure, they have identified a pathway, endothelial CD36, that may play a key role. Blocking this pathway could prevent destructive lipid accumulation and improve insulin sensitivity.

CD36: A MULTIFUNCTIONAL METABOLIC PROTEIN

Circulating fatty acids must transfer across the endothelial cell barrier to get from blood to tissues. The molecular events behind this process are not yet known. Several proteins have been implicated in both the uptake and the accumulation of fatty acids in tissue and organs, including a scavenger protein called cluster of differentiation 36, or CD36, first linked to lipid metabolism 25 years ago. Since then, the protein has been proven to play important and diverse immune-metabolic roles, from the activation of peroxisome proliferator-activated receptors (PPARs) to lipid accumulation, inflammation, and generation of arterial foam cells. In collaboration with researchers at Washington University in St. Louis, NYU Langone investigators studied its role in lipid transport across the endothelium of blood vessels.

RESEARCH UNCOVERS A KEY FAT TRANSPORTER

In this latest study of CD36, Ira J. Goldberg, MD, the Clarissa and Edgar Bronfman, Jr. Professor of Endocrinology and director of the Division of Endocrinology, Diabetes, and Metabolism, investigated the distribution of CD36 receptors on endothelial cells and cardiomyocytes in both mouse and human heart tissue. Then, using mouse models, his team sought to determine whether fatty acid uptake into muscle, organs, and other tissue depends on endothelial CD36 and/or CD36 found on parenchymal cells like cardiomyocytes.

Dr. Goldberg and his team showed that endothelial cells robustly express CD36 in small blood vessels of human and mouse hearts. Cardiomyocytes also express this protein. Deleting CD36 in either type of cell in mice reduced the lipid accumulation that normally occurs in the heart during fasting. However, there were significant differences between the functions of CD36 in endothelial cells and in cardiomyocytes. “We discovered that if you knock out only the endothelial CD36, there is a defect in fat uptake by the heart, skeletal muscles, and brown adipose tissue,” says Dr. Goldberg. The same was not seen in cardiomyocyte-CD36-deficient mice, a crucial difference, suggesting that only endothelial CD36 is necessary to move fatty acids from the blood into the heart and other tissues.

“On top of that, the endothelial-CD36-deficient mice that were fed high-fat diets showed improved glucose tolerance and became more insulin sensitive, presumably because they had less fat in the muscle,” says Dr. Goldberg. Moreover, expression of several genes in the heart that mediate glucose metabolism and insulin action increased in the endothelial-CD36-deficient mice but decreased in the cardiomyocyte-CD36-deficient mice.

We discovered that if you knock out only the endothelial CD36, there is a defect in fat uptake by the heart, skeletal muscles, and brown adipose tissue.”

—Ira J. Goldberg, MD

Our affiliate, NYU Winthrop Hospital, is continuing to expand its portfolio and team of scientists at the Diabetes and Obesity Research Center, with a growing list of active collaborations with prominent national and international medical institutions. The center is conducting innovative, multidisciplinary research to gain a deeper understanding of the primary and secondary risk factors that contribute to diabetes and obesity, as well as finding new ways to prevent, treat, and cure these diseases. In addition to performing cutting-edge research, the center is training a new generation of leaders and educating the community to improve general health.

“NYU Winthrop has made a major commitment by investing in a new building, equipment, and research scientists to provide a rich environment for collaborative and competitive research, as well as for individual growth,” says M. Mahmood Hussain, PhD, director of the Diabetes and Obesity Research Center, and director of basic science at NYU Winthrop Hospital.

Spotlight on NYU Winthrop Hospital: Diabetes and Obesity Research Center

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“We are now trying to better understand the relationship between the movement of fat across endothelial cells and into tissues, and in turn how it affects insulin signaling and diabetes,” says Dr. Goldberg.

TARGETING CD36 FOR TREATMENT

The ultimate goal, notes Dr. Goldberg, is to refine this process—perhaps directly targeting endothelial CD36 to block lipid uptake into tissues—to make insulin work better and treat diabetes. “We want to know whether it can be a therapy for other diseases as well, such as heart failure associated with too much fat uptake into the heart,” says Dr. Goldberg. In an upcoming study, his team will test whether one form of heart disease can actually be cured in mice by targeting this transport system.

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**Uncovering the Link Between Bariatric Surgery, Inflammation, and Type 2 Diabetes**

Within days of bariatric surgery, long before weight loss occurs, obese patients are seeing dramatic improvements in insulin resistance and chronic inflammation. Now, researchers at NYU Langone are investigating exactly how bariatric surgery can remodel adipose tissue, reshape the microbiome, and, most remarkably, put diabetes into remission.

**DELVING DEEPER INTO THE BENEFITS OF SURGERY**

Over the past decade, the number of patients undergoing bariatric surgery has been steadily rising, but the percentage of obese adults who seek this treatment is still very small, despite the promising outcomes. “In addition to significant and sustained weight loss, most bariatric surgery patients experience almost immediate improvement in nearly all metabolic indicators, including insulin, glucose, and cholesterol, as well as resolution of the chronic low-grade inflammation that is linked to obesity complications like diabetes and cardiovascular disease,” says José O. Alemán, MD, PhD, assistant professor of medicine and head of NYU Langone’s Laboratory of Translational Obesity Research. While the association between surgery and these benefits is clear, the mechanisms driving these outcomes is less so.
NEW IMAGING SEQUENCES SURFACE HARD-TO-DETECT MICROADENOMAS

When microadenomas are correctly identified and localized preoperatively in the pituitary gland, a minimally invasive surgery can be curative. But pituitary microadenomas present as small as one-third the size of a pea, making them difficult to detect with traditional MRI imaging sequences. Radiologists at NYU Langone instead rely on two novel sequences with higher soft-tissue resolution that localize even the smallest pituitary lesions: golden-angle radial sparse parallel, or GRASP, and constructive interference in steady state, or CISS.

Compared to conventional sequences, GRASP provides greater through-plane resolution, improved motion and flow sensitivity, and improved fat suppression; CISS, a fast-gradient echo sequence, is characterized by high signal-to-noise ratio and high spatial resolution (0.6 mm). Once the microadenomas are successfully localized and surgical removal is recommended, surgeons rely on these same high-resolution imaging techniques in the operating room to ensure that the tumor has been completely resected.

In addition, neuroradiologists and nuclear medicine physicians combine these MRI sequences with Ga68-DOTATATE PET scans to find rare ectopic tumors in patients with acromegaly or Cushing’s syndrome. Physicians image the body from the top of the skull to the toes, taking advantage of the molecular and physiologic features from Ga68-DOTATATE PET and structural features from high-resolution MRI to identify the source with increasing diagnostic precision, making changes in real time as necessary.

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QUANTIFYING MICROBIOME SHIFTS AFTER SURGERY

In early 2017, Dr. Alemán’s lab joined the NYU Langone arm of the American Heart Association’s multi-institution Strategically Focused Obesity Research Network Center, a nearly $4 million, four-year research collaboration among basic, clinical, and population health groups that is under the direction of Ann Marie Schmidt, MD, the Dr. Iven Young Professor of Endocrinology. With the AHA funding, Dr. Alemán’s lab has been working alongside Ira J. Goldberg, MD, the Clarissa and Edgar Bronfman, Jr. Professor of Endocrinology and director of the Division of Endocrinology, Diabetes, and Metabolism, to study the bariatric populations at Tisch Hospital and Bellevue Hospital as part of a longitudinal trial on surgery outcomes.

Specifically, his team is focused on identifying the factors in adipose tissue that are linked to increased inflammation and insulin resistance, and learning how these factors are altered by the hormonal and microbiome changes that follow bariatric surgery.

“We know that a large component of the early metabolic improvement that happens with bariatric surgery is strictly related to caloric restriction. For instance, the diabetes remission we are seeing after surgery is comparable to what we saw in a recent trial of patients undergoing weight loss by a very low-calorie diet,” says Dr. Alemán.

Yet, while obese subjects have a gut microbiome that differs from that of lean subjects, undergoing weight loss by very low-calorie diet produced only modest functional changes, at best, in the gut microbiome and fecal bile acids.

“When the other hand, bariatric surgery changes the hormonal profile of the patient in a way that is very different from diet-induced changes, in large part because when we rearrange the gut we drastically change the profile of gut hormone secretion and induce big shifts in the microbiome,” says Dr. Alemán.
Uncovering the Link Between Bariatric Surgery, Inflammation, and Type 2 Diabetes

Dr. Alemán’s team is targeting these changes in the current bariatric surgery study, which is halfway through enrolling normoglycemic and diabetic patients undergoing sleeve gastrectomy. For each subject, the team conducts a metabolic characterization, tracks energy expenditure, and profiles hormones impacted by surgery, then repeats these tests six weeks after surgery. Investigators also collect and biosample adipose tissue at both time points and measure the microbiome changes from fecal samples. Because of the variability in the human population, the large data sets of genetic, metabolic, and histologic information generated for each subject are compared against his or her history. “We believe this unbiased approach will uncover factors that differ between patients and will define how individual patients respond to weight-reduction surgery,” says Dr. Alemán.

**INFLAMMATORY RESPONSE COULD HELP PREDICT OUTCOMES**

To that end, the team is looking for specific markers in adipose-tissue formation that predict which patients will experience weight loss and diabetes remission. One marker the team is paying particular attention to is RAGE (receptor for advanced glycation end products), a protein discovered by Dr. Schmidt two decades ago that promotes inflammation and is a key player in diabetic complications. In mouse models, Dr. Schmidt has shown that inhibiting RAGE protected mice from developing obesity and insulin resistance. “We’re working to translate those mice models to a real-world setting and uncover how rapid weight loss from bariatric surgery impacts RAGE-signaling pathways—and the associated inflammatory and metabolic effects,” says Dr. Alemán. “We hope to provide a tool to help clinicians determine who will respond best to various surgeries versus other treatment options.”

Disclosure: José O. Alemán receives funding from the American Heart Association and the Doris Duke Charitable Foundation, and honoraria from Medscape and the Medical Education Speakers Network.

In vitro adipose tissue inflammation modeling in weight loss patients (Oil Red O staining).

Expert Review of Proteomics

wounded vascular system. The receptor for advanced glycation end products (RAGE)

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Lab Chip

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