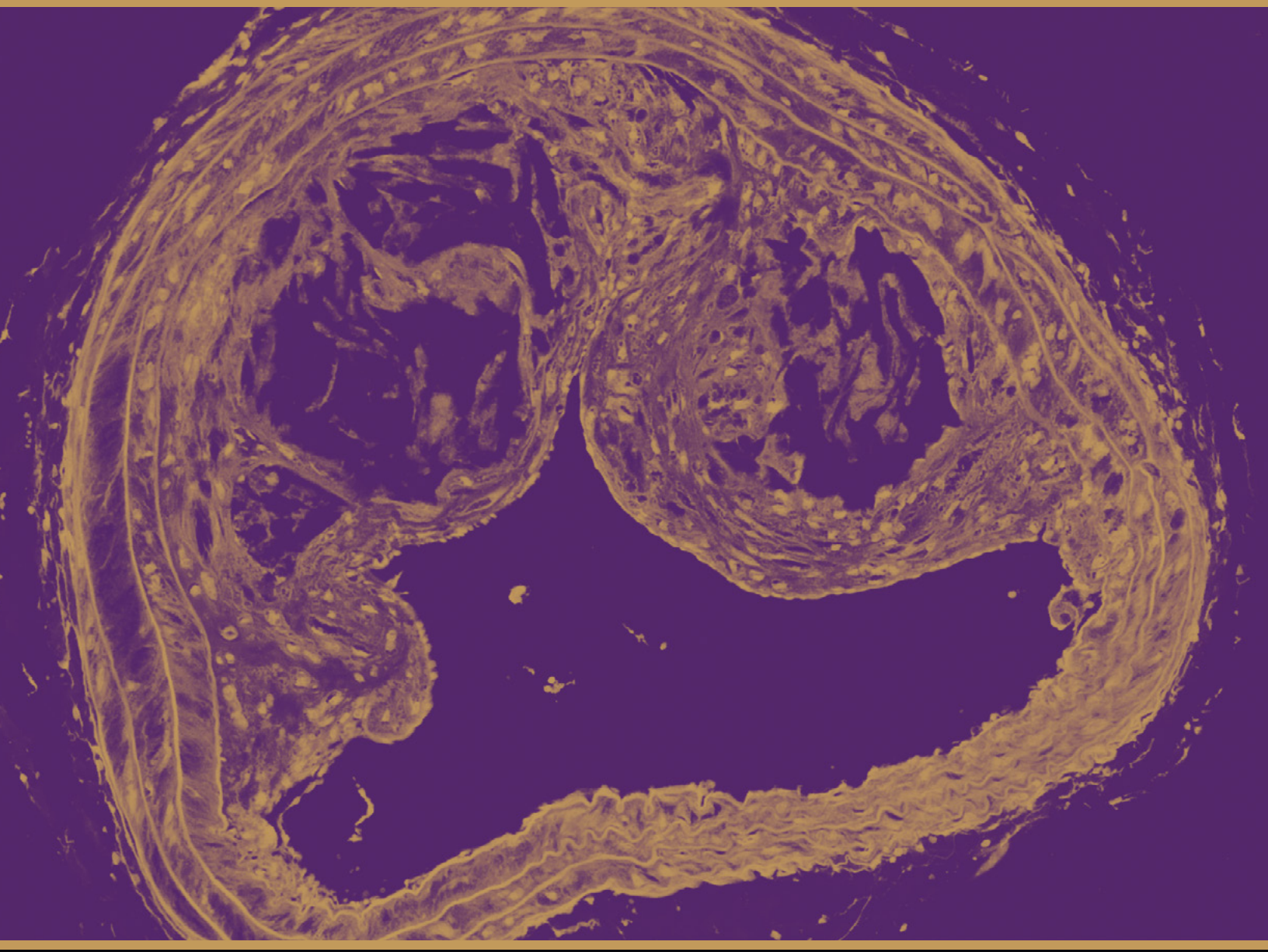
NYU Langone Health

Endocrinology

2017 YEAR IN REVIEW

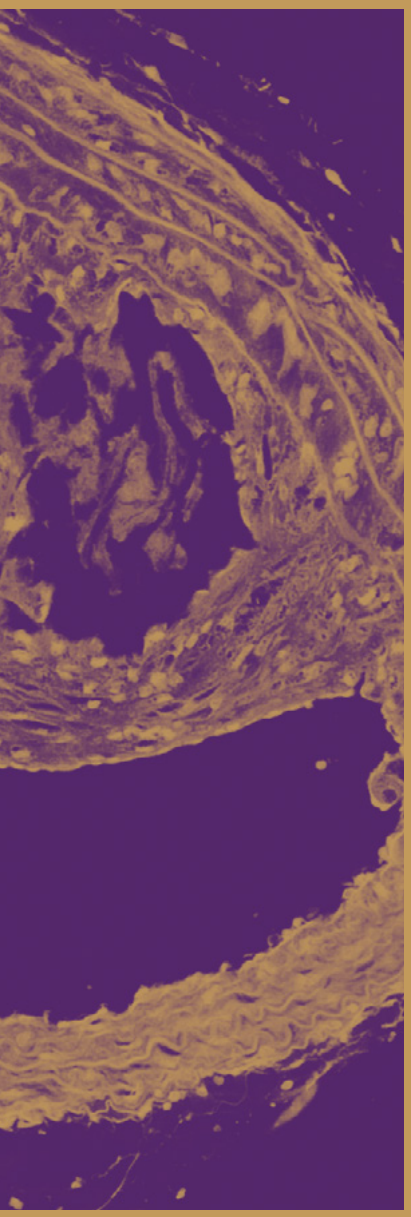


Established
AHA OBESITY NETWORK CENTER

$7.6 million
IN RESEARCH FUNDING

47%
INCREASE IN PATIENT VOLUME OVER TWO YEARS

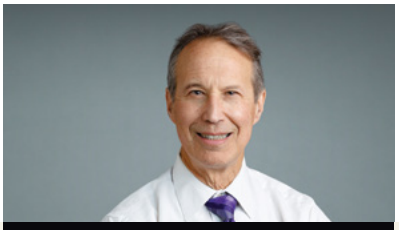
Contents



On the cover: Aortic atherosclerosis in a mouse with diabetes

MESSAGE FROM THE DIRECTOR

Dear Colleagues and Friends:



IRA J. GOLDBERG, MD

Clarissa and Edgar Bronfman, Jr. Professor of Endocrinology

Director, Division of Endocrinology, Diabetes and Metabolism

This past year has been one of growth and momentum, as we continue to build our clinical practice, recruit top faculty, and expand our research portfolio. In the pages that follow, you will see that our team is not only improving patient care, we are improving the standard of care.

With NYU Langone's strong institutional commitment, we have entered a new era in clinical diabetes care. Our burgeoning Center for Diabetes and Metabolic Health is not only providing the best possible care for our growing volume of patients, the new center is taking advantage of all the latest technological and scientific developments available to us. We are using mobile devices and apps to improve self-care and increase communication with doctors and educators; providing patients access to just-approved continuous glucose monitors; and offering more opportunities for patients to participate in clinical trials that make cutting-edge research treatments available. We are excited to see the Center's new Diabetes Biobank collecting tissue samples with coinciding data that is already helping physicians and researchers address some of the most pressing issues in clinical care today, while at the same time providing a fertile bed from which future research questions will grow.

We all know that diabetes and obesity are significant health problems at all strata of income and in all ethnic groups, and now our researchers are closer than ever to uncovering the molecular underpinnings of these conditions and finding new drug targets to go beyond treating the primary manifestations of disease. To support this work, we received a $4 million grant from the American Heart Association, funding that bolsters a collaboration between basic, clinical, and population health groups at NYU Langone that is under the direction of Ann Marie Schmidt, MD. You will read about Dr. Schmidt's lab and the culmination of decades of research on crucial molecular RAGE pathways that could translate to novel therapies for diabetes and its most damaging complications. We are also proud to welcome our most recent recruits, and I invite you to read about the outstanding basic and translational research they are conducting to advance this core mission.

With endocrinologist Valentina Rodriguez, MD, and preventive cardiologists, Arthur Z. Schwartzbard, MD, and Howard Weintraub, MD, we have worked to develop a new algorithm that determines therapeutic options for diabetes patients based on their risk for cardiovascular disease, the number-one killer of people with diabetes.

Mary Ann Sevick, PhD, launched a clinical trial that could pave the way for best practices for incorporating mobile-health technology into diabetes self-management. In fact, all across the endocrinology department, our physician-scientists are fostering interdisciplinary collaborations that will lead to better care in the future for patients here and elsewhere.

Under the guidance of Steven P. Hodak, MD, we now offer experienced guidance on diabetes management in patients with excessive hyperglycemia or hypoglycemia, many of whom are identified by computer-based monitoring of all hospitalized patients.

FACTS & FIGURES

Endocrinology

RESEARCH & EDUCATION

$7.6M
IN RESEARCH FUNDING
including $5.5 million in NIH grants

2
NEW NIH AWARDS

2
NEW DOD AWARDS

39
FACULTY MEMBERS

8
FELLOWS

Established
AHA OBESITY NETWORK CENTER

CLINICAL CARE

47%
INCREASE IN PATIENT VOLUME
over the past two years

2
NEW CLINICAL TRIALS

New Center
FOR DIABETES AND METABOLIC HEALTH

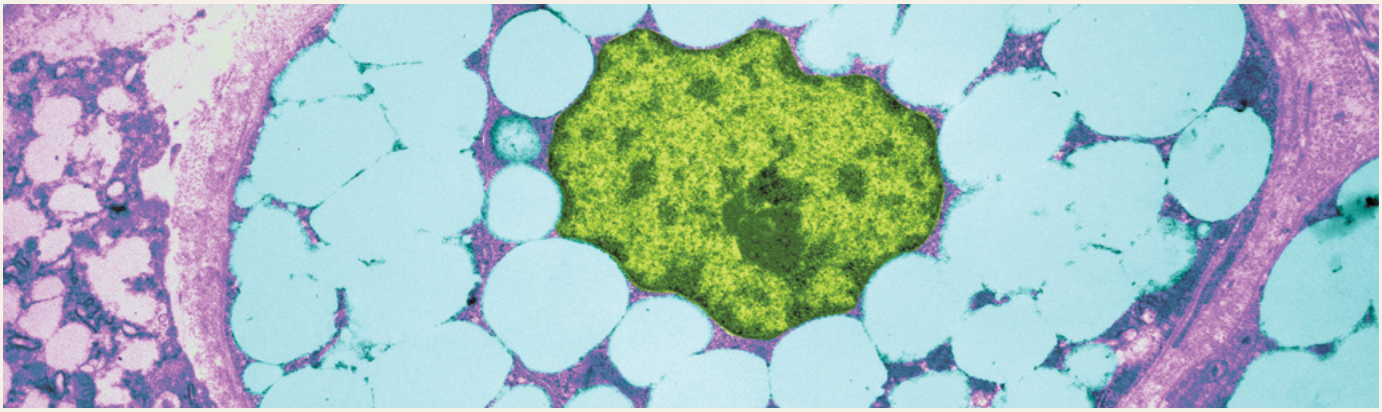
AWARDS &HONORS

Lifetime Achievement Award

FROM NATIONAL LIPID ASSOCIATION
presented to Ira J. Goldberg, MD

Gabor Kaley Memorial Lectureship

AWARDED TO
Ann Marie Schmidt, MD



Color enhanced transmission electron micrograph of a fat cell

NYU Langone Health

View of NYU Langone Health's main Manhattan campus, including renderings of the new Science Building (left) and the Helen L. and Martin S. Kimmel Pavilion (right), both set to open in 2018.
(Image credit: Ennead Architects)

BEST HOSPITALS U.S.News & World Report HONOR ROLL 2017-18

#19

IN THE NATION

and nationally ranked in 12 specialties: Rehabilitation, Orthopedics, Rheumatology, Neurology & Neurosurgery, Geriatrics, Urology, Cardiology & Heart Surgery, Gastroenterology & GI Surgery, Diabetes & Endocrinology, Pulmonology, Cancer, and Nephrology

BEST GRAD SCHOOLS U.S.News & World Report MEDICAL RESEARCH 2018

#12

IN THE NATION
BEST MEDICAL SCHOOLS FOR RESEARCH

and a leader in innovation in medical education, including accelerated pathways to the MD degree

Bernard A Birnbaum, MD Quality Leadership Award 2017 Winner vizient

Leader

IN QUALITY CARE AND PATIENT SAFETY

For the past four years, NYU Langone has received top rankings for overall patient safety and quality of care from Vizient, Inc., formerly the University HealthSystem Consortium. In 2017, NYU Langone received two significant awards from Vizient—the Bernard A. Birnbaum, MD, Quality Leadership Award and the Ambulatory Care Quality and Accountability Award for demonstrated excellence in delivering high-quality, patient-centered outpatient care.

5 Star Rating

FROM CMS HOSPITAL COMPARE

NYU Langone Health is the only full-service hospital in New York State and one of 9 percent of hospitals nationwide to receive a five-star rating from the Centers for Medicare and Medicaid Services (CMS). The rating reflects overall safety, quality, and patient experience.

2017 IN BRIEF

Growth, Innovation, and Collaboration

Changing Paradigms in Thyroid Cancer Diagnosis and Treatment

At least half of all thyroid cancers are due to a mutation that makes tumors respond poorly to radioactive iodine (RAI) therapy and to recur at a high rate. Along with colleagues, Steven P. Hodak, MD, professor of medicine, director of the Center for Diabetes and Metabolic Health, and chief of endocrinology at Tisch Hospital, is conducting experiments in cell lines and animal models to evaluate the use of inhibitor drugs to make these tumors more sensitive to RAI. If the experiments are successful, it could quickly become standard of care to pretreat patients with a sensitizing therapy, resulting in better responses, fewer recurrences, and less risk of advanced metastatic cancer developing down the line.

On the other end of the spectrum are the least-aggressive tumors, with low-grade, bland mutations that show no signs of invasiveness. For these, the standard of care has just undergone a major change. An international panel of experts that included Dr. Hodak dropped "cancer" from the diagnosis and revised the treatment guidelines, sparing patients from not only unnecessary thyroidectomies and a lifetime dependence on medication but also the psychological burden of a cancer diagnosis.

Read more on **PAGE 10**

A New CVD-Centric Approach to Treating Diabetes

A majority of patients with diabetes ultimately die from cardiovascular disease (CVD), yet many of the antihyperglycemic drugs used to treat type 2 diabetes fail to demonstrate a clear cardiovascular benefit, according to a new review conducted by Ira J. Goldberg, MD, the Clarissa and Edgar Bronfman, Jr. Professor of Endocrinology and director of the Division of Endocrinology, Diabetes, and Metabolism. Dr. Goldberg, along with colleagues at NYU Langone Health, examined studies dating as far back as 1970 that involved anti-diabetes therapies and their effects on CVD and, relying on patient outcomes, determined that a new approach to selecting medications is long overdue.

Instead of choosing drugs solely on their potential to lower hemoglobin A1c, the current standard, Dr. Goldberg and colleagues propose a new algorithm that determines treatment based on a patient's risk of atherosclerotic CVD and heart failure, prioritizing those drugs that have a cardiovascular-protective effect. In a July 2017 paper published in the *Journal of Clinical Lipidology* that outlines this algorithm, the team provides new guidelines.

"When I see patients I tell them that treatment for diabetes requires a focus on two issues," says Dr. Goldberg. "The first is the hyperglycemia that will cause acute symptoms and eye and kidney diseases. But the second line of treatment is to reduce risk of the cardiovascular diseases by lowering cholesterol, managing blood pressure, and increasing adherence to a heart-healthy lifestyle."

Using RAGE to Treat Obesity and Diabetes Complications

Today, treatments for obesity and diabetes are largely limited to tackling the core manifestations of these disorders (i.e., weight and blood-glucose management), but they do not address the underlying mechanisms driving these chronic conditions. Ann Marie Schmidt, MD, the Dr. Iven Young Professor of Endocrinology, is studying how molecules that increase in obesity and diabetes bind to RAGE, the receptor for advanced glycation end products, and then signal adverse inflammatory and metabolic effects—and how to inhibit these adverse effects. Researchers had long suspected that inflammatory and metabolic pathways are tightly coupled, but what they didn't know is that RAGE itself is involved in these processes.

This discovery by Dr. Schmidt and her collaborators opened up the possibility of a range of new RAGE-centric, targeted treatments for both obesity and diabetes complications. Currently, her team is focusing on small molecules that inhibit interaction between RAGE and intracellular effector DIAPH1, a key signaling pathway implicated in inflammation. If they are successful in showing that these small molecules work in mice, the molecules may serve as the foundation for new drugs that improve metabolic responses to weight-loss regimens and block the inflammation associated with diabetes complications in the heart, eyes, and kidneys.

Read more on **PAGE 9**

HARNESSING NEW TECHNOLOGY IN DIABETES CARE

NYU Langone's new Center for Diabetes and Metabolic Health is outfitting some of its patients with the first wearable continuous glucose-monitoring system as part of a recently launched five-year longitudinal study of diabetes complications. Approved by the FDA in September 2017, the devices can be worn continuously for up to 10 days, enabling patients and doctors to identify patterns and trends they might not otherwise detect to improve diabetes management.

Michael Bergman, MD

Earlier and Easier Screening for Diabetes and Prediabetes

Findings from a new study are bringing the one-hour oral glucose-tolerance test another step closer for consideration as a standard screening tool in clinical practice, one that could potentially reduce the risk for diabetes, vascular disease, and mortality in screened patients. In a prospective population-based cohort study that followed 4,867 men for up to 39 years, Michael Bergman, MD, clinical professor of medicine and population health, and his fellow researchers found that elevated one-hour post-load glucose levels were superior predictors of future type 2 diabetes and complications than their two-hour levels. The results appeared online in November 2017 in the journal *Diabetes Care*.

Previously, Dr. Bergman and colleagues demonstrated that the one-hour test better identifies patients with abnormalities in blood glucose levels than the current gold standard test, hemoglobin A1c (HbA1c). The enhanced predictive capability appears to be due to the one-hour test's increased sensitivity to early changes in beta cell function, which is paramount to preserving normal glucose tolerance. Taken together, these studies suggest that the test could serve as an early screening tool (more convenient than the current two-hour oral glucose tolerance test) that identifies high-risk individuals before they lose beta cell function and when lifestyle intervention is most effective.

Akankasha Goyal, MD

Biobanking Turns Specialty Care Center into Living Laboratory

This past spring, NYU Langone Health's new Center for Diabetes and Metabolic Health established a specimen repository and mineable database, called the Diabetes Biobank, that will help physicians and researchers address some of the most pressing questions in clinical care: Why do some people fare better with diabetes than others? Why do some develop cardiovascular complications and others do not?

Leading the effort is Akankasha Goyal, MD, instructor of medicine and specialist in diabetes complications and insulin-clamping studies, who recently joined NYU Langone Health from Montefiore Medical Center. Dr. Goyal has already begun recruiting the 400 to 500 patients with diabetes or prediabetes needed for the biobank's first initiative, a five-year longitudinal study that focuses primarily on risk stratification. Her team will collect urine, stool, and blood samples at regular intervals and provide an ongoing stream of data from questionnaires, patient interviews, physical examinations, and standard-of-care cardiac and metabolic tests and treatments. "So, for example," explains Steven P. Hodak, MD, professor of medicine and director of the Center for Diabetes and Metabolic Health, "if we discover a genetic marker that we could use to identify people at the greatest or lowest risk for disease, we can go back to the specimen repository and validate that laboratory finding in an actual population of patients. We learn from our patients, and that learning directly translates back to improved patient care."

RESEARCHERS AWARDED $12 MILLION NIH GRANT TO STUDY OBESITY, DIABETES, AND ATHEROSCLEROSIS

Three researchers at NYU Langone Health were jointly awarded a $12 million, five-year grant from the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) to study the role of the immune cells known as macrophages in obesity, diabetes, and atherosclerosis. Ann Marie Schmidt, MD, the Dr. Iven Young Professor of Endocrinology, cardiologist Edward A. Fisher, MD, PhD, the Leon H. Charney Professor of Cardiovascular Medicine, and immunologist Kathryn J. Moore, PhD, the Jean and David Blechman Professor of Cardiology, are collaborating to pinpoint factors that activate or repress macrophage inflammatory activity in each disease. While macrophages are normally beneficial, serving as the immune system's first responders against dangerous pathogens, these same macrophages can become the body's worst enemy when an individual becomes obese and develops diabetes or atherosclerosis. "Instead of taking a protective role, the macrophages become inflamed and exacerbate the damage caused by the disease," Dr. Schmidt says.

José Alemán, MD, PhD

Expanding Research Initiatives with New Investigators

NYU Langone Health's rapidly growing endocrinology team is quickly expanding its research portfolio, especially in areas of translational research. Our new recruits are exploring the molecular underpinnings behind obesity and diabetes, paving the way for more effective treatments in the future. To reveal new drug targets to treat or prevent type 2 diabetes and other metabolic diseases, Andisheh Abedini, PhD, assistant professor of medicine, is studying pancreatic beta cells and the molecular factors that cause the loss of their function. In his newly established Laboratory of Translational Obesity Research, José Alemán, MD, PhD, assistant professor of medicine, is investigating how rapid weight loss reverses inflammation in white adipose tissue and resolves the accompanying insulin resistance, identifying new metabolic pathways that drug developers can harness for better treatments. Elisabetta Mueller, PhD, associate professor of medicine, is studying adipose tissue biology and the role fat cells play in obesity, aging, and metabolic disease. Focusing on the transcription factors that act as molecular energy switches, her team is reprogramming fat cells in mice to be energy burners instead of energy hoarders, preventing them from developing obesity.

Read more on **PAGE 12**

Diabetes Self-Management: Leveraging Mobile-Health Technologies for Better Outcomes

For patients living with diabetes and other chronic conditions, mobile-health applications have the potential to make it significantly easier to adhere to the self-care strategies and lifestyle changes recommended to them by caregivers, but there is limited data on how best to incorporate the technology.

In a randomized clinical trial funded by the NIH's National Institute of Diabetes and Digestive and Kidney Diseases, Mary Ann Sevick, PhD, professor of population health at NYU Langone Health, issued iPads loaded with mobile-health apps to overweight individuals with type 2 diabetes and concurrent chronic kidney disease. The team is now evaluating the efficacy of three tech-supported interventions, compared with a control group. Depending on group assignment, participants either track daily meals and exercise through a self-monitoring app; receive social-cognitive-theory-based counseling via a videoconferencing app; or do a combination of both monitoring and counseling. All participants have the same behavioral goals: to restrict intake of calories, sodium, and phosphate additives and to increase physical activity. "We know, from decades of research," says Dr. Sevick, "that behavioral methods are needed to engage people in simple behavior change. But even the most motivated individual will have difficulty making multiple behavior changes, due to human limitations in information management. While we are unable to unblind data from this ongoing study, we expect that the largest behavior changes will be observed in the combined group, which receives both behavioral counseling and uses technology to manage complex information."

2017 IN DEPTH

Leading the Way in Clinical Care and Research

Ann Marie Schmidt, MD; Ira J. Goldberg, MD; Kathryn Moore, PhD; Edward A. Fisher, MD

Novel Therapeutic Approach to Obesity and Diabetes

Several years ago, a team of NYU Langone Health researchers made a surprising discovery when conducting a gene-deletion study. In mice fed high-fat diets, knocking out the gene RAGE, which was previously linked to diabetic complications, protected the mice from developing both obesity and insulin resistance.

"It was an unexpected result but not inconsistent with the idea that these molecules, which we know are involved in inflammation, would also regulate metabolism," says Ann Marie Schmidt, MD, the Dr. Iven Young Professor of Endocrinology, who first discovered RAGE, the receptor for advanced glycation end products, nearly three decades ago and now leads RAGE research at NYU Langone.

RAGE AS A METABOLIC PLAYER

Since then, the team has been studying this link between RAGE and obesity. In March 2017, the American Heart Association (AHA) awarded Dr. Schmidt a $1 million Center grant to support this work as part of the multi-institution AHA Strategically Focused Obesity Research Network Center, a nearly $4 million, four-year research collaboration between basic, clinical, and population health groups that is under the direction of Dr. Schmidt, Ira J. Goldberg, MD, the Clarissa and Edgar Bronfman, Jr. Professor of Endocrinology and director of the division of endocrinology, diabetes, and metabolism, and Mary Ann Sevick, MD, professor of population health. "One question the AHA grant wants answered in both mouse models and human subjects: Is the RAGE mechanism not only suppressing energy expenditure, leading to obesity, but also impairing the ability of patients to achieve and sustain weight loss?" says Dr. Schmidt.

Researchers had long suspected that inflammatory and metabolic pathways are tightly coupled, but what they didn't know is that RAGE itself is implicated in the process. That discovery, along with related research at other institutions, opened up the possibility of a range of new, targeted treatments for both obesity and one of its key consequences, diabetes (and its complications). "Today's therapeutic approaches—managing weight and blood glucose—are largely aimed at tackling the core manifestations of these disorders, but these therapies are often not effective and do not address the fundamental cause," says Dr. Schmidt. Now her team is specifically trying to understand how molecules that increase in obesity and diabetes bind to RAGE and then signal adverse inflammatory and metabolic effects, which suppress energy expenditure—and how to inhibit these effects and release the brakes on optimal use of energy in obesity and in weight loss.

TARGETING THE RAGE-DIAPH1 PATHWAY TO TREAT METABOLIC DISEASE

There are efforts under way by others to therapeutically inhibit RAGE and the ligands that bind to it in its extracellular regions in order to mimic the deletion effects seen in high-fat-diet mice. So far, the evidence suggests that the role RAGE plays in the human body is predominantly a negative one. "The brand of inflammation that this receptor imparts is not the kind of inflammation that facilitates survival. Rather, it seems to facilitate inexorable tissue damage," says Dr. Schmidt. But proving that it doesn't also serve some unknown important function in the body will take some time. So Schmidt's team is exploring another approach. Instead of targeting RAGE directly, she is focusing on the intracellular effector DIAPH1, which binds to the RAGE "tail" and is essential for RAGE-mediated signaling—a pathway her team discovered in 2008 and the one that so far seems to be important in transducing the effects of RAGE in inflammation.

In collaboration with Alexander Shekhtman, PhD, professor of chemistry at the University at Albany, Dr. Schmidt used high-throughput assays to screen a library of 58,000 small molecules for any that block RAGE-DIAPH1 interaction. Based on dose-response testing, NMR spectroscopy, and fluorescence-titration experiments, the researchers identified 13 candidates that bind to the site on the RAGE tail so that DIAPH1 can't. Further studies showed how well these competitive inhibitors blocked signal transduction, cellular migration, and inflammatory gene expression, as well as, ex vivo, ischemia-induced perturbation of heart function and, in vivo, inflammation in both a delayed-type hypersensitivity reaction and upon direct injection of RAGE ligands into normal mice. "If we're successful in showing that these molecules work in mice," says Dr. Schmidt, "we may have the foundation for ways not only to block disadvantageous inflammation that leads to macro- and microvascular diabetes complications but maybe also to facilitate prevention of obesity and to improve metabolic responses in weight loss to mitigate obesity."

Changing Paradigms in Thyroid Cancer Diagnosis and Treatment

The incidence of thyroid cancer in the United States has doubled in the past two decades, yet until recently the standard of care—thyroidectomy, often followed by radioactive iodine—had remained largely unchanged. Now, with advances in genotyping and other diagnostic and prognostic tools, researchers and clinicians are rethinking the way we diagnose and treat thyroid nodules, and patients, in turn, are receiving diagnoses and treatments that are better matched to their disease.

GENETIC MUTATION *BRAFV600E* CAUSES CANCER AND INTERFERES WITH RADIOACTIVE IODINE TREATMENT

At least half of all thyroid cancers are due to one very nasty genetic mutation in a single nucleotide that causes uncontrolled cell division and tumorigenesis. In fact, the most aggressive cancers have a much higher frequency of this mutation, closer to 70 to 80 percent. The focus of intense study in recent years, this mutation, *BRAFV600E*, has another serious consequence: it interferes with the unique ability of thyroid tissue to take up iodine, including radioactive iodine, the mainstay for treating diagnosed thyroid tumors in patients who can't be cured by surgery alone. Papillary thyroid cancers that contain a *BRAFV600E* mutation often respond poorly to radioactive iodine and frequently recur at a high rate within the first two to three years after treatment. "For those patients who need it most, radioactive iodine is the least effective," explains Steven P. Hodak, MD, professor of medicine, director of the Center for Diabetes and Metabolic Health, and chief of endocrinology at Tisch Hospital.

Over the past year, Dr. Hodak's team, co-led with his collaborator Melissa A. Wilson, MD, PhD, assistant professor of medicine, has been trying to reverse this effect, exploring the possibility of using drugs already approved for other cancers to pretreat thyroid cancer patients who have clinically aggressive *BRAFV600E* tumors. The experiments represent NYU Langone's first foray into translational thyroid cancer research. Evidence shows that even at the initial tumor presentation, overactivation of a main cell-signaling pathway controlled by *BRAFV600E* causes the de-expression of a membrane protein called the sodium iodide symporter. This transporter acts as the machinery for moving iodine into thyroid cells—including into thyroid cancer cells. For patients with this mutation, a drug that blocks this signaling pathway could increase the tumor's sensitivity to radioactive iodine therapy.

"But cancer cells are smart," says Dr. Hodak, "and they have escape pathways to get around the drug blockade." So the team is targeting two additional molecules: a membrane signaling protein called ERBB3 and another signaling molecule downstream of *BRAFV600E* known as MEK. In the researchers' first cell-line experiments, they are using small interfering RNAs to block all three molecules alone and in combination to determine which cocktail induces maximum re-expression of the symporter. If that works, they will use already-approved drugs that inhibit these specific molecules to see if they can get the cancer cells to exhibit the same re-expression. Once this combination therapy is validated in vitro, the team can move directly to testing it in phase II clinical trials.

"We'll see fewer recurrences and reduce the incidence of life-threatening advanced metastatic cancer down the line."

—Steven P. Hodak, MD

Steven P. Hodak, MD

Other researchers have explored similar approaches for restoring radioactive iodine uptake in advanced widely metastatic, iodine-refractory tumors. However, the application in earlier-stage cancers has not been sufficiently studied, despite the fact that these tumors constitute the vast majority of thyroid cancers. "If we can prove it, and I believe we will, we really are going to explode the paradigm for how we treat these patients," says Dr. Hodak. "It will become standard of care to pretreat patients with sensitizing therapy to enhance the radioactive iodine effect, and patients will do much better. We'll see fewer recurrences and reduce the incidence of life-threatening advanced metastatic cancer down the line."

RECLASSIFYING LOW-GRADE TUMORS AS "NOT CANCER" REDUCES OVERTREATMENT

On the other end of the spectrum are the least-aggressive tumors, with low-grade, bland mutations that show no signs of invasiveness, a type of cancer called encapsulated follicular variant of papillary thyroid carcinoma. Over the course of a year, using molecular genetic testing, clinical-outcome studies, and evaluation of a large sample set of tumors provided by a number of institutions, an international panel of doctors determined that these tumors are very low-risk in their behavior and shouldn't be called cancer at all. The word "cancer," they determined, misrepresents the biological nature of this tumor and often drives doctors to overtreatment, exposing patients to unnecessary risk and expense.

"We wanted to remove the word 'cancer' from this tumor's name because it was being overtreated and in fact it's not a cancer in the sense that it does not behave invasively," says Dr. Hodak, who served as one of two endocrinologists on the 31-member panel. The team renamed the tumor "noninvasive follicular thyroid neoplasm with papillary-like nuclear features," or NIFTP, and established new diagnostic criteria. In April 2017, the World Health Organization codified NIFTP as a diagnosis, a move that will spare more than 45,000 patients worldwide each year from thyroidectomies and a lifetime dependence on medication and regular checkups, along with the psychological burden of a cancer diagnosis. "We recognize that these are tumors with invasive potential and they need to be discovered and surgically removed, but the goal is to eliminate the overtreatment with excessive surgery or radioactive iodine that would then often follow," says Dr. Hodak.

New Talent in Translational Research

NYU Langone Health's rapidly growing endocrinology team is fostering multidisciplinary collaborations that will lead to better care for patients here and elsewhere. Below is a look at three new faculty members who are contributing to our understanding of the molecular underpinnings behind obesity and diabetes and paving the way for more effective treatments in the future.

REVERSING BETA CELL DYSFUNCTION TO TREAT METABOLIC DISEASE

Andisheh Abedini, PhD, assistant professor of medicine, came to NYU Langone Health in 2010 as a doctoral fellow in the lab of Ann Marie Schmidt, MD, the Dr. Iven Young Professor of Endocrinology. There, she studied insulin-producing beta cells and the molecular factors that cause the loss of their function and, in turn, the onset and progression of diabetes. Now, as a principal investigator in the Diabetes Research Program and a 2016 recipient of the American Heart Association's Scientist Development Grant, Dr. Abedini leads a team of researchers who are continuing that work, demonstrating that the preservation of beta cells is a promising avenue for treating and preventing metabolic disease.

In healthy individuals, pancreatic beta cells secrete the hormone amylin alongside insulin to help maintain energy homeostasis. In patients with type 2 diabetes, however, amylin misfolds and aggregates to form oligomers that are toxic to the very beta cells that produce it. These proteotoxic amylin aggregates further self-associate into amyloid plaques in the pancreas. Through a series of studies that included in vitro experiments, transgenic-mouse models, and human subjects with type 2 diabetes, the team made two key discoveries: They found that these toxic amyloidogenic aggregates are surprisingly distinct from those produced by other amyloidogenic proteins, like those in Alzheimer's disease. "This overturned a more than 10-year-long paradigm in the field that held to the idea that toxic species derived from different amyloidogenic proteins have the same properties, and explained why drugs that

Andisheh Abedini, PhD

effectively inhibit toxicity in one do not always work for the others," says Dr. Abedini. Next, they discovered they could mitigate the source of the beta-cell dysfunction by inhibiting the interactions between toxic amylin molecules and RAGE (receptor for advanced glycation end products), a sugar-modified protein first identified by Dr. Schmidt nearly three decades ago. These findings, which will appear in the *Journal of Clinical Investigation* early this year, reveal new drug targets and provide critical information for the design of new drugs to treat or prevent not only type 2 diabetes, but other metabolic diseases as well.

In other research, Dr. Abedini is examining endocrine cell cross-talk, with novel in vitro experiments simulating the way pancreatic beta cells directly communicate with different types of adipocytes, and how that impacts insulin secretion and beta-cell fate. To understand the pathogenesis of human diabetes, her group is working to translate studies from animal models into human islet biology.

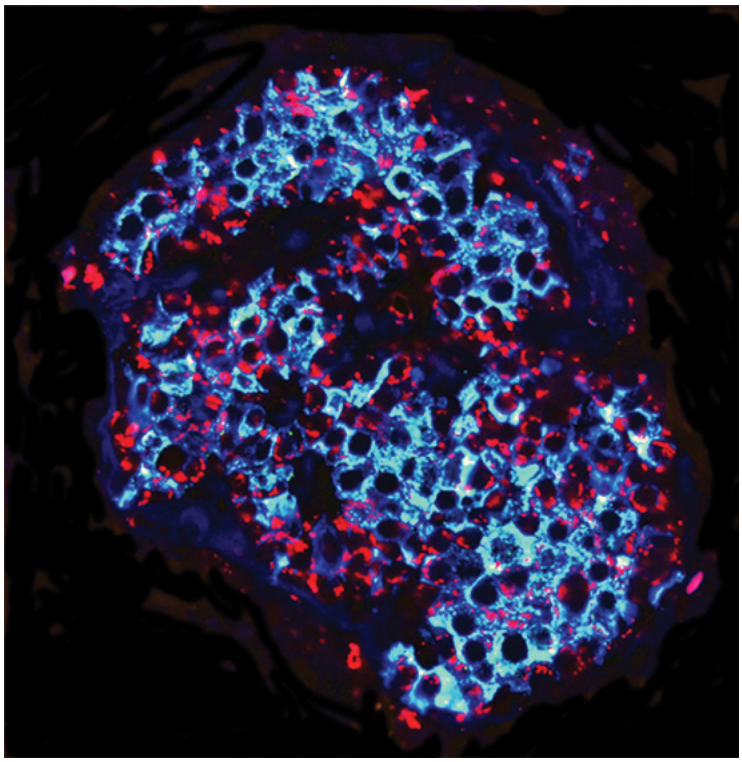
SHEDDING NEW LIGHT ON THE LINK BETWEEN INFLAMMATION, OBESITY, AND DIABETES

José Alemán, MD, PhD, assistant professor of medicine, joined NYU Langone Health in 2016 to establish the Laboratory of Translational Obesity Research. Prior to coming to NYU Langone, Dr. Alemán was an instructor in clinical investigation at Rockefeller University, where he initiated a translational research program. Trained as an endocrinologist and a biomedical engineer, he is studying the link between low-grade inflammation that is characteristic of fat tissue in obese patients and chronic complications like type 2 diabetes and cardiovascular disease.

Last March, 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 between 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 is working with Ira J. Goldberg, MD, the Clarissa and Edgar Bronfman, Jr. Professor of Endocrinology and director of the Division of Endocrinology, to figure out exactly how it is that rapid weight loss through surgery reverses inflammation in white adipose tissue and resolves the accompanying insulin resistance; a large clinical trial studying bariatric-surgery patients at NYU Langone and Bellevue Hospital Center is under way. Meanwhile, Dr. Alemán is helping launch a new weight-management clinic at the Manhattan VA Medical Center, where he is both treating obese veterans who have complications from their weight and conducting a similar clinical trial, this one focusing on medication-induced weight loss.

The large data sets from these two trials will shed light on unexpected findings from a study of weight loss in obese women undergoing a seven-week, very-low-calorie diet. "We discovered that the macrophage immune cells in inflamed adipose tissue acted in a surprisingly non-inflammatory metabolic manner during rapid weight loss," says Dr. Alemán. If researchers can better understand the metabolic cues mediating this process, they could potentially harness these pathways to find new adipose-centric drug targets to treat inflammation and prevent obesity complications.



Immunofluorescence image of a human pancreatic islet from a type 2 diabetic subject with islet amyloidosis shows significant co-localization of insulin (red), IAPP (blue) and RAGE (green), consistent with an IAPP-induced, RAGE-mediated mechanism of beta cell/islet proteotoxicity in type 2 diabetes.

REPROGRAMMING FAT CELLS TO PREVENT OBESITY

Elisabetta Mueller, PhD, associate professor of medicine, joined NYU Langone in 2016 after spending 12 years at the National Institutes of Health studying adipose tissue biology and the role fat cells play in obesity, aging, and metabolic disease. It is widely understood that white fat stores energy and brown fat burns it, but the discovery of beige fat—a newly identified adipocyte that develops in white adipose tissue but expresses characteristics of brown—has opened the door to new therapeutic possibilities, such as inducing the "browning" of white fat. To that end, Dr. Mueller and her team are focusing on the cascade of molecular events that determine whether fat-cell precursors become white, brown, or beige adipocytes and which transcription factors, the proteins that control gene expression, act as molecular switches for energy storage or expenditure.

Recently, Dr. Mueller and her team identified and validated in vitro and in vivo two such switches, transcription regulators HSF1 and ZNF638, and demonstrated that pharmacological activation of HSF1 in mice can protect them from the development of obesity and metabolic disease. The researchers are now testing these factors genetically in animal models to see if they can reprogram fat cells to be energy burners instead of energy hoarders. "If we tweak or overexpress these factors in transgenic mice, can we make a leaner animal, despite their being fed a high-fat diet?" asks Dr. Mueller. She is also conducting in vitro trials to identify therapeutic compounds that target specific transcription factors.

Elisabetta Mueller, PhD

GROWING TEAM OF CLINICAL EXPERTS

In addition to the growth of its research arm, the division also welcomed a new physician, **Melissa Sum, MD,** in 2017. Dr. Sum joined NYU Langone following a fellowship at Columbia University and is now directing the diabetes pillars course for medical students, helping develop an early understanding of the clinical practice of endocrinology and diabetes care, along with the pathophysiology.

Melissa Sum, MD

Academic Activities

SELECTED PUBLICATIONS

Aberle D, Charles H, Hodak S, O'Neill D, Oklu R, Deipolyi AR. Optimizing care for the obese patient in interventional radiology. *Diagnostic & Interventional Radiology*. March 2017; 23(2): 156–162. doi: 10.5152/dir.2016.16230.

Agrawal N, Abbott CE, Liu C, Kang S, Tipton L, Patel K, Persky M, King L, Deng F-M, Bannan M, Ogilvie JB, Heller K, Hodak S. Non-invasive follicular tumor with papillary-like nuclear features (NIFTP): not a tempest in a teapot. *Endocrine Practice*. April 2, 2017; 23(4): 451–457. doi: 10.4158/EP161632.OR.

Akter R, Abedini A, Ridgway Z, Zhang X, Kleinberg J, Schmidt AM, Raleigh DP. Evolutionary adaptation and amyloid formation: does the reduced amyloidogenicity and cytotoxicity of ursine amylin contribute to the metabolic adaption of bears and polar bears? *Israel Journal of Chemistry*. July 2017; 57(7–8): 750–761. doi: 10.1002/ijch.201600081.

Asadipooya K, Graves L, Greene LW. Transient osteoporosis of the hip: review of the literature. *Osteoporosis International*. June 2017; 28(6): 1805–1816. doi: 10.1007/s00198-017-3952-0.

Bergman M, Jagannathan R, Buysschaert M, Medina JL, Sevick MA, Katz K, Dorcely B, Roth J, Chetrit A, Dankner R. Reducing the prevalence of dysglycemia: is the time ripe to test the effectiveness of intervention in high-risk individuals with elevated 1 h post-load glucose levels? *Endocrine*. March 2017; 55(3): 697–701. doi: 10.1007/s12020-017-1236-2.

Buysschaert M, Bergman M, Yanogo D, Jagannathan R, Buysschaert B, Preumont V. An elevated 1-h post-load glucose level during the oral glucose tolerance test detects prediabetes. *Diabetes & Metabolic Syndrome*. April–June 2017; 11(2): 137–139. doi: 10.1016/j.dsx.2016.12.002.

Caraher EJ, Kwon S, Haider SH, Crowley G, Lee A, Ebrahim M, Zhang L, Chen L-C, Gordon T, Liu M, Prezant DJ, Schmidt AM, Nolan A. Receptor for advanced glycation end-products and World Trade Center particulate induced lung function loss: a case-cohort study and murine model of acute particulate exposure. *PLOS One*. September 19, 2017; 12: e0184331. doi: 10.1371/journal.pone.0184331

Carey M, Gospin R, Goyal A, Tomuta N, Sandu O, Mbanya A, Lontchi-Yimagou E, Hulkower R, Shamoon H, Gabriely I, Hawkins M. Opioid receptor activation impairs hypoglycemic counterregulation in humans. *Diabetes*. November 2017; 66(11): 2764–2773. doi: 10.2337/db16-1478.

Chiosea S, Asa SL, Berman MA, Carty SE, Currence L, Hodak S, Nikiforov YE, Richardson MS, Seethala RR, Sholl LM, Thompson LDR, Wenig BM, Worden F. Template for reporting results of biomarker testing of specimens from patients with thyroid carcinoma. *Archives of Pathology & Laboratory Medicine*. April 2017; 141(4): 559–563. doi: 10.5858/arpa.2016-0326-CP.

Desai D, Rao D, Sukrithan V, Weinstein E, Goyal A, Schubart U. Pancreatic cancer heralded by worsening glycemic control: a report of two cases. *Journal of Investigative Medicine High Impact Case Reports*. June 8, 2017; 5: 2324709617714286. doi: 10.1177/2324709617714286.

Dorcely B, Katz K, Jagannathan R, Chiang SS, Oluwadare B, Goldberg IJ, Bergman M. Novel biomarkers for prediabetes, diabetes, and associated complications. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. August 14, 2017; 10: 345–361.

Hulman A, Vistisen D, Glumer C, Bergman M, Witte DR, Faerch K. Glucose patterns during an oral glucose tolerance test and associations with future diabetes, cardiovascular disease and all-cause mortality rate. *Diabetologia*. January 2018; 61(1): 101–107. doi: 10.1007/s00125-017-4468-z.

Inman CK, Aljunaibi A, Koh H, Abdulle A, Ali R, Alnaeemi A, Al Zaabi E, Oumeziane N, Al Bastaki M, Al-Houqani M, Al-Maskari F, Al Dhaheri A, Shah SM, Wareth LA, Al Mahmeed W, Alsafar H, Al Anouti F, Al Hosani A, Haji M, Galani D, O'Connor MJ, Ahn J, Kirchhoff T, Sherman S, Hayes RB, Li H, Ramasamy R, Schmidt AM. The AGE-RAGE axis in an Arab population: The United Arab Emirates Healthy Futures (UAEHFS) pilot study. *Journal of Clinical & Translational Endocrinology*. December 2017; 10: 1–8. doi: 10.1016/j.jcte.2017.08.001.

Jagannathan R, Bergman M. Use of 1-h post-load plasma glucose concentration to identify individuals at high risk of developing type 2 diabetes. *Diabetic Medicine*. July 2017; 34(7): 877–878. doi: 10.1111/dme.13370.

Liu Z, Han T, Fishman S, Butler J, Zimmermann T, Tremblay F, Harbison C, Agrawal N, Kopchick JJ, Schaffler MB, Yakar S. Ablation of hepatic production of the acid labile subunit in the bovine-GH transgenic mice; effects on organ and skeletal growth. *Endocrinology*. August 1, 2017; 158(8): 2556–2571. doi: 10.1210/en.2016-1952.

Lopez-Diez R, Shen X, Daffu G, Khursheed M, Hu J, Song F, Rosario R, Xu Y, Li Q, Xi X, Zou YS, Li H, Schmidt AM, Yan SF. *Ager* deletion enhances ischemic muscle inflammation, neoangiogenesis, and blood flow recovery in diabetic mice. *Arteriosclerosis, Thrombosis, & Vascular Biology*. August 2017; 37(8): 1536–1547. doi: 10.1161/ATVBAHA.117.309714.

Mandel L, Greene LW. Differentiating 131I radiation sialadenitis from autoimmune (Sjogren Syndrome) sialadenitis: case report. *Journal of Oral & Maxillofacial Surgery*. November 2017; 75(11): 2379–2382. doi: 10.1016/j.joms.2017.04.008.

Nielsen TB, Pantapalangkoor P, Yan J, Luna BM, Dekitani K, Bruhn K, Tan B, Junus J, Bonomo RA, Schmidt AM, Everson M, Duncanson F, Doherty TM, Lin L, Spellberg B. Diabetes exacerbates infection via hyperinflammation by signaling through TLR4 and RAGE. *mBio*. August 2017; 8(4): e00818–17. doi: 10.1128/mBio.00818-17.

Noto MJ, Becker KW, Boyd KL, Schmidt AM, Skaar EP. RAGE-mediated suppression of interleukin-10 results in enhanced mortality in a murine model of *Acinetobacter baumannii* sepsis. *Infection & Immunity*. March 2017; 85(3): e00954–16. doi:10.1128/IAI.00954-16.

Pareek M, Bhatt DL, Nielsen ML, Jagannathan R, Eriksson K-F, Nilsson PM, Bergman M, Olsen MH. Enhanced predictive capability of a 1-hour oral glucose tolerance test: a prospective population-based cohort study. *Diabetes Care*. January 2018; 41(1): 171–177. doi: 10.2337/dc17-1351.

Rodriguez V, Weiss MC, Weintraub H, Goldberg IJ, Schwartzbard A. Cardiovascular disease leads to a new algorithm for diabetes treatment. *Journal of Clinical Lipidology*. September–October 2017; 11(5): 1126–1133. doi: 10.1016/j.jacl.2017.07.004.

Schmidt AM. 2016 ATVB Plenary Lecture: receptor for advanced glycation endproducts and implications for the pathogenesis and treatment of cardiometabolic disorders: spotlight on the macrophage. *Arteriosclerosis, Thrombosis, & Vascular Biology*. April 2017; 37(4): 613–621. doi: 10.1161/ATVBAHA.117.307263.

Thiagarajan D, O'Shea K, Sreejit G, Ananthakrishnan R, Quadri N, Li Q, Schmidt AM, Gabbay K, Ramasamy R. Aldose reductase modulates acute activation of mesenchymal markers via the beta-catenin pathway during cardiac ischemia-reperfusion. *PLOS One*. November 30, 2017; 12: e0188981. doi: 10.1371/journal.pone.0188981.

Yu Y, Wang L, Delguste F, Durand A, Guilbaud A, Rousselin C, Schmidt AM, Tessier F, Boulanger E, Neviere R. Advanced glycation end products receptor RAGE controls myocardial dysfunction and oxidative stress in high-fat fed mice by sustaining mitochondrial dynamics and autophagy-lysosome pathway. *Free Radical Biology & Medicine*. August 2017; 112: 397–410. doi: 10.1016/j.freeradbiomed.2017.08.012.

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Director, Division of Endocrinology, Diabetes and Metabolism

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Chief of Endocrinology at Tisch Hospital

Michael Bergman, MD
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Chief of Endocrinology at Veteran Affairs-New York Harbor Healthcare System

Gillian Katz, MD
Clinical Assistant Professor of Medicine
Chief of Endocrinology at Bellevue Hospital Center

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1,519
Beds

98
Operating Rooms

172,072
Emergency Room Visits

68,884
Patient Discharges

4,500,000
Outpatient Faculty Practice Visits

9,654
Births

3,633
Physicians

5,104
Nurses

516
MD Candidates

85
MD/PhD Candidates

263
PhD Candidates

418
Postdoctoral Fellows

1,327
Residents and Fellows

5,087
Original Research Papers

549,707
Square Feet of Research Space

$359M
NIH Funding

$364M
Total Grant Revenue

*Numbers represent FY17 (Sept 2016–Aug 2017) and include NYU Langone Hospital—Brooklyn

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