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IGNITING A TRANSFORMATION

ANN MARIE SCHMIDT '83, MELANIE JAY '00, AND BRIAN ELBEL, PHD, ARE USING DATA AND TECHNOLOGY TO CONNECT RESEARCH IN BASIC SCIENCE, CLINICAL MEDICINE, AND POPULATION HEALTH.

BY JEN SWETZOFF

Ann Marie Schmidt '83 has never forgotten the patients she saw as a resident in internal medicine at Bellevue more than 30 years ago. Back then, blood tests for type 2 diabetes, the most common kind of diabetes and the one most often associated with obesity, had only recently emerged. Insulin pumps were just becoming available. Many of her patients worked two or more jobs, unable to monitor their insulin levels regularly or compute a daily step count. There was no affordable diabetes drug to prescribe.

"Those patients in the clinic had so many stresses and complications related to diabetes, including blindness, plus a lot of economic challenges," recalls Dr. Schmidt, the Dr. Iven Young Professor of Endocrinology and Professor of Medicine, Biochemistry and Molecular Pharmacology, and Pathology at NYU School of Medicine. "Those patients are the ones I think about on a daily basis. They're the reason I keep pushing ahead with my research, trying to give back, to find a better solution."
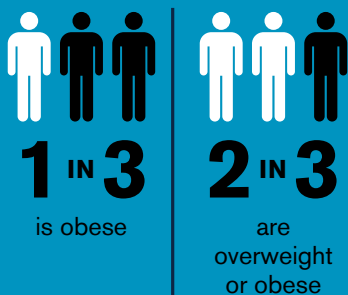
FOLLOWING THE SCIENCE

A world-renowned diabetes researcher, Dr. Schmidt has dedicated her life to medical science. She earned her BA in biology and history from NYU, and she is a graduate of the NYU School of Medicine, where she also completed her medical re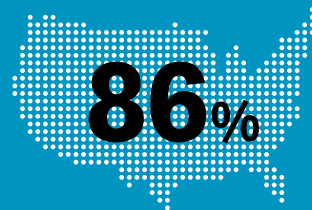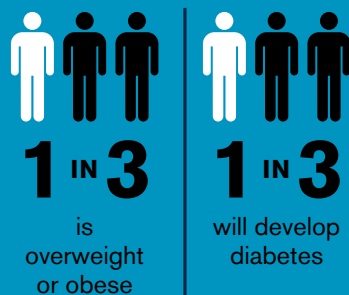sidency and a fellowship in hematology and medical oncology. Her Bellevue experience has shaped her career and her professional focus.

After completing her fellowship, she spent nearly two decades in academia at Columbia University—where she discovered the protein called RAGE (receptor for advanced glycation end products) that has proven to promote inflammation and to be a key player in diabetic complications. Dr. Schmidt found that giving

> ## "WHEN IT COMES TO COMPLEX DISEASES LIKE OBESITY, TRANSFORMATIVE THINGS TAKE TIME."
>
> Ann Marie Schmidt '83

A nurse teaching a patient how to use an insulin pump without tubing, managed with an electronic control unit

mice a RAGE inhibitor or genetically deleting the animals' receptor protected them from diabetic complications. The animals had less atherosclerosis and considerably less nerve, retinal, and kidney damage.

"It was a wonderful example of what I continue to tell people in the lab: Just follow the science," Dr. Schmidt says.

Today, while still steering NYU's diabetes research program, Dr. Schmidt is expanding her scope to help stop one of the most dangerous and complex epidemics facing humanity: obesity. Over the past year, she and a multidisciplinary team of physicians, scientists, and economists at NYU Langone have been collaborating on a project they believe can result in novel therapeutic interventions and prevention.

OBESITY'S HARSH REALITY

Obesity plays a role in 86 percent of annual healthcare spending, according to a recent report from McKinsey. Two-thirds of adults in the U.S. are overweight or obese, and one out of three children will develop diabetes. Half of the world's population is projected to be overweight by 2030. At $2 trillion a year, obesity has roughly the same economic impact as smoking or armed conflict.

NYU Langone is committed to changing this harsh reality, and has been recruiting faculty who prioritize innovation and collaboration. In March 2017, in recognition of NYU's efforts, the American Heart Association (AHA) awarded a $4 million grant to Dr. Schmidt's research lab, "NYU IGNITION" (InvestiGating Novel obesIty soluTIONs), with support from the recently launched NYU Comprehensive Program on Obesity, to evaluate the anti-obesity effects of blocking RAGE. The initiative, which makes NYU part of the national AHA Obesity Research Network, is breaking new ground by bringing together faculty spanning basic science, clinical medicine, and population health.

Leading the basic science research team, Dr. Schmidt is studying new models in mice to determine the role of RAGE-dependent inflammation and adipocyte (fat cell) biology in energy expenditure and weight loss.

"We've already discovered that mice that have no RAGE whatsoever are largely protected from high fat diet–induced obesity," Dr. Schmidt says. "When they eat high-fat food, unlike their RAGE-expressing counterparts, they do not become obese. So, we believe that if we antagonize the receptor pharmacologically, we might be able to improve the metabolic effects. Right now, we're doing our tests in mice, but we're optimistic that this will ultimately also work with people."

To begin making those human connections, Ira J. Goldberg, MD, director of the NYU Division of Endocrinology, Diabetes, and Metabolism, and the center's deputy director, along with Jose Aleman, MD, PhD, assistant professor of medicine, will manage IGNITION's clinical team. Their groups will assess the involvement of the RAGE signaling pathway as well as novel, yet-to-be-identified pathways, and perform an unbiased analysis to determine the inflammatory pathways activated within people who are obese, and how these are changed with surgical and dietary weight reduction.

A COMPREHENSIVE PLAN

NYU IGNITION's comprehensive scope will be rounded out by the work of Mary Ann Sevick, ScD, professor of population health and co-investigator with Eran Segal, PhD, of the Weizmann Institute in Israel. In a community-based clinical trial, Drs. Sevick and Segal will compare two behavioral weight loss interventions delivered using mobile technology: a one-size-fits-all calorie- and fat-restricted

Photo: BSIP SA / Alamy

diet, versus a calorie-restricted diet plus personalized feedback to reduce glycemic response to meals. In addition to the projects led by Drs. Schmidt, Goldberg, and Sevick, the research plan will contain a rigorous training program, overseen by Ira Goldberg, MD, leader of the clinical project in the AHA Center and director of the division of endocrinology, diabetes, and metabolism at NYU.

The Comprehensive Program on Obesity, led by Associate Professors of Medicine and Population Health Brian Elbel, PhD, MPH, director of the program, and Melanie Jay '00, co-director of the program, also plays a significant role in the AHA project. The program, which launched in September 2016, was spearheaded by Dafna Bar-Sagi, PhD, senior vice president and vice dean for science, chief scientific officer at NYU Langone, to integrate multidisciplinary research, including data science, with the hope of preventing and curing obesity within one generation.

"Such large, synergistic, institution-wide collaborations help further establish NYU Langone as a center of true excellence in the fight against obesity," says Dr. Bar-Sagi. "We're taking scientific discovery from the lab bench all the way to affected communities."

The core mission of the Comprehensive Program on Obesity is to discover treatments that target each patient's unique biology; to develop methods and strategies that can help stop obesity in its earliest stages; and to pioneer solutions that can scale up to reach entire communities. NYU Langone is home to the first program on obesity in the United States that intertwines breakthroughs in basic science, clinical interventions, and population health through a new initiative called DataBridge.

"There are physiological, psychological, and environmental reasons for obesity," Dr. Jay says, "and they all interact. It's clear that we need intentional collaboration to make

leaps and bounds in terms of how we're going to deal with this epidemic."

Dr. Jay, an expert in obesity-related health services research and collaborative science, studied behavioral science as an undergraduate at the University of Pennsylvania and then focused on primary care at NYU School of Medicine. She stayed on for her residency, during which time she founded a weight management clinic at Gouverneur Hospital that continues today at Bellevue, and has since extended her career at NYU.

One of her most recent collaborative research projects is a longitudinal study of bariatric surgery outcomes, which she is leading in partnership with Dr. Schmidt; Christine Ren-Fielding, MD, chief of bariatric surgery; and Dr. Segal. This study, which is currently enrolling patients at Tisch Hospital and Bellevue Hospital, will offer a unique opportunity to investigate how environmental factors, interactions with the microbiome, and other variables affect the dramatic weight loss prompted by bariatric surgery.

INCENTIVIZING PATIENTS

"I've learned a lot about basic science from Dr. Schmidt," Dr. Jay says. "If new drugs can be discovered through NYU's work on obesity, it is a fact that such drugs can help only those who have access to it. My research tends to be about how we get a treatment or a solution to as many people as possible, and how they can use it in the most effective way."

In addition to co-directing research through the Comprehensive Program on Obesity, Dr. Jay still sees patients once a week at the Veterans Affairs (VA) Medical Center and runs a lab called MOTIVATE (Managing Obesity Through InnoVATion and Effectiveness), where the focus of her research is on how to improve the treatment and prevention of obesity in primary care settings.

"OUR COMMITMENT TO MENTORSHIP AND TO BRINGING PEOPLE TOGETHER IS HOW WE INCREASE THE ODDS OF MAKING IMPORTANT DISCOVERIES."

Melanie Jay '00

Above: Dr. Jay with the MOTIVATE lab's research team

NYU SCHOOL OF MEDICINE CONDUCTS OBESITY STUDY IN ABU DHABI

DR. SCHMIDT HAS TRAVELED to the emirate of Abu Dhabi more than 20 times over the past eight years. She has been part of a research team that is testing RAGE hypotheses in clinical samples and using epidemiology to understand why in one generation people have become more substantially obese and insulin-resistant.

This is the first mechanism-seeking study on the biochemical and molecular risk factors that contribute to the pathogenesis of obesity, metabolic dysfunction, and diabetes in citizens of Abu Dhabi. The ultimate goal is to develop and prospectively study a large cohort of subjects, with the target set at 20,000 citizens between the ages of 18 and 40, by 2020, to identify risk factors and propose novel targets for therapeutic intervention in Abu Dhabi. Already, more than 5,000 participants have been enrolled and monitored.

"WE REALLY NEED THE VARIOUS PLAYERS—AND THEIR DATA—TO TALK TO EACH OTHER."

Brian Elbel, PhD, MPH

Her current studies on health services include "Goals for Eating and Moving (GEM)," which examines technology-centered health coaching interventions; "Peer Assisted Lifestyle and Weight Management Study (PAL)," which adds peer coaches to primary care teams; and "Financial Incentives for Weight Reduction (FIreWoRk) Study," in partnership with Joseph Ladapo, MD, PhD, at UCLA, which compares goal-directed financial incentives to outcome-directed financial incentives for low-income primary care patients with obesity.

"All the patients in the financial incentives study receive resources," Dr. Jay explains. "They all get free Weight Watchers memberships, a Fitbit, and a scale. We teach them how to self-monitor their diet and increase physical activity, and we provide brief counseling about ways to improve their lifestyle. That's the baseline. Participants in a process-based group are also paid for participating in the program and doing their own self-monitoring. And finally, in the outcomes-based group, people get paid for losing weight. We're trying to see if it's better to incentivize the process or the outcome, or if it matters to incentivize people at all."

Throughout all her research, Dr. Jay likes to involve students and residents from NYU School of Medicine. This year, she has 22 interns who volunteer approximately 15 hours a week in her MOTIVATE lab, some of whom train to become health coaches, as well as post-docs, graduate-level researchers, and junior faculty. She is also working with Dr. Holly Lofton to start an obesity medicine fellowship.

"In science," says Dr. Jay, "I believe that the best way to have a lasting impact is to inspire other people. I've been very lucky to have my own mentors at NYU, and now my students make me incredibly proud. I think that's one of our most important traditions at NYU School of Medicine: Our commitment to mentorship and to bringing people together is how we increase the odds of making important discoveries."

TACKLING TECHNOLOGY: DATABRIDGE

Dr. Elbel, who serves as director of the Comprehensive Program on Obesity, is tackling another critical part of 21st-century science. As part of the program, he is managing an institution-wide initiative at NYU Langone Health called DataBridge, a powerful big-data platform that integrates data from basic science, clinical medicine, and population health research. Soon, investigators will be able to look at large amounts of data—from biological samples, clinical studies, and environmental research—in order to address long-standing questions from completely new perspectives using advanced machine learning and other techniques.

"Data is at the core of what most scientists do," Dr. Elbel says. "They collect it, they analyze it, they draw inferences from it. But in many cases, different groups or silos or disciplines think about data in their own way. That doesn't work when you're trying to solve a problem like obesity, which is big and multifaceted and determined by multiple factors. In this case, we really need the various players—and their data—to talk to each other."

The first project to utilize DataBridge is a pediatric obesity study that will draw on the electronic health records of more than 52,000 children from NYU Langone Hospital–Brooklyn to create a series of models predicting which children will be affected by childhood obesity. Understanding the broader predictors early in life—perhaps in children as young as 5—can help scientists learn how to prevent and better treat obesity.

Photo: Richard Splash / Alamy

"Even with just 500 subjects in our pilot study," Dr. Schmidt says, "we were able to attract males and females in all the different decades, and we saw predictive levels of our soluble RAGEs that suggest who's going to be more insulin resistant and have more tendency toward diabetes. This project has immediate public health interest, and hopefully it will result in long-term public interest assistance."

The conditions in Abu Dhabi are increasingly dire, as diets and lifestyles have changed significantly. According to research from the American Diabetes Association, 44 percent of the emirate's population has either pre-diabetes or diabetes. Without intervention, 41 percent of the pre-diabetes population will convert to diabetes in five years. Recent prevalence rates of obesity and being overweight in Abu Dhabi were 35 percent and 32 percent, respectively; 57 percent had central obesity. Although similar rates apply in the United States, the population of Abu Dhabi is much younger.

"Our work began in diabetic complications," Dr. Schmidt says, "but we soon learned that the biology of this receptor puts it square in the face of the development of obesity as well, which is a major risk factor for type 2 diabetes. This is a global public health epidemic that we're trying to stop."

By ultimately linking data on public school students—for example, their obesity rates and their environment, along with their health records from NYU Langone Hospital–Brooklyn—plus the soluble RAGE measurements that Dr. Schmidt is collecting and the clinical interventions that Dr. Jay is studying, scientists may be able to make groundbreaking new discoveries.

"Our vision," Dr. Elbel explains, "is to think about DataBridge as a model for how such work can be adopted at an institutional level."

Outside his work on DataBridge, Dr. Elbel—who joined the NYU Langone faculty in 2007 after receiving his PhD in health policy from Yale—has focused his own behavioral economics research in two areas: how people make decisions about their health, and how public policy and the environment affect obesity and related chronic diseases. He also uses statistical and econometric methods and diverse data sources to inform policy and science on obesity prevention.

"NYU recognizes that a broad, collaborative approach is the best way [forward]," Dr. Elbel says. "We have great depth in related research areas. We have a very broad clinical network that we are increasingly tapping into. On top of all that, we're using our strengths in data and technology to make a sustained impact."

In less than two years, the Comprehensive Program on Obesity has made great strides in fostering team science. Looking ahead, DataBridge will help take the science even farther, helping to better predict outcomes in a wide array of research areas, including, for instance, which patients might do better with self-achieved weight loss, which with bariatric surgery, and which with orthopedic surgery.
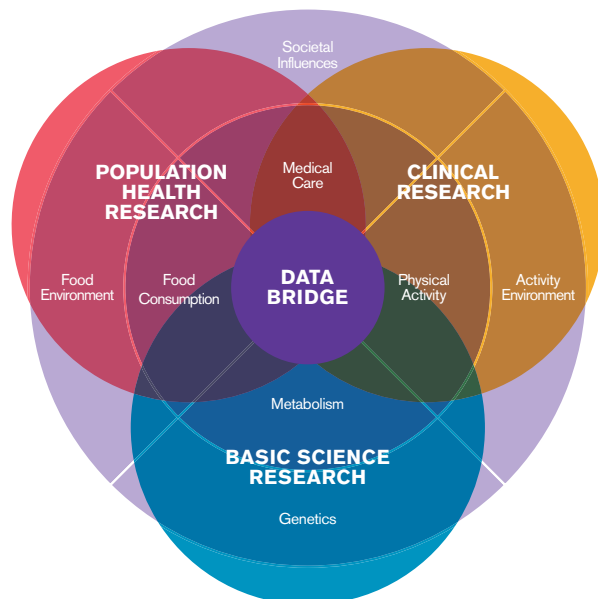
"Science is hard," Dr. Schmidt admits. "When it comes to complex diseases like obesity, transformative things take time. So what I try to do every day is remember the patients, work toward my goals, and think creatively with our team."

JOIN US

This fall, NYU Langone will host its inaugural Obesity Summit, a symposium for the scientific and clinical community as well as the general public.

Learn more:
med.nyu.edu/research/obesity/comprehensive-program-obesity

Societal Influences
POPULATION HEALTH RESEARCH
Medical Care
CLINICAL RESEARCH
Food Environment
Food Consumption
DATA BRIDGE
Physical Activity
Activity Environment
Metabolism
BASIC SCIENCE RESEARCH
Genetics

DataBridge
This visual illustrates the scope of a new big-data platform, which will integrate research from three key spheres to account for the influence of many factors related to obesity and diabetes.

Credit: NYU Langone Comprehensive Program on Obesity