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The Dr. Henry D. Janowitz Division of Gastroenterology

INCLUDING GI SURGERY

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Endoscopic Surgery Speeds Healing In Esophageal and Gastric Cases

Aleksander Nika was concerned. The 50-year-old Rockland County, New York, resident had just returned from visiting a sister in Italy who has colon cancer when he began experiencing an episode of gastrointestinal bleeding. He made an appointment with his doctor, got a referral to a local cancer specialist, and underwent a series of tests, which culminated in an endoscopic ultrasound that revealed an early-stage gastric cancer.

Mr. Nika knew the cancer would have to be removed, but traditional surgery would be long, painful, and likely result in the removal of half of his stomach. "My primary care and cancer doctors told me about the Surgical Endoscopy Program at The Mount Sinai Hospital," he says, "so I decided to look into it."

Launched in August 2016, the Program specializes in minimally invasive, incisionless endoscopic procedures that

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Bruce E. Sands, MD, MS

At the Mount Sinai Health System's Division of Gastroenterology, we are pursuing a broad array of initiatives with a central focus on translational research that will lead to advances in care for gastrointestinal and liver diseases.

Our COMPASS IBD program is a great example: an innovative care model that provides early intervention and personalized treatment plans for ulcerative colitis and Crohn's disease patients. We aim to keep patients on track for controlling their disease while we gain a greater understanding of the factors that govern response to particular drugs. On another Crohn's-related front, we recently led an international clinical trial suggesting that a new anti-interleukin-23 antibody could be an effective treatment for the condition.

Nonalcoholic steatohepatitis (NASH), the most troublesome form of nonalcoholic fatty liver disease, is increasing at a rapid rate in the United States. Mount Sinai's Division of Liver Diseases is now focusing on NASH, to develop both awareness of and new therapies for this long underappreciated condition.

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In our cover story, you will read about our advances in endoscopic surgery that allow minimally invasive, incisionless treatments for conditions of the esophagus and stomach, including achalasia and gastric cancer. We are also developing a center of excellence in gastrointestinal motility disorders, including Barrett's esophagus, which will offer innovative technology for imaging and treatment.

Researchers from Mount Sinai and elsewhere are now making progress in discovering the mechanisms by which the gut microbiome shapes health and disease. This growing understanding may soon allow manipulation of the microbiome for therapeutic treatments.

Finally, we pay tribute to Mark W. Babyatsky, MD, a mentor to many in medicine and gastroenterology, in whose honor a new lecture series has been established. Dr. Babyatsky embodied our commitment to excellence in gastroenterology and medical education, a tradition the Icahn School of Medicine at Mount Sinai—now celebrating its 50th anniversary—aims to carry on into the future. ■

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ENDOSCOPIC SURGERY SPEEDS HEALING

are making a positive difference in the treatment and recovery of patients with gastrointestinal conditions.

"Our goal is to provide world-class care at the forefront of innovation," says Nikhil A. Kumta, MD, MS, an Assistant Professor of Medicine (Gastroenterology) at the Icahn School of Medicine at Mount Sinai and founder and Director of the Program. "There are only a handful of dedicated centers nationwide that have the expertise and training to perform these endoscopic procedures."

Dr. Kumta typically performs two types of surgical endoscopy procedures. One, peroral endoscopic myotomy (POEM), is used to treat achalasia—a condition in which the lower esophageal sphincter remains tight and fails to relax, preventing food from passing into the stomach. Using an endoscope and an electrosurgical knife, Dr. Kumta creates a tunnel within the layers of the esophagus, enabling him to cut the muscle fibers of the lower esophageal sphincter and significantly enhance the patient's ability to swallow.

The other procedure, which Dr. Kumta used to resect Mr. Nika's early-stage gastric cancer, is endoscopic submucosal dissection (ESD). In this technique, Dr. Kumta marks the perimeter of the tumor with cautery, injects a solution into the submucosa to lift the tumor away from the deeper layers of the gastrointestinal tract wall, and then resects the tumor in one complete piece using an electrosurgical knife.

"Our mindset is similar to that of a surgical oncologist," Dr. Kumta says. "The goals that we have are to remove the cancer with negative lateral and vertical margins, and to remove it en bloc. Based on the literature, the R0 resection rate is approximately 95 percent, and en bloc resection rate is also approximately 95 percent."

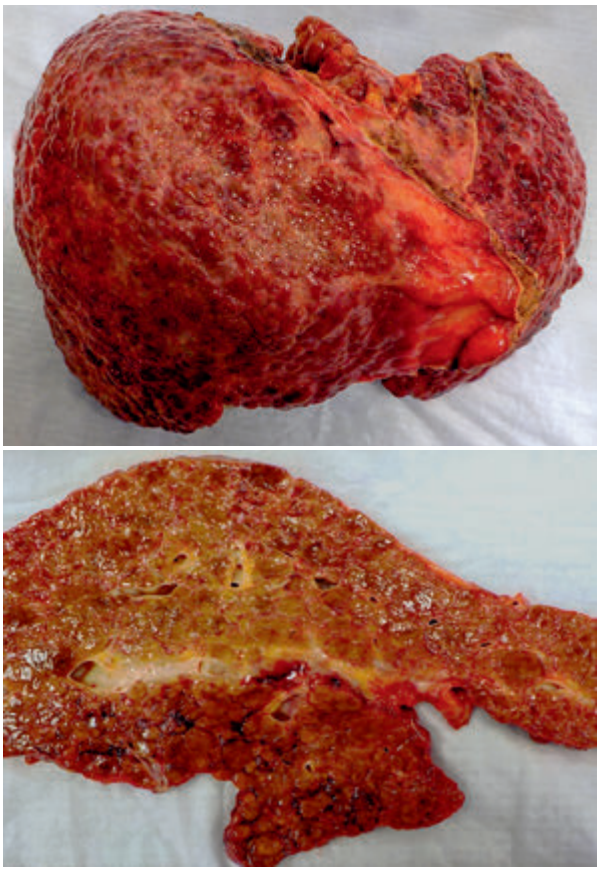
Dr. Kumta was able to remove Mr. Nika's gastric cancer in one piece in just 90 minutes. "Our pathology department confirmed that we had fully removed his gastric adenocarcinoma, staged pT1a, with negative lateral and vertical margins, and no evidence of lymphovascular invasion," he says. Mr. Nika, who said he felt no pain after the surgery, was discharged from the hospital the next day and given a proton pump inhibitor and a course of antibiotics.

Mr. Nika experienced a curative endoscopic resection without the need for invasive surgery and is now undergoing gastric cancer surveillance. "This is the type of successful outcome we strive to achieve for all of our surgical endoscopy patients," Dr. Kumta says. ■

IN THIS ISSUE

Hepatology's Next Challenge: NASH

As the obesity epidemic continues to grow nationwide, so too has the incidence of related diseases such as nonalcoholic fatty liver disease (NAFLD). Estimates suggest that nearly one-third of all Americans have some form of fat in their livers, and as many as one-third of that population have the most worrisome form of NAFLD—nonalcoholic steatohepatitis (NASH), or liver inflammation and damage caused by fat buildup. Left unchecked, the disease may progress to a state of advanced scarring or cirrhosis, and also significantly increase the risk of primary liver cancer.



A liver with nonalcoholic steatohepatitis (NASH)-induced cirrhosis. Approximately 20 million to 35 million Americans have NASH, and the number is growing.

"There are approximately 20 million to 35 million Americans who have NASH," says Scott L. Friedman, MD, Dean for Therapeutic Discovery and Irene and Dr. Arthur M. Fishberg Professor of Medicine and Liver Diseases at the Icahn School of Medicine at Mount Sinai. "The likelihood is that, within three years, NASH will supplant hepatitis C as the most common indication for liver transplantation."

Long underappreciated and underdiagnosed, in part because patients often exhibit no specific symptoms that indicate liver disease (that is, no pain or jaundice), NASH is emerging as a primary focus of study and investment as the prevalence rate grows. Dr. Friedman has been at the forefront of those efforts as a researcher and pharmaceutical consultant. Now he is launching a new multidisciplinary working group that brings together the considerable resources of the Mount Sinai Health System and of external stakeholders to advance the understanding, diagnosis, and treatment of NASH.

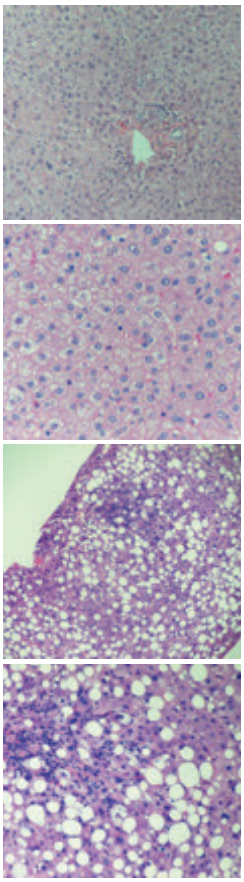
"This is an effort to link all the strengths across the campus and throughout the health system so we can establish standards for diagnosing and treating NASH," Dr. Friedman says. "We also want to play a lead role in defining new therapies and offering them to our patients as quickly as possible, either through clinical trials or effective medications once they are approved, because there are currently no therapies approved for the treatment of NASH."

In support of that effort, the working group has recruited Amon Asgharpour, MD, an Assistant Professor of Medicine and Liver Diseases at the Icahn School of Medicine. Formerly a gastroenterologist at Virginia Commonwealth University, where he trained under renowned expert Arun Sanyal, MD, Dr. Asgharpour is working with colleagues across the Mount Sinai Health System to raise awareness about NASH and identify patients to participate in clinical trials.

Dr. Asgharpour is currently visiting the Mount Sinai Diabetes Center on Fridays to see patients and risk-stratify them, "because we know that patients with diabetes are more likely to have NAFLD," he says. "We have also started screening for liver disease patients participating in the Weight and Metabolism Management Program at Mount Sinai St. Luke's, and we are providing them with strategies for weight loss. If we can help these patients lose weight, they can reduce the amount of fat and scarring in their livers and thus reduce their risk of developing potential complications from NASH."

Many other collaborative initiatives are currently being discussed by the working group, ranging from researching the link between pathogenesis and fibrosis in liver adipose tissue to engaging the Mount Sinai Liver Cancer Clinical Program to better understand the risk of liver cancer among NASH patients. In the meantime, Dr. Friedman says, the working group's immediate goals are to further consolidate collaborations, generate the data necessary for extramural funding applications that enable clinical trials, and share best practices for diagnosing and treating NASH.

"It's going to be a very fertile time for generating ideas and establishing links across the various disciplines that are concerned about this disease," Dr. Friedman says. "Based on the unmet need, the commitment of leadership at Mount Sinai Health System to initiatives such as this, and my own capacity to engage stakeholders, I am optimistic about the outcomes we can achieve." ■



Standard hematoxylin and eosin-stained liver sections viewed by light microscopy; from top, a normal liver seen at normal and high power, and a NASH liver at normal and high power.

Anabella Castillo, RN, MPH (left), and Ryan Ungaro, MD, are helping newly diagnosed IBD patients like Yvette Johnson manage their disease.

New IBD Patients Get Needed Support

As consensus grows that early intervention is crucial for improved long-term outcomes in inflammatory bowel disease (IBD), The Susan and Leonard Feinstein Inflammatory Bowel Disease Clinical Center at The Mount Sinai Hospital is launching a new program to help recently diagnosed IBD patients manage the disease.

Early intervention is crucial for improved long-term outcomes.

The COMPASS-IBD (**Com**prehensive Care for **P**atients with Recently Di**a**gnosed Inflammatory Bowel Di**s**ea**s**e) program connects patients who have received a diagnosis of Crohn's disease or ulcerative colitis within the last 12 months with patient-centered, comprehensive personalized care. Ryan Ungaro, MD, Assistant Professor of Medicine (Gastroenterology) at the Icahn School of Medicine at Mount Sinai, says the goal is to support each patient in controlling the course of the disease.

"We know that we can treat patients more effectively if we can engage them earlier in the course of the disease," says Dr. Ungaro, who serves as Director of the program. "By taking a multidisciplinary approach, we can ensure that they are getting optimal care right from the start."

Dr. Ungaro says program participants can be referred internally, externally, or through self-referral. Each participant first undergoes a half-day multidisciplinary evaluation involving a gastroenterologist, the nutritional team, the behavioral health team, and a clinical pharmacologist. Care coordinators then gather team recommendations and prepare a personalized disease-management plan for each patient within one week of the evaluation. Coordinators also perform annual health-maintenance reviews with patients to assess vaccination status and other health issues.

"The overarching goal is to provide a tailor-made, personalized care plan for each patient so he or she stays on track in controlling IBD," Dr. Ungaro says. "Patients can continue receiving care with us or through their referring gastroenterologists. Our care coordinators will regularly follow up with patients who are not receiving care from us to see how they are doing and then intervene if there is any change in their disease course. We will also offer an assessment of each patient's prognosis and risk stratification for disease complications."

Over the coming months, Dr. Ungaro and his colleagues will focus on raising awareness about the program among gastroenterologists and patients throughout the tristate area and will gather patient feedback to ensure that the program meets their requirements.

"We want the program to continually deliver the support and knowledge patients want, so they can feel confident that they're making the right decisions and taking the right actions with their IBD care," Dr. Ungaro says. ■

New Antibody Studied in Crohn's Disease

An international clinical trial suggests that a new anti-interleukin-23 (IL-23) antibody could be an effective treatment for patients with Crohn's disease.

Overseen by Bruce Sands, MD, the Dr. Burrill B. Crohn Professor of Medicine and Chief of the Dr. Henry D. Janowitz Division of Gastroenterology at the Icahn School of Medicine at Mount Sinai, the phase II trial involved MEDI2070 (brazikumab), an antibody developed by MedImmune that targets the P19 subunit of IL-23.

"For a long time, medical literature suggested that IL-23 would be an important target for treatment of inflammatory bowel diseases such as Crohn's disease," Dr. Sands says. "This antibody binds to P19, a component of IL-23, and thereby helps clear the cytokine and reduce inflammation."

The 119 patients participating in the 10-week, double-blind portion of the clinical trial had been receiving tumor necrosis factor (TNF) antagonists but were failing in their treatments. Approximately half received 700 mg of MEDI2070 intravenously at weeks zero and four, and the rest received a placebo. Response rates measured at weeks 8 and 10 revealed that 49.2 percent of treatment patients achieved a clinical response, compared to 26.7 percent of placebo patients. Moreover, 42.4 percent of treatment patients experienced at least a 50 percent decrease in inflammation biomarkers (fecal calprotectin or C-reactive protein) compared to 10 percent of patients receiving the placebo.

"This was considered a very promising result, considering how sick these patients were and the fact that all had failed anti-TNF antibody therapy," Dr. Sands says.

Dr. Sands says there is one additional finding of the phase II trial that could lead to improved outcomes: patients with higher-than-average levels of interleukin-22 (IL-22) were more likely than participants with lower-than-average levels to respond to treatment.

"Unlike in cancer therapy, we have not identified many biomarkers that can predict response to a drug in this field," Dr. Sands says. "I'm really interested in the possibility that these findings might lead to a blood test that will help us determine which patients would respond to this particular treatment." ■

A trial finds both a potential new treatment and a biomarker that may predict response.

Lecture Series Honors Mark W. Babyatsky, MD

When Bruce Sands, MD, recalls his close friend and colleague Mark W. Babyatsky, MD, he marvels at Dr. Babyatsky's unique ability to connect with just about everyone he met.

"It was almost instantaneous," says Dr. Sands, the Dr. Burrill B. Crohn Professor of Medicine and Chief of the Dr. Henry D. Janowitz Division of Gastroenterology at the Icahn School of Medicine at Mount Sinai. "You can imagine how useful that was, particularly for a consummate medical educator as he was."

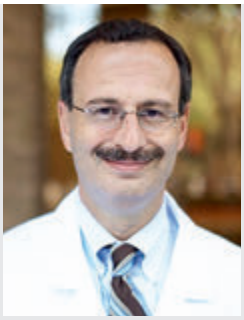
Dr. Babyatsky, whose roles at Mount Sinai included Vice Chair for Education and Director of the Internal Medicine Residency Program, passed away in 2014, leaving behind a remarkable legacy of educational leadership and research that ranged from promoting the careers of more than 400 residents to advancing understanding of gastrointestinal mucosal repair. To honor that legacy, the Mount Sinai Health System launched the Dr. Mark W. Babyatsky Memorial Lecture series in fall 2017.

The inaugural presentation, "Colon Cancer Screening: From Molecular Genetics to Health Equity," was delivered by Steven Itzkowitz, MD, Professor of Medicine (Gastroenterology) and Oncological Sciences and Director of the Gastroenterology Fellowship Program at the Icahn School of Medicine.

Dr. Itzkowitz discussed advances in developing molecular colon cancer tests that can detect colon cancer and precancerous polyps by analyzing stool DNA markers. He shared positive results from a multicenter clinical trial, for which he was a lead investigator, that explored the efficacy of a multitarget marker panel that included seven mutations of the KRAS gene and two methylated genes—NDRG4 and BMP3—along with a fecal immunochemical test (FIT)-DNA.

Dr. Itzkowitz also highlighted a citywide initiative addressing racial disparities in colon cancer screening that increased screening adherence from 42 percent in 2003 to 69 percent in 2013 among New York residents 50 and older. (A video of the Babyatsky Lecture is at icahn.mssm.edu/babyatskylecture.)

Dr. Itzkowitz says it was an honor to deliver the first in what is planned to be an annual series honoring Dr. Babyatsky. "It was an opportunity to pay homage to my dear friend and his work, and I hope future presentations will reflect his passion for advancing medical education, science, and ethics." ■



An annual lecture series will honor Dr. Babyatsky, a mentor to many in gastroenterology.

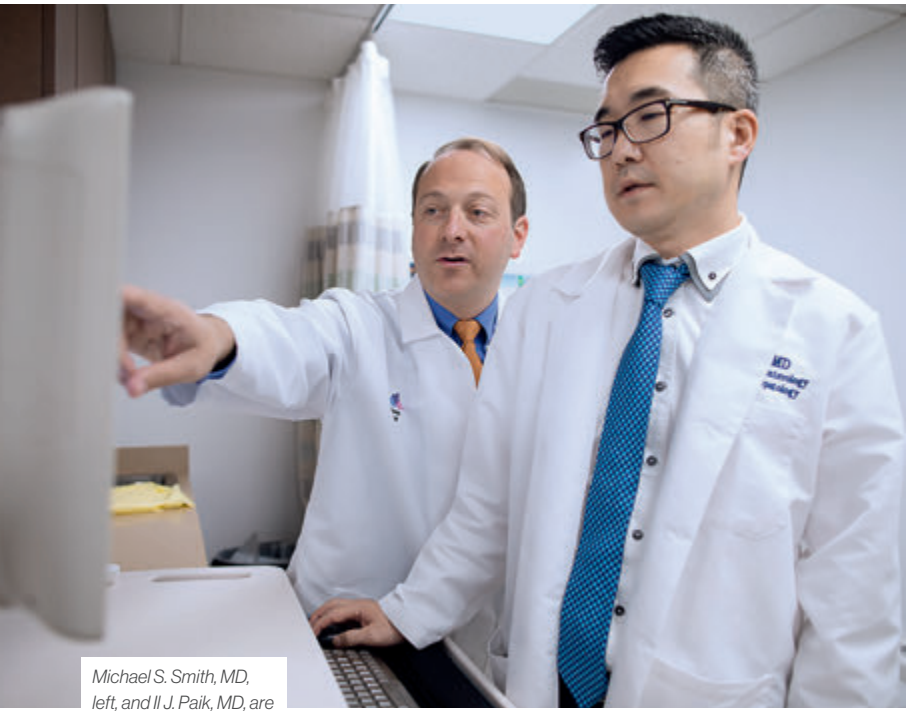
Esophageal and Motility Centers for Innovation

The Mount Sinai Health System is developing centers of excellence for both esophageal and gastrointestinal motility disorders under the direction of Michael S. Smith, MD, MBA, the newly recruited Chief of Gastroenterology and Hepatology at Mount Sinai St. Luke's and Mount Sinai West.

A technology-driven approach to managing GERD, Barrett's esophagus, swallowing disorders, IBS, and more

The esophageal and motility centers, which will reside primarily at Mount Sinai West, will consolidate the expertise and services of Mount Sinai while enhancing the academic and research missions of the faculty at Mount Sinai West. They will take a highly innovative, technology-driven approach to the management of conditions ranging from gastroesophageal reflux disease (GERD), Barrett's esophagus, and esophageal cancer to swallowing disorders, gastroparesis, irritable bowel syndrome, chronic constipation, and pelvic-floor dysfunction.

"No matter the presenting symptoms or findings, the goal is to look at each patient's unique situation and deliver an individualized plan of care that draws on innovative practices and technologies that lead to a successful outcome," Dr. Smith says.



Michael S. Smith, MD, left, and Il J. Paik, MD, are leading Mount Sinai's innovation initiatives in the treatment of esophageal and gastrointestinal motility disorders.

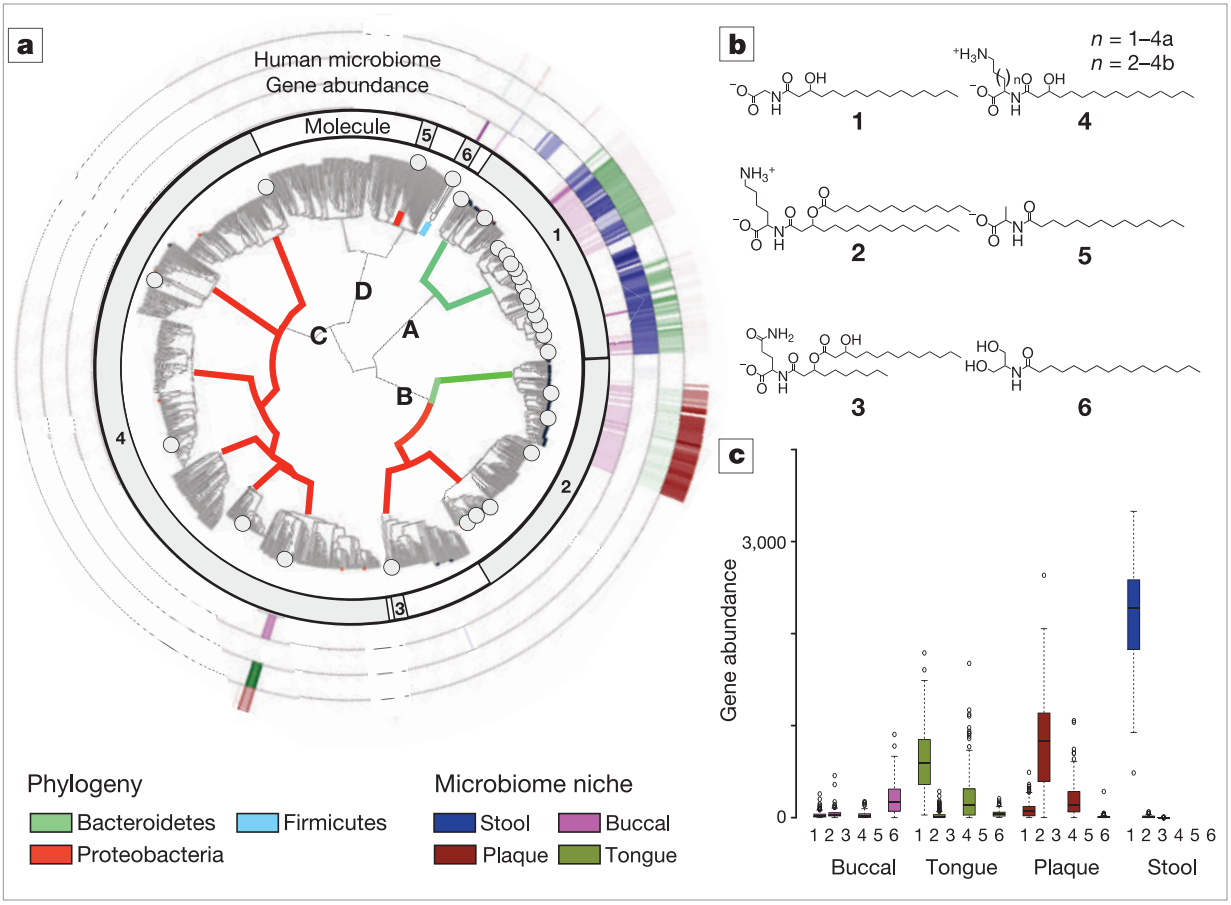
As part of the Mount Sinai team, Dr. Smith will bring his expertise with the latest technologies to manage Barrett's esophagus and esophageal cancer. One diagnostic tool he will use, volumetric laser endomicroscopy, or VLE, employs a laser to scan the esophageal wall to look for early signs of cancer. In just 90 seconds, it can evaluate a 6 cm segment of esophagus to a resolution of 7 microns and a depth of 3 mm—a combination other imaging techniques cannot provide. Dr. Smith has led a nationwide 1,000-patient study evaluating this technology.

Dr. Smith also is Principal Investigator for a study of nearly 13,000 patients whose esophagi were evaluated using wide-area transepithelial sampling (WATS)—a brush-based technique to sample for Barrett's esophagus, dysplasia, and cancer. "WATS was able to detect over 150 percent more of Barrett's esophagus and over 240 percent more dysplasia and cancer than standard forceps biopsies," Dr. Smith says. "These results are promising, and now, as national Co-Principal Investigator on a related 10-year study, I'm evaluating the longitudinal benefits of this technology."

To eradicate Barrett's esophagus and esophageal cancer, Dr. Smith brings extensive experience with both radio-frequency ablation and cryotherapy. He was the first physician in the world to utilize the truFreeze® liquid nitrogen spray cryotherapy system in the esophagus, a device that treats Barrett's esophagus, cancer, and other esophageal diseases. He also performs balloon-based cryotherapy using liquid nitrous oxide to remove precancerous tissue.

For the management of GERD, Dr. Smith works closely with his surgical partner Faiz Y. Bhora, MD, Chief of Thoracic Surgery at Mount Sinai West and Mount Sinai St. Luke's, to offer both traditional surgical fundoplication and transoral incisionless fundoplication, an endoscopic approach to reconstructing the antireflux valve, as well as magnetic lower esophageal sphincter augmentation using the LINX® system. According to Dr. Smith, the centers will make the most of Mount Sinai's outstanding West Side faculty, including Dr. Bhora and Il J. Paik, MD, a highly trained expert in gastrointestinal motility who is the Director of the Mount Sinai Doctors GI Motility Center.

Dr. Smith earned his medical degree from the University of Pennsylvania and his MBA from its Wharton School of Business. He then stayed for his internal medicine residency at the Hospital of the University of Pennsylvania. During his gastroenterology fellowship at NewYork-Presbyterian/Columbia Medical Center, Dr. Smith was mentored by Charles Lightdale, MD, a pioneer in the field of endoscopic management of Barrett's esophagus. Prior to joining Mount Sinai, Dr. Smith served as Medical Director of the Esophageal Program at Temple University Hospital in Philadelphia, where his clinical practice and research focused on how best to incorporate new techniques and strategies into both the diagnostic and therapeutic aspects of managing esophageal disorders. ■



Phylogenetic tree of N-acyl genes from PFAM13444. hm-NAS genes have a dot at the branch tip. Large grey dots mark genes that produced N-acyl amides. Illustration credit: Nature

New Insights Into How Microbiome Affects Health

A joint study by Mount Sinai and The Rockefeller University offers new insights into how bacteria living in the human microbiome affect human health—findings that could lead to genetic therapies for microbiome-related diseases.

Using a combination of bioinformatics and synthetic biology, Louis Cohen, MD, Assistant Professor of Medicine (Gastroenterology) at the Icahn School of Medicine at Mount Sinai, isolated N-acyl amides, a class of bacterial metabolites that interact with a wide range of G-protein-coupled receptors (GPCRs). These receptors regulate gastrointestinal-tract physiology related to immunity, inflammation, metabolism, and wound healing.

"Researchers have long hypothesized that bacteria living in the human microbiome play a key role in human health, but no one had quite identified the mechanisms that make this possible," Dr. Cohen says.

"We had determined in previous research that bacteria have the capacity to produce families of metabolites and then, based on small structural variations, these metabolites can target various human cellular functions. Using this lead, and a function-first approach, we were able to identify this one molecule as the mechanism."

Working in collaboration with Sean Brady, PhD, an Evnin Associate Professor and Tri-Institutional Associate Professor at The Rockefeller University, Dr. Cohen determined that the genes that encode for N-acyl amides are found in more than 80 percent of patient microbiome samples. Moreover, he found that the structures of these metabolites are virtually identical to the signaling molecules that human cells produce.

"This ability for the bacterial molecule to mimic human ones in both structure and function is something that, to the best of our knowledge, had not been identified before," Dr. Brady says. "It made sense because, when you look at how human cells perform the same type of tissue repair, they do so using a very simple molecule that is similar to these bacterial metabolites."

Based on these findings, which were published in the September 7, 2017, edition of *Nature*, Dr. Cohen says there is significant potential to develop biosynthetic gene-therapy treatments for a variety of diseases. For example, using mouse models, he was able to demonstrate that it is possible to regulate metabolic hormones such as GLP-1 and modify the host blood glucose by increasing the expression of N-acyl synthase genes.

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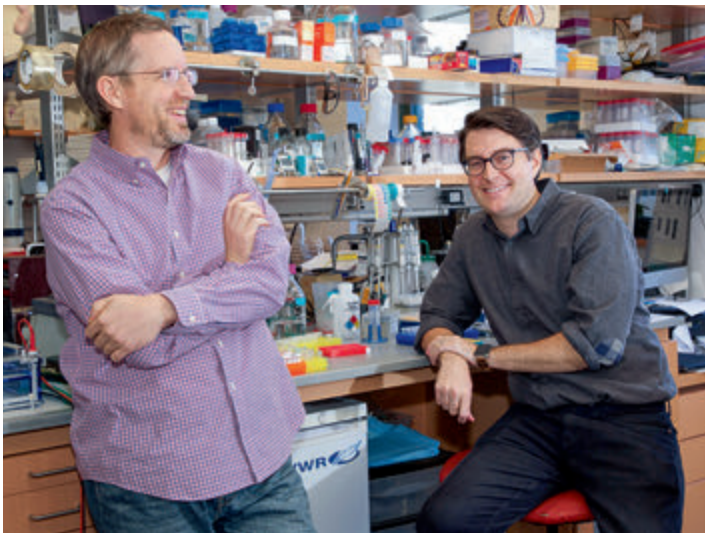

Sean Brady, PhD, left, and Louis Cohen, MD, have made important breakthroughs in understanding the mechanisms by which bacteria in the human microbiome affect human health.

"What we've demonstrated is that if you take bacteria, introduce these genes, and increase their expression, you can have a targeted impact on the host," Dr. Cohen says. "This means that the genes and the molecules they make could very well play a key role in the physiology of a range of diseases."

Dr. Cohen is particularly interested in studying the presence of these molecules in diseases associated with the human microbiome, such as obesity, diabetes, and inflammatory bowel disease, to see how they could be manipulated for therapeutic treatments. He also sees the potential to develop therapeutic treatments involving immune-system diseases.

"Some of these molecules target GPCRs that are very specific to the immune system and its function," Dr. Cohen notes. "It's difficult to make specific conclusions, but I think there is enough evidence here to suggest that we can use these bacteria and manipulate their normal functions to our advantage. As more researchers identify bacterial genes with interesting functions, we can think about how to manipulate them natively for therapeutic treatments." ■