NewYork-Presbyterian Advances
Gastroenterology and GI Surgery

2019 • Issue 1

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Research Highlights: Targeting Challenges in Digestive Disease

Each and every day, NewYork-Presbyterian researchers and clinician-scientists are advancing knowledge in virtually every medical specialty. At Weill Cornell Medicine and Columbia University Vagelos College of Physicians and Surgeons, faculty are targeting some of today's most formidable health challenges, pushing scientific discoveries forward and applying research breakthroughs to improving the lives of patients everywhere. In this issue of *Advances*, we share several of our recent investigations in digestive disease.

New Clinical Trial for Borderline Resectable Pancreatic Cancer

Pancreatic cancer is the third most common cause of cancer-related death in the U.S. In some cases, surgical removal of the pancreas is considered the only chance for cure, but many patients are not able to have surgery due to involvement of nearby blood vessels. Even after surgery some patients will redevelop cancer due to the growth and spreading of cancer cells both at the operative stage and once removed.

> The primary goal of the study is to see whether adding radiation therapy to an intensive chemotherapy regimen will improve the survival rate of patients with borderline resectable pancreatic cancer.

The Pancreas Center at NewYork-Presbyterian/Columbia University Irving Medical Center has partnered with the Alliance for Clinical Trials in Oncology, a national cooperative clinical trials group, in a new pre-operation clinical trial – Preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas.

National cooperative groups like the Alliance for Clinical Trials in Oncology develop and conduct clinical trials with promising new cancer therapies and utilize the best science to develop ideal treatment and prevention strategies for cancer, as well as research methods to lessen side effects.

Michael D. Kluger, MD, MPH, Medical Director of Surgical Oncology, and **David P. Horowitz, MD**, Department of Radiation Oncology, serve as site investigators at Columbia. The primary goal of the study is to see whether adding radiation therapy to an intensive chemotherapy regimen will improve the survival rate of patients with borderline resectable pancreatic cancer. While on the study, patients are randomized to receive one of two neoadjuvant chemotherapies (one arm has the addition of radiation) before intended surgical resection.

In previous studies at the Pancreas Center and elsewhere, investigators have seen positive outcomes when patients receive intensive chemotherapy prior to surgery. Their hope is that this study will benefit patients and provide new and improved options for anyone with pancreatic cancer.

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Introducing the Interstitium: A New Anatomical Structure

As **David L. Carr-Locke, MD**, sees it, the achievement that made international headlines – the identification of a previously unknown anatomical structure in the human body – harkens back to the medical discoveries of centuries past. "You'd think we had run out of things like that, because everything has been described," says Dr. Carr-Locke, Clinical Director of the Center for Advanced Digestive Care at NewYork-Presbyterian/ Weill Cornell Medical Center and Professor of Medicine at Weill Cornell Medicine. "And yet that's how it came about – by observing a clinical phenomenon in a new way."

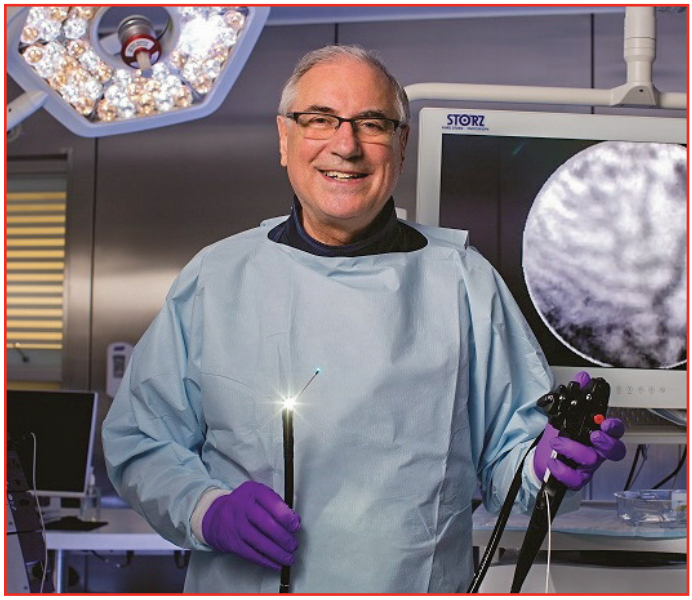
The discovery that brought Dr. Carr-Locke and his colleagues to worldwide attention is something they dubbed the "interstitium" and described in a paper published in *Nature: Scientific Reports* in March 2018. In the words of the *The New York Times*, which featured the research in its health section, the interstitium is a "fluid-filled, 3-D latticework of collagen and elastin connective tissue that can be found all over the body." And what's more – as some news outlets enthused, to the researchers' chagrin – the structure could potentially be considered something even more remarkable: a previously unidentified organ.

"We're not saying that; the press did," stresses Dr. Carr-Locke, a native of the United Kingdom. But then again, he admits, "it's not so crazy. You have to decide, what is the definition of an organ? If you define an organ as something that's recognizable as a structure and has a function of some sort, then it probably fulfills those criteria. That's why we haven't said, 'No, you can't call it that.' It's a nice idea."

> "The reason the interstitium hadn't been seen before is that when you take a specimen or biopsy and fix it in formalin, it takes all the water out, so the spaces disappear."
>
> — Dr. David L. Carr-Locke

The work that led to the identification of the interstitium has its roots in the mid-aughts, when Dr. Carr-Locke, then at Beth Israel Medical Center, and colleagues began using a new piece of diagnostic equipment: a powerful, miniaturized microscope that works with an endoscope. Observing the bile duct in a live patient, he says, "We saw a pattern, a network of black wiggly lines with white spaces in between." Years later, they set about identifying what those structures were. With patient consent during related procedures, they took small biopsies of the bile duct, and rather than fixing them in the preservative formalin, they froze them.

"The reason the interstitium hadn't been seen before is that when you take a specimen or biopsy and fix it in formalin, it takes all the water out, so the spaces disappear," he explains. "In all the textbooks, that's what you see: a band of stuff, mostly collagen, underneath the surface, that has no spaces."



Dr. David L. Carr-Locke

Further study revealed that the black lines were indeed collagen, and the spaces in between were filled with something akin to lymphatic fluid. They wondered if it could be found in other parts of the body, and the answer was a resounding yes. They identified interstitium in the pancreas, duodenum, stomach, intestine, bladder, skin, lungs, and more. "Everywhere there was a lining to something, it seemed to be there," he says. "We called it the interstitium because it's between things – a layer between the surface and something deeper."

Organ or not, Dr. Carr-Locke says, the interstitium could have implications for a wide variety of diseases and conditions, including how cancer spreads, what triggers some aspects of Crohn's disease, and how scars form after injury. Now, he and his collaborators are deciding on their next steps in exploring its specific composition and its role in the human body. "It could explain a lot of phenomena; it may be that when things are diseased, the interstitium gets interrupted or interfered with," he says. "It really is everywhere. It's real. It's reproducible. And once you know it's there, you see it all the time."

Source: *Weill Cornell Medicine, Summer 2018*

Reference Article
Benias PC, Wells RG, Sackey-Aboagye B, Klavan H, Reidy J, Buonocore D, Miranda M, Kornacki S, Wayne M, Carr-Locke DL, Theise ND. Structure and distribution of an unrecognized interstitium in human tissues. *Nature: Scientific Reports.* 2018 Mar 27;8(1):4947.

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Allergic Airway Diseases Affected by Fungal Community Imbalance

According to researchers at Weill Cornell Medicine, common drug treatments that lead to changes in gut fungi can persistently exacerbate allergic airway diseases such as asthma. In a study published online November 29, 2018 in *Cell Host & Microbe*, the investigators suggest that the enormous modern prevalence of allergic airway diseases may be attributable in part to the widespread use of antimicrobials, including antifungals and other therapies that disrupt the normal balance between bacterial and fungal species in the gut.

"We were able to identify gut-resident immune cells that sense fungal community imbalance in the intestines and transmit these immune signals to the lung contributing to aggravated allergy," says senior study author **Iliyan D. Iliev, PhD**, Assistant Professor of Immunology in Medicine in the Division of Gastroenterology and Hepatology and a researcher in the Jill Roberts Institute for Research in Inflammatory Bowel Disease at Weill Cornell Medicine.

> "We were able to identify gut-resident immune cells that sense fungal community imbalance in the intestines and transmit these immune signals to the lung contributing to aggravated allergy."
> — Dr. Iliyan D. Iliev

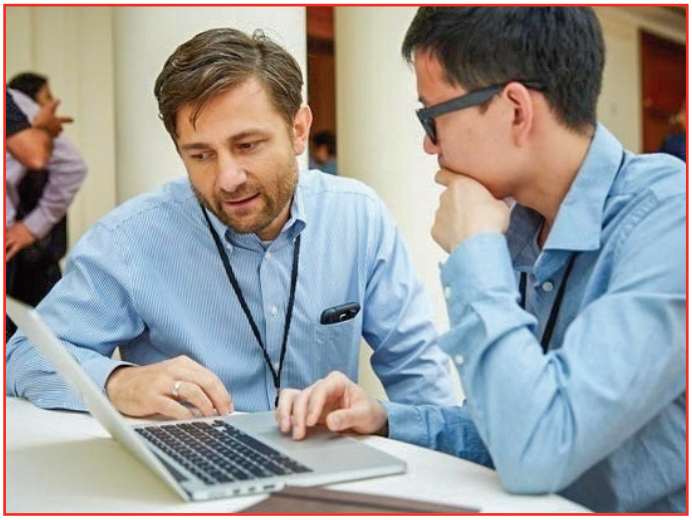
Scientists have learned in recent years that disruptions of intestinal bacteria, for example, due to antibiotic overuse, can trigger or worsen immunologic diseases within the gut and even elsewhere in the body. Dr. Iliev and colleagues reported in 2016 that disruptions of gut-resident fungal communities can have a similar effect, worsening intestinal inflammation as well as allergic airway disease in mice. The disruption of gut-resident fungi, also known as fungal dysbiosis, may be a widespread public health problem.

The use of antifungal drugs is now so common, for example, in modern agriculture or to treat patients with compromised immune systems, that the U.S. Centers for Disease Control and Prevention has expressed concern over rising drug-resistance among fungal species. Antibiotic drugs are also widely used and can affect gut fungal populations by removing or promoting gut bacteria that co-exist with the fungi.

In the new study, Dr. Iliev and his team demonstrated that several weeks of treatment with the antifungal drug, fluconazole, which leads to the overgrowth of drug-resistant fungal strains in the gut, exacerbates asthma-like allergic response in mice to house dust mites, a classic airway allergen. The scientists also demonstrated that this effect was persistent, showing up even three weeks after they had terminated the fluconazole treatment.

By contrast, mice bred without any gut fungi showed no exacerbation of airway allergy when treated with fluconazole, demonstrating that the effect was indeed mediated by fungi. The allergy exacerbation immediately manifested, however, when the scientists transplanted a dysbiotic population of gut fungi into these formerly fungi-free mice.

In a study earlier in 2018, Dr. Iliev and colleagues showed that a certain type of white blood cell, the CX3CR1+ mononuclear phagocyte, is the immune system's chief fungi-sensing representative in the gut. The scientists in the new study found that this same cell type mediates the gut-to-airway effect of fluconazole treatment in mice. When depleting the CX3CR1+ phagocytes from the rodents' intestines or blocking key signaling molecules, these cells activate after sensing fungi, largely reversing the worsening of the allergic response to house dust mites.



Dr. Iliyan D. Iliev, left, with Dr. Xin Li

Dr. Iliev and first author **Xin Li, PhD**, a postdoctoral associate in medicine at Weill Cornell Medicine, now hope to find a method to target CX3CR1+ phagocytes or the molecules they produce so that it might someday be useful clinically to alleviate diseases related to fungal dysbiosis.

"It's a challenge," says Dr. Iliev, "because these phagocytes are needed to sense and engulf fungi, bacteria, and food antigens. We'll need to find a way to modulate their responses to specific organisms reversibly, and only during specific conditions."

Reference Article
Li X, Leonardi I, Semon A, Doron I, Gao IH, Putzel GG, Kim Y, Kabata H, Artis D, Fiers WD, Ramer-Tait AE, Iliev ID. Response to fungal dysbiosis by gut-resident CX3CR1+ mononuclear phagocytes aggravates allergic airway disease. *Cell Host & Microbe*. 2018 Dec 12;24(6):847-56.e4.

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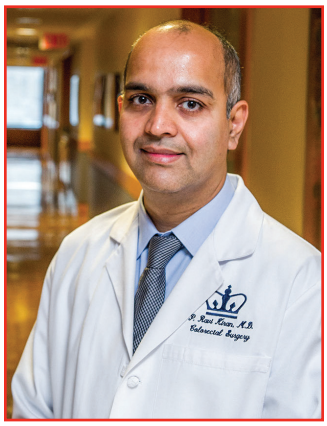
ACS Quality Program Improves Colorectal Surgery Outcomes

Researchers at NewYork-Presbyterian/Columbia University Irving Medical Center have shown that complications stemming from colorectal surgery decreased after introducing a national quality improvement program. "This is one of the few studies to evaluate whether the introduction of the American College of Surgeons National Surgical Quality Improvement Program [ACS NSQIP®] has improved postoperative outcomes over time," says **P. Ravi Kiran, MD**, Chief of the Division of Colorectal Surgery at Columbia.



Dr. P. Ravi Kiran

The ACS NSQIP® is an outcomes-based program created and implemented by surgeons nationwide to measure and improve the quality of surgical care. Analyzing data from 301,632 patients from 2007 to 2016, Dr. Kiran and the team noted several key improvements in colectomies, including a 9 percent decrease in surgical site infections (SSIs) and a nearly 40 percent increase in early discharges. They attributed the improved outcomes to several factors:

- Using NSQIP national data allows surgeons to benchmark and compare outcomes with peers and identify areas for improvement
- NSQIP participation encourages providers to follow evidence-based recommendations for decreasing SSIs and more quickly and safely getting patients through the acute postoperative phase and back at home
- Procedure-targeted datasets enable participants to report additional, optional data specific to an operation

The research team divided the NSQIP data into two groups: resection procedures before (n=131,122) and after (n=179,510) the introduction of colectomy-targeted dataset into practice. Controlling for potentially influential factors – including differences in surgical technique – the authors found the introduction of colectomy-targeted data was linked to a 22 percent risk reduction of SSIs, 30 percent decrease in the odds of developing a urinary tract infection, and a 12 percent decrease in the need for reoperation.

"The reduced odds of experiencing a complication likely translate to hundreds of complications each year," says Dr. Kiran, who presented his findings at the 2018 American College of Surgeons Clinical Congress.

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