

# ADVANCES IN GASTROENTEROLOGY AND GI SURGERY

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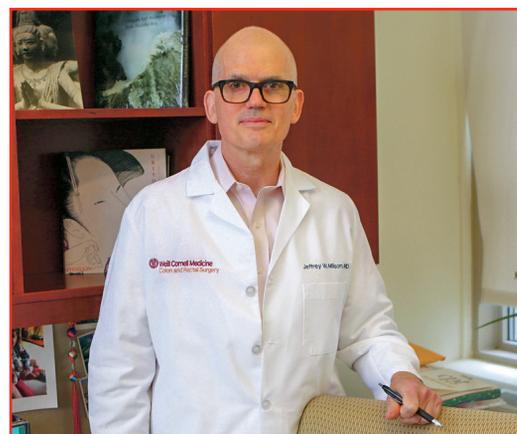
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## A Long and Winding Road: Scoping Out Uncharted Territory in the Colon

Colon polyps can hide, but they can't escape the prying eye of the DiLumen™. The DiLumen Endolumenal Interventional Platform (EIP) developed by **Jeffrey W. Milsom, MD**, Chief of Colon and Rectal Surgery at NewYork-Presbyterian/Weill Cornell Medical Center, and colleagues in the Minimally Invasive New Technologies (MINT) program at Weill Cornell Medicine, is paving the way for dramatic changes in the treatment of many intestinal diseases.

The DiLumen, a dual balloon sleeve that fits securely over a standard endoscope, ensures complete positioning of the scope in the large intestine and assists with optical visualization, diagnosis, and endoscopic treatment. Six years in the making, the device was approved by the Food and Drug Administration in December 2016, and Dr. Milsom and his team began using it in humans last summer. "It is now available for commercial use, manufactured by our industry partner, Lumendi, and its uptake has been rapid," says Dr. Milsom. "The exciting news is that this endoscopic platform is allowing doctors to



Dr. Jeffrey W. Milsom

perform procedures that were previously either very difficult or impossible to execute. Its main indication for use is for removing very difficult or large polyps inside the intestinal tract."

*(continued on page 2)*

## Revealing the Role of Stem Cells in Gut Regeneration

In the laboratory of **Kelley Yan, MD, PhD**, a gastroenterologist in the Division of Digestive and Liver Diseases, NewYork-Presbyterian/Columbia University Irving Medical Center, and the Dorothy L. and Daniel H. Silberberg Assistant Professor of Medicine at Columbia, recent studies of intestinal

**"The intestinal epithelium is the most rapidly self-renewing tissue in the body and its vigorous regeneration is enabled by highly active intestinal stem cells."**

— Dr. Kelley Yan

stem cells are shedding light on the mechanisms of gut regeneration in normal circumstances and under conditions of injury. As a physician-scientist, Dr. Yan

has set her sights on applying the discoveries made in her lab to improve tissue healing and treatment for the many diseases that can affect the gut.

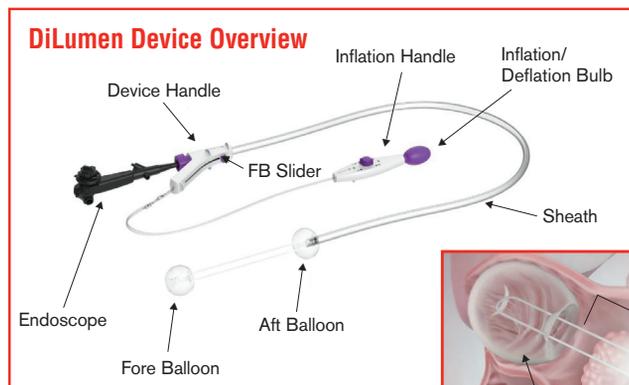
"The intestinal epithelium is the most rapidly self-renewing tissue in the body and its vigorous regeneration is enabled by highly active intestinal stem cells," says Dr. Yan, whose interest in gastroenterology and training in basic science research began as a medical student in the combined MD/PhD program at the Icahn School of Medicine at Mount Sinai.

It was only a short time before Dr. Yan began her GI fellowship and a postdoctoral research fellowship conducting studies in intestinal stem cell (ISC) biology at Stanford University that scientists, for the first time, had identified and isolated a stem cell in the gut. The timing was fortuitous, helping to solidify Dr. Yan's own scientific direction.

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## A Long and Winding Road: Scoping Out Uncharted Territory in the Colon *(continued from page 1)*



*An accessory to an endoscope, the DiLumen device ensures complete positioning of an endoscope in the large intestine and assists with optical visualization, diagnosis, and endoscopic treatment.*

Advanced diagnosis and endolumenal procedures are currently limited by the lack of visibility in the colon, especially around flexures and behind folds. As a result, up to 41 percent of polyps are missed during colonoscopy because of poor visibility. The DiLumen improves the visualization provided by current endoscopes and enables better diagnosis and advanced endolumenal therapeutic procedures to be performed for the first time in difficult locations.

As Dr. Milsom explains, the dual balloon system creates a stabilized diagnostic and therapeutic zone within the intestine, allowing clinicians to visualize, manipulate, and treat isolated segments of bowel. “The endoscope is still somewhat free-floating inside the intestine – something like a boat on the water, it bobs up and down,” says Dr. Milsom. “The sheath fits over the endoscope with two balloons on the end of the scope. One balloon is permanently anchored behind the tip. The forward balloon can be advanced about 15 cm beyond the tip of the scope, creating a closed zone between the two balloons.”

Clinicians can precisely extend and retract the forward balloon and manipulate the colon between the two balloons that define the therapeutic zone, reducing the angle of bends and flattening folds in the colon to expose lesions for diagnosis and treatment. “You start to take control of the area,” says Dr. Milsom. “The DiLumen not only appears to be able to be used in all parts of the colon, but it actually makes it easier to navigate through the intestine by virtue of its being a stabilizing device, like a boat moored to a dock. If you can imagine getting to a sharp bend in the colon where you blow up the balloons, that’s what anchors the scope right at that bend. And then you can slide the scope forward and beyond the sheath, making it easier to go around corners and bends.”

### The Endolumenal Evolution Continues

Dr. Milsom, his MINT team, and Lumendi have continued to develop additional innovative devices in the evolution of the EIP. In April 2018, the FDA approved the DiLumen C2™. Similar in design to the DiLumen EIP, the DiLumen C2 incorporates two 6 mm diameter tool channels, which accommodate two independent flexible articulating hand instruments.

Dr. Milsom is optimistic about future innovations and their applications to digestive diseases. “The short-term proclamation

is that EIP works for the uses in which it was intended, which is always great,” he says. “A lot more needs to be done, however. We want to open up this era of working inside the channel, which is very analogous to what cardiac interventions have done in vascular disease. I think we have even greater potential because we don’t have to arrest the circulation to work inside the channel. The intestine isn’t rushing blood through it, so you don’t have fluid. You can fill the channel with air and it’s safe. You can stabilize the intestine and look directly in with a high-resolution camera. You can also put tools in there. There are so many possibilities that open up.”

According to Dr. Milsom, those possibilities can dramatically impact the way intestinal diseases are treated in the future. “People used to have operations under general anesthesia and a week stay in the hospital,” he says.

“We’re now doing outpatient procedures with no incisions, so the patient is able to go home the same day. Local treatment of a tumor may change. By isolating a zone of the intestine, we have the capability of not only surgically removing the lesion, we will probably be able to give intensified chemotherapy, radiation, or immunotherapy directly to the localized site.”

Dr. Milsom stresses that their goals are to make gastrointestinal therapies not only safer, but also less expensive. “If you can apply a local therapy and avoid the need for incisions and hospitalization, these procedures will be safer, more tolerable, and less expensive, and that will decrease healthcare costs,” he says.

Currently the EIP is primarily used for large and difficult-to-access polyps in the colon. “However, this stabilizing device is equally applicable to the upper GI tract, so in the future it will be used for esophageal, gastric, duodenal, bile duct, and pancreatic diseases,” says Dr. Milsom. “Pipeline developments include advanced tools that will provide better surgical capabilities, enabling the development of endolumenal approaches for additional therapeutic areas, such as diverticular disease, stricture, intestinal fistulae, prolapse, volvulus, anastomosis leaks, and early cancers. There will also be other treatments that will emerge – local intensive therapies – not just for cancer, but for conditions such as inflammatory bowel disease.”

Dr. Milsom predicts that endolumenal technology will merge with other types of advanced imaging, including MR CT, which will allow surgeons to look outside of the intestine simultaneously as they look into the channel. “We envision a whole new set of tools and instruments that we’re going to be using,” he says. “At the same time, we’ll be working with other specialties to create new paradigms and a revolution in the way health care is carried out for gastrointestinal problems. This is just the beginning.”

#### Reference Article

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#### For More Information

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## Revealing the Role of Stem Cells in Gut Regeneration (continued from page 1)

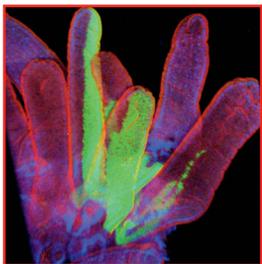
Today, the Yan Laboratory at Columbia focuses on understanding tissue renewal in health and disease using the intestine as a model system to study adult stem cell biology.

### ISCs: Understanding How They Replenish and Repair

To better understand the behavior of stem cells, Dr. Yan and her team use mouse models and also human organoids derived from patient tissues that are grown as “mini-guts” in dishes to study intestinal stem cells as they divide to produce more cells to endlessly replenish or repair the intestinal epithelium.

“The intestine is remarkably dynamic,” says Dr. Yan. “Cells that line the intestine get replaced every few days throughout life by new cells generated by intestinal stem cells. These stem cells are the mother of all other cells. They face the most decisions. Stem cells generate more stem cells but they also generate all the mature cell types that work in nutrient absorption, hormone secretion, and interfacing with the external world. So the main question that we had was, ‘Given all its choices, how does a stem cell *actually* decide what it wants to do? Is a stem cell hardwired to act in a predictable fashion or can we alter its behavior?’”

For Dr. Yan this is the most fundamental question in stem cell biology, with an answer that she and her team deciphered in the intestine itself. “It turns out that the intestinal stem cell takes instructional cues from its environment. In fact, it requires multiple types of signals from its surroundings,” explains Dr. Yan. “It requires Wnts and R-spondins, which are signals released by other cells in the vicinity. Wnts convey a signal to the stem cells that they are in the right location and prepares them to act. R-spondins then instruct them to divide and to generate more stem cells. Stem cells are so powerful that two separate signals are needed to activate their power. If either signal is lost, then ‘stemness’ is lost and a stem cell becomes just another typical cell destined to die after a few days.”

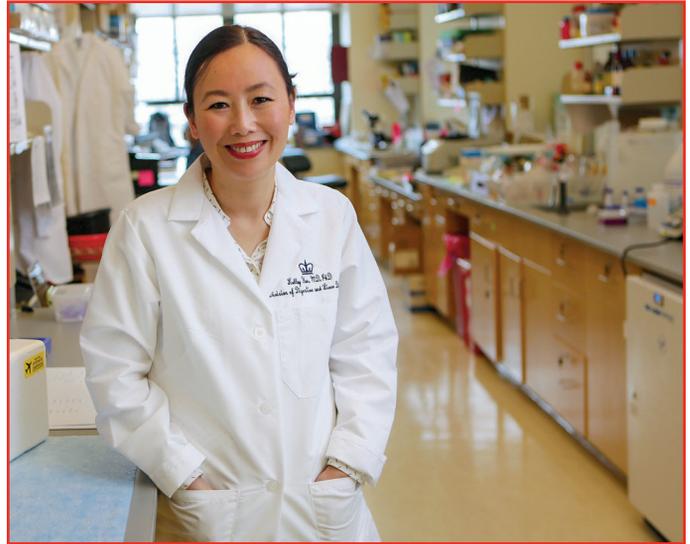


*A single intestinal stem cell repairs an entire patch of tissue (green) in seven days after injury, highlighting its regenerative capacity.*

“These signals not only control tissue regeneration, but they also are involved in the development of cancer,” continues Dr. Yan. “Colorectal cancer, for example, starts from mutations within the Wnt pathway, which is activated by the Wnts and R-spondins that control stem cell behavior. There is growing evidence that cancer originates from a runaway stem cell that no longer is reliant on environmental signals for its activity.”

The results of the research of Dr. Yan and her colleagues, which were published in the May 11, 2017, edition of *Nature*, provided a major advance in identifying discrete and separate functions of the Wnt and R-spondin proteins.

“We developed tools for manipulating levels of Wnts and R-spondins that enabled us to identify their function within an animal,” notes Dr. Yan. “Essentially, we revealed the external cues that a stem cell



*Dr. Kelley Yan*

receives from its environment to enable it to act as a stem cell. We were very excited to discover that stem cell behavior is malleable. We were able to easily manipulate stem cells to make the choices we desired once we de-coded and understood their signals. This has broad implications for precision control of tissue regeneration and for treatment of cancer.”

The Yan Lab at Columbia is focused on bringing these findings into clinical practice. “My love for clinical gastroenterology drew me to the science, and my goal is to help patients through our discoveries,” says Dr. Yan. “If we can understand the mechanisms for how the gut normally regenerates and how it regenerates under conditions of injury, then we will actually be able to promote and enhance the process of healing after injury.”

“The gut is really interesting because it has so many different functions,” continues Dr. Yan. “It absorbs nutrients and it is our major interface with the outside world and with the immune system. The gut is also a powerful endocrine organ that regulates appetite and metabolism. I want to use stem cell biology to enhance all those functions.”

Dr. Yan notes that one of her long-term goals is to use stem cell biology to enhance the gut’s endocrine function. “We have shown that we can manipulate stem cell behavior to influence the types of cells produced in the gut. I want to figure out how to make more of the types of cells that would optimize our metabolism to treat diseases like obesity and diabetes, which we normally think of as endocrine rather than GI diseases. My vision is to ultimately tailor your gut cells to your individual needs – a designer gut, if you will.”

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