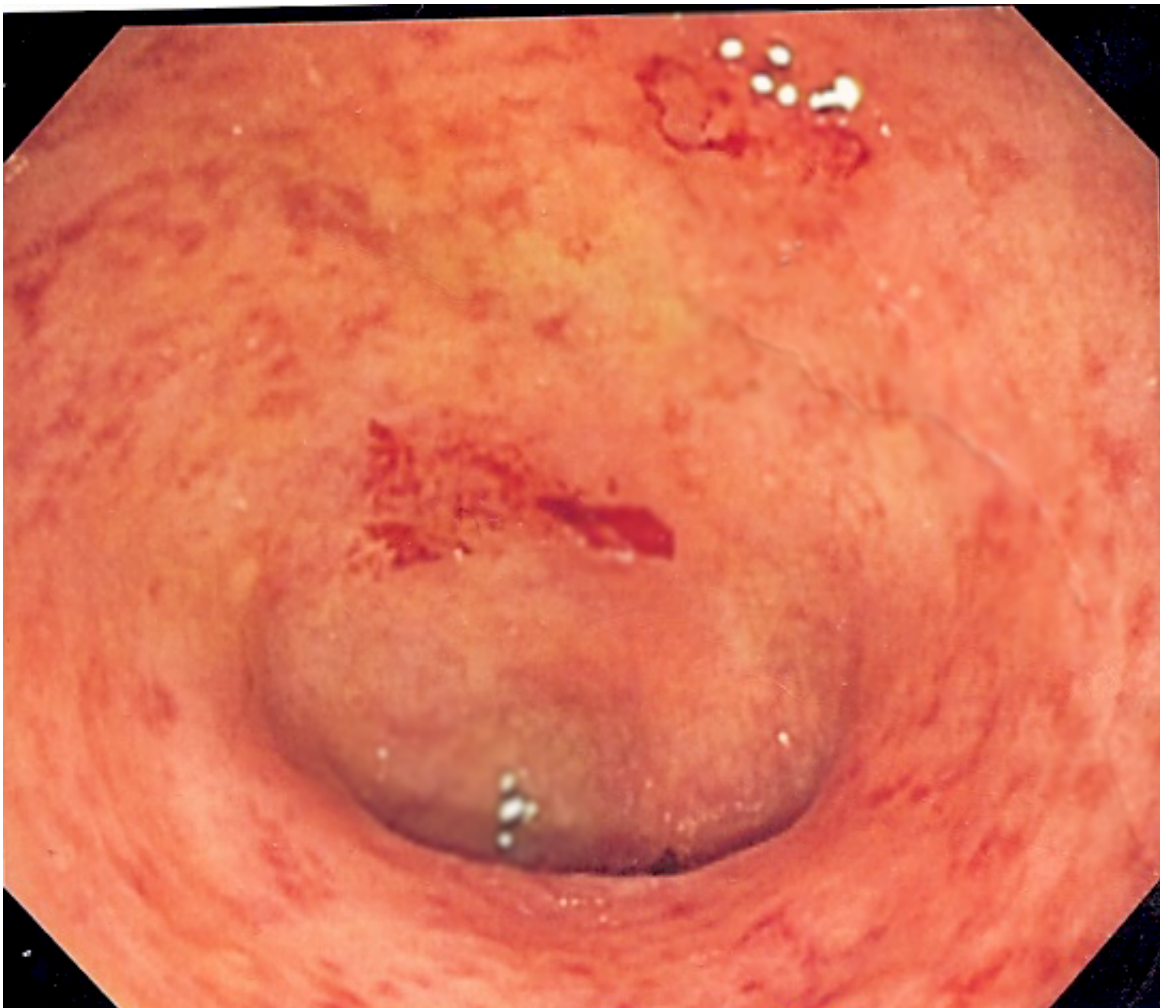


Researchers engineer novel disease model to identify potential targets for ulcerative colitis drugs

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Endoscopic image of a bowel section known as the sigmoid colon afflicted with ulcerative colitis. The internal surface of the colon is blotchy and broken in places. Credit: Samir/Wikipedia

As reported in *Nature Communications*, researchers from Cleveland Clinic's Lerner Research Institute have developed a novel, patient-derived model of ulcerative colitis, which will help advance studies into new treatments for the chronic inflammatory bowel disease.

The team used the model to identify a promising target that could be inhibited to slow [disease](#) progression. Ulcerative colitis is characterized by abnormal reactions of the immune system that lead to inflammation and ulcers on the inner lining of the large intestines. It is a highly heterogeneous condition, both in terms of patients' symptoms and disease pathology.

Suppressing the overactive immune response with [anti-inflammatory drugs](#) is the current mainstay treatment for inflammatory bowel diseases, although these therapies have limited long-term efficacy in ulcerative colitis patients.

Research suggests that elements of both the [immune system](#) and the ulcerative colitis microenvironment (the surrounding, less diseased cellular components) interact to drive disease development and progression.

Considering that immune-suppressing drugs have demonstrated limited success in treating ulcerative colitis, researchers are interested to learn whether targeting elements of the microenvironment—including components of the intestinal lining (called the epithelium) and stem cell-like cells called [stromal cells](#)—may be a better or complementary treatment approach.

"Gaining a more comprehensive understanding of the complex interplay between immune and other [cell types](#) will be critical to developing new

and more effective ulcerative colitis therapies and tailored, patient-specific treatment approaches," said Emina Huang, MD, staff in the Departments of Cancer Biology and Colorectal Surgery, and the study's lead author.

Dr. Huang, who is also a practicing colorectal surgeon, and her team developed their model using tissue samples from patients with ulcerative colitis who underwent surgery at Cleveland Clinic. They isolated a specific type of cell (called fibroblasts) that can be "reprogrammed" to develop into all-purpose, undifferentiated cells called induced [pluripotent stem cells](#), which have emerged as a growing research priority.

The researchers then grew the stem [cells](#) in the lab into tiny, three-dimensional tissues that mimic actual organs (called organoids). They found that compared to healthy colon organoids, the diseased organoids reflected histological and functional features commonly observed in ulcerative colitis patients, including reduced mucus secretions, faulty barrier integrity of the intestinal lining and overexpression of select proteins (including one called CXCL8).

"Our in vitro model accurately mirrors what we observe in patients in the clinic and is much more dynamic than current models. For example, other organoid models only focus on the contributions of the epithelium, where ours reflects the contributions of other microenvironment components, too, like the stroma," said Dr. Huang.

After developing the model, the team was able to rapidly identify novel drug targets and candidates. They showed that inhibiting CXCL8 expression with a small molecule called repertaxin helped to slow disease progression.

"We look forward to further exploring repertaxin's potential benefit in

other preclinical and eventual clinical studies," said Dr. Huang. "We are hopeful that others will also find this model useful in identifying other potential anti-ulcerative colitis drugs." She also noted that the approach used to develop this new [ulcerative colitis](#) model may also be used to [model](#) other complex diseases.

More information: Samaneh K. Sarvestani et al, Induced organoids derived from patients with ulcerative colitis recapitulate colitic reactivity, *Nature Communications* (2021). [DOI: 10.1038/s41467-020-20351-5](#)

Provided by Cleveland Clinic

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