Engineered yeast probiotic developed to treat inflammatory bowel disease

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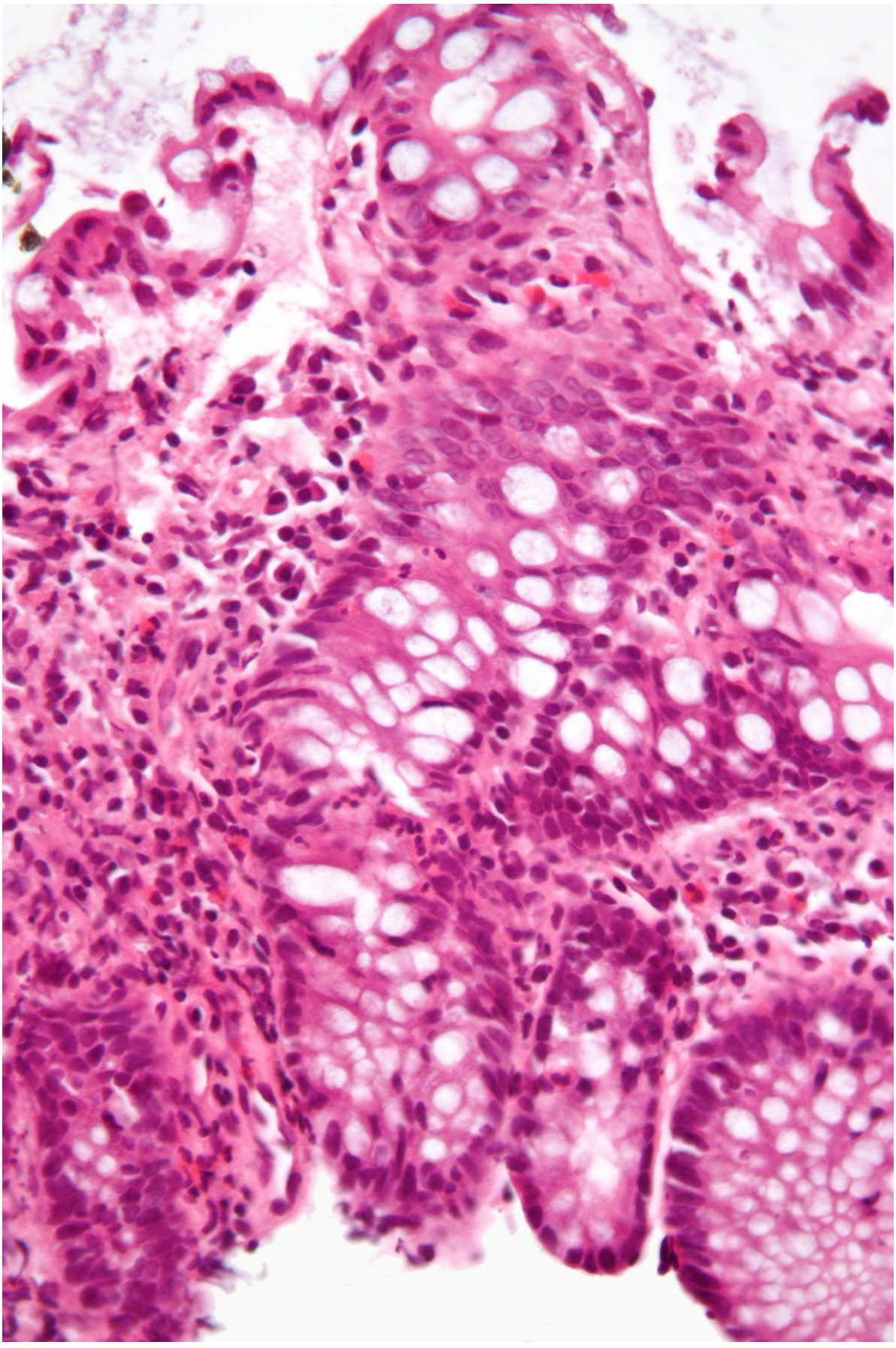

Micrograph showing inflammation of the large bowel in a case of inflammatory bowel disease. Colonic biopsy. Credit: Wikipedia/CC BY-SA 3.0

The world of microbes living in the human gut can have far-reaching effects on human health. Multiple diseases, including inflammatory bowel disease (IBD), are tied to the balance of these microbes, suggesting that restoring the right balance could help treat disease. Many probiotics—living yeasts or bacteria—that are currently on the market have been optimized through evolution in the context of a healthy gut. However, in order to treat complex diseases such as IBD, a probiotic would need to serve many functions, including an ability to turn off inflammation, reverse damage and restore the gut microbiome. Given all of these needs, researchers from Brigham and Women's Hospital have developed a "designer" probiotic—a thoughtfully engineered yeast that can induce multiple effects for treating IBD. Preclinical results from their work are published in *Nature Medicine*.

"We've taken yeast—the very yeast that's used to make beer—and we've given it the ability to sense inflammation and secrete an anti-inflammatory molecule," said corresponding author Francisco Quintana, Ph.D., an investigator in the Ann Romney Center for Neurologic Diseases at the Brigham. "We call this new platform 'Y-bots' (yeast robots) and see the potential here for developing therapeutics that can treat diseases of the gut tissue and more."

Previous research from the Quintana lab has helped illuminate the connection between the gut and diseases that affect the brain, suggesting potential applications for engineering probiotics beyond IBD.

Quintana and colleagues developed their probiotic using Saccharomyces cerevisiae, a species of yeast used in winemaking, baking and brewing. Using the gene editing technology CRISPR/Cas9, the researchers introduced genetic elements that could sense inflammation and respond to it by secreting an enzyme that can degrade a key molecule involved in inflammation. The engineered yeast can secrete different levels of enzyme, depending upon how much of the inflammatory signal is present at a location in the gut. This means that the probiotic can have a highly localized response to inflammation. In mice, the engineered yeast successfully suppressed intestinal inflammation, reduced fibrosis and restored a balanced gut microbiome.

To bring this new therapeutic platform to bear on IBD and other diseases in humans, Quintana and colleagues will need to conduct safety studies. They also plan to further refine and test the engineered yeast to see if they can speed up tissue repair. Beyond IBD, the team plans to investigate the use of engineered probiotics for treating a common side effect of cancer immunotherapy, colitis.

"We want to use the tools of synthetic biology to engineer what can be found in nature," said Quintana. "By engineering probiotics, our goal is to create more personalized, localized and highly controlled medications for treating diseases of the gut and beyond."

More information: Self-tunable engineered yeast probiotics for the treatment of inflammatory bowel disease, *Nature Medicine* (2021). DOI: 10.1038/s41591-021-01390-x , www.nature.com/articles/s41591-021-01390-x

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