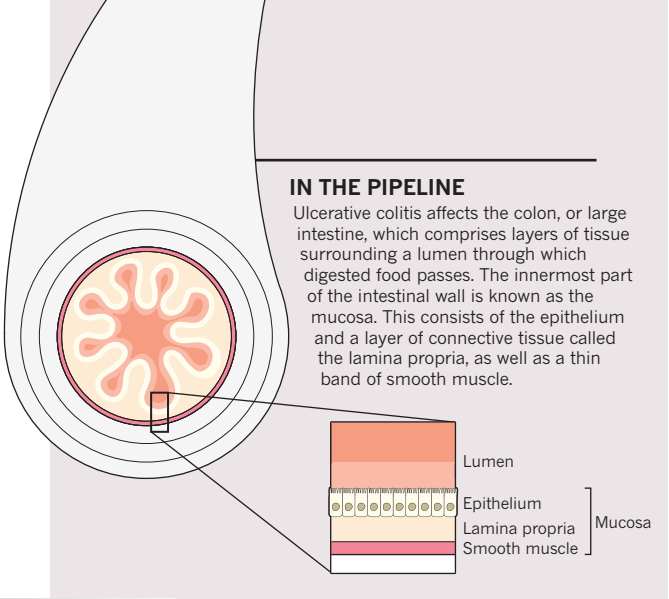
GUT REACTION

Existing treatments bring only temporary relief to people with ulcerative colitis, a common form of inflammatory bowel disease. Insights into the immunobiology of the condition are driving the development of therapies that could lead to prolonged periods of remission. By **Michael Eisenstein**; *illustration by* **Alisdair Macdonald**



IN THE PIPELINE

Ulcerative colitis affects the colon, or large intestine, which comprises layers of tissue surrounding a lumen through which digested food passes. The innermost part of the intestinal wall is known as the mucosa. This consists of the epithelium and a layer of connective tissue called the lamina propria, as well as a thin band of smooth muscle.

ANATOMY OF A BARRIER

The events that underlie the onset of ulcerative colitis are not well understood. Disruption of the intestinal wall is thought to enable bacteria in the lumen that are normally well tolerated (or even beneficial to health) to trigger a poorly controlled immune response that causes chronic inflammation and tissue damage.

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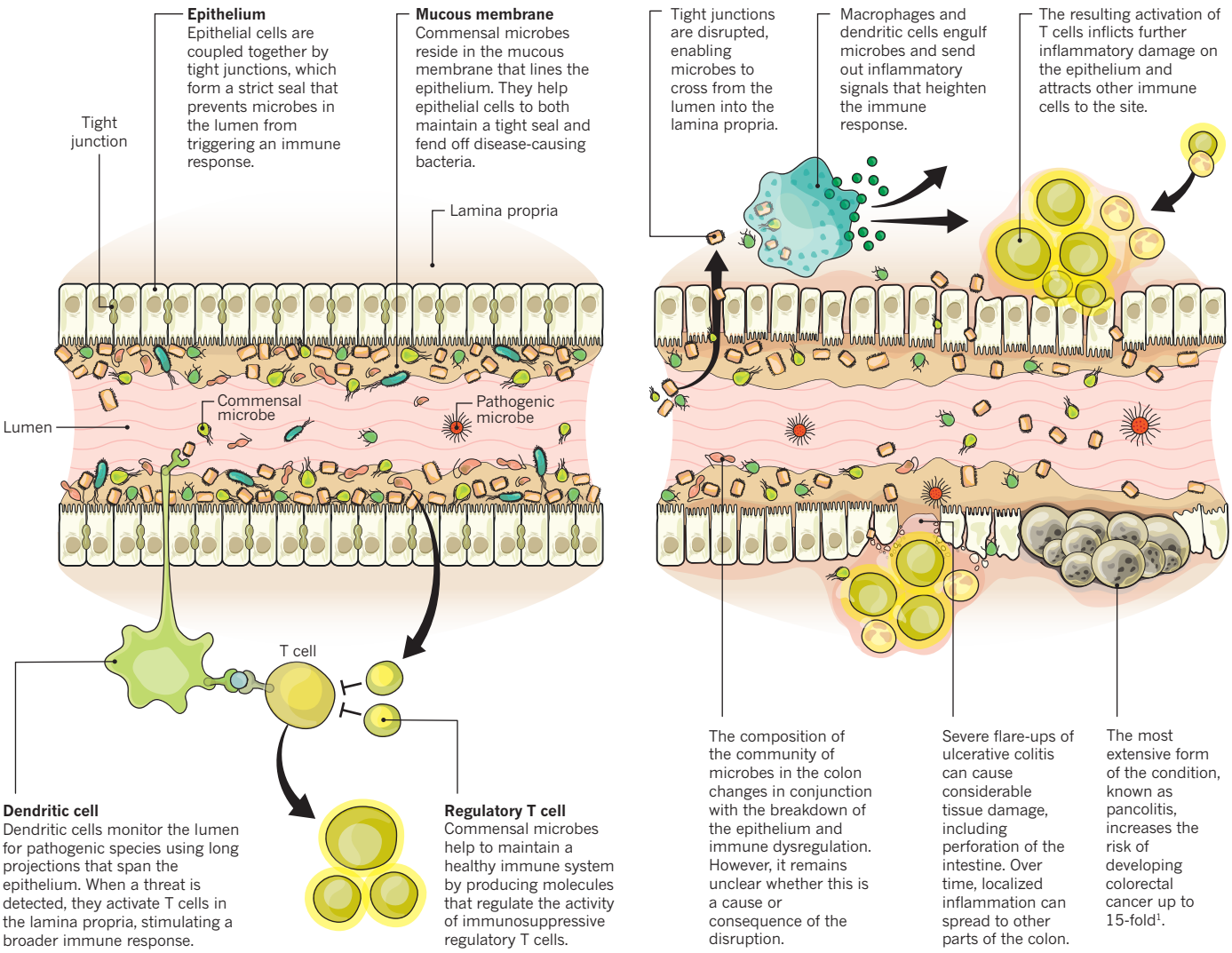
PICTURE OF HEALTH

In the healthy colon, the epithelium, immune cells and commensal microbes collaboratively maintain a stable equilibrium that both preserves intestinal health and protects the gut from potential threats.

BARRIER BREAKDOWN

In people with ulcerative colitis, factors such as a genetic predisposition, environmental triggers and infection set into motion a cycle of uncontrolled inflammation that wreaks havoc on the intestinal wall.



FIGHTING THE FLAMES

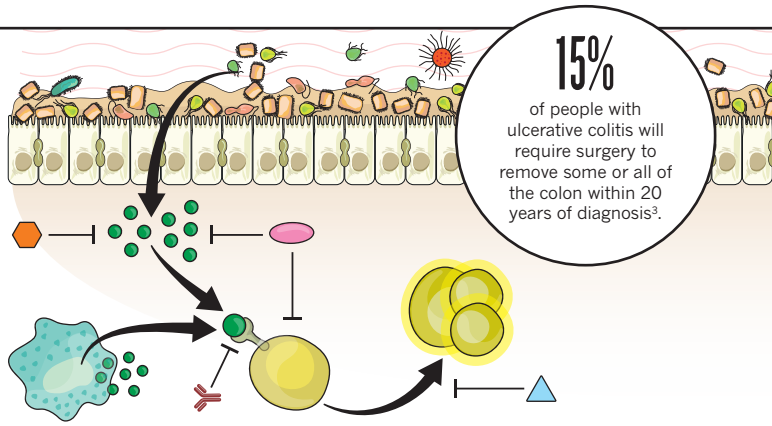
Treatments that promote and maintain remission from ulcerative colitis do not work in all people, and some can cause serious side effects.

Aminosalicylates
Mesalazine (5-aminosalicylic acid) can quell the production of inflammatory signals, but the drug is effective mainly in people with mild to moderate disease.

Biological drugs
Antibody-based drugs such as infliximab inhibit the effects of inflammatory signals. But the beneficial effects of infliximab wear off in many people, and up to a third of recipients do not respond[2].

Corticosteroids
Anti-inflammatory drugs act on immune cells and the epithelium, and are used to treat severe ulcerative colitis. However, they are associated with side effects and dependency.

Immunosuppressants
Drugs such as azathioprine deliver sustained relief by limiting T-cell numbers, but this can leave recipients vulnerable to infection and other side effects.



15%
of people with ulcerative colitis will require surgery to remove some or all of the colon within 20 years of diagnosis[3].

A CALL FOR REINFORCEMENTS

Fresh strategies for delivering relief to people with ulcerative colitis who no longer benefit from existing therapies are being explored in clinical trials. A wide variety of work is under way, but four broad approaches seem to hold particular promise.

1 TRAFFIC CONTROL

Limiting the ingress of immune cells into the lamina propria could control localized inflammation without the need for broad immunosuppression.

Drugs that bind to the sphingosine-1-phosphate receptor on T cells, such as etrasimod, aim to halt inflammation by interfering with T-cell migration.

Etrolizumab prevents T cells from crossing from blood vessels into the lamina propria by blocking a crucial binding protein.

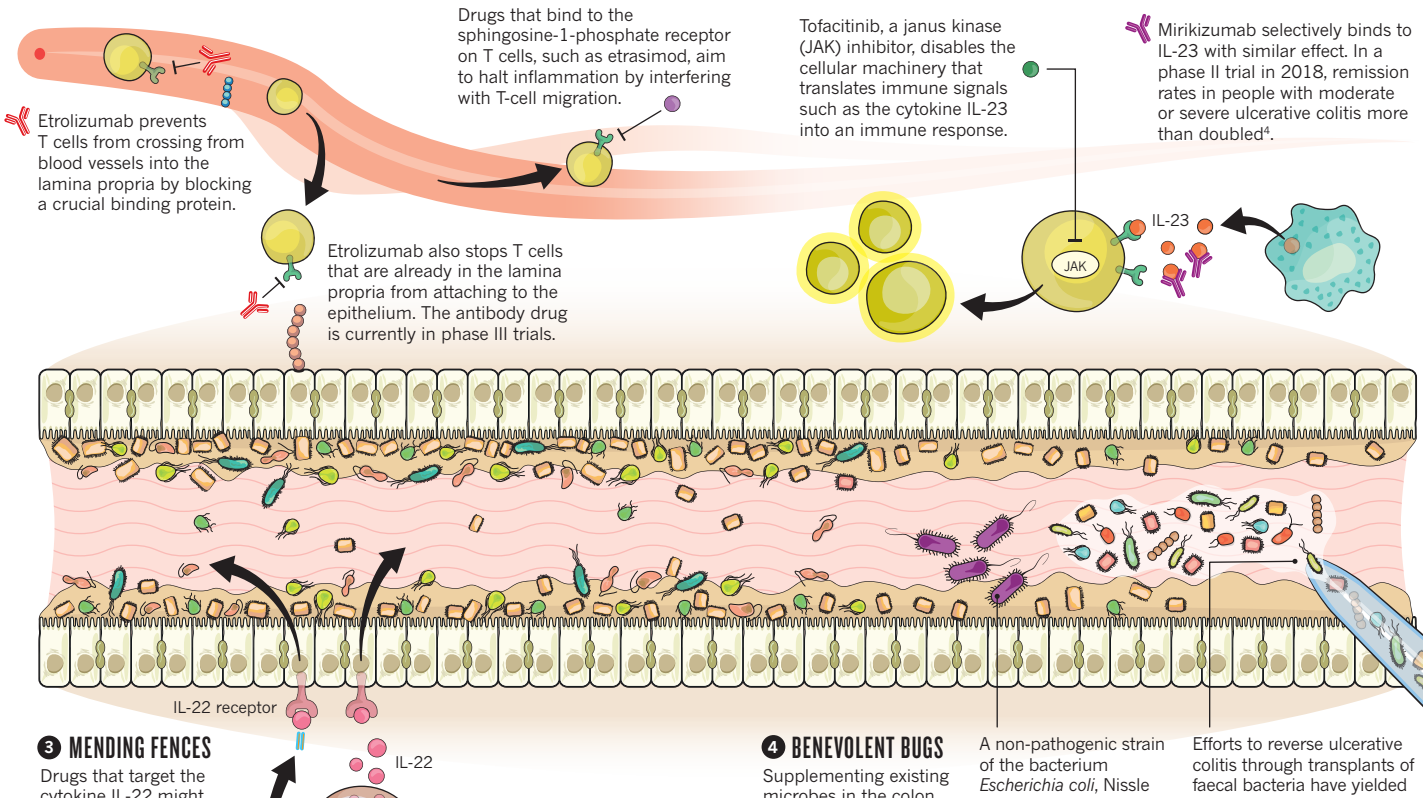
Etrolizumab also stops T cells that are already in the lamina propria from attaching to the epithelium. The antibody drug is currently in phase III trials.

2 COMMUNICATION BREAKDOWN

Drugs that selectively sabotage key inflammatory signaling pathways can help to disarm destructive immune cells.

Tofacitinib, a janus kinase (JAK) inhibitor, disables the cellular machinery that translates immune signals such as the cytokine IL-23 into an immune response.

Mirikizumab selectively binds to IL-23 with similar effect. In a phase II trial in 2018, remission rates in people with moderate or severe ulcerative colitis more than doubled[4].



3 MENDING FENCES

Drugs that target the cytokine IL-22 might counteract damage in ulcerative colitis by reinforcing the epithelium and halting leakage of immunity-triggering microbes into the lamina propria.

Antibody-based drug UTTR1147A activates the IL-22 receptor on epithelial cells to set this healing in motion. It is now being tested in a phase II trial.

Plant product indigo naturalis acts indirectly on the same signalling pathway, promoting IL-22 release by binding to the aryl hydrocarbon receptor on the surface of certain immune cells. In a randomized, controlled trial in 2018, the compound significantly increased short-term remission in recipients[5].

4 BENEVOLENT BUGS

Supplementing existing microbes in the colon might help to quell inflammation and restore normal intestinal function.

A non-pathogenic strain of the bacterium *Escherichia coli*, Nissle 1917, can deliver therapeutic efficacy that is roughly equivalent to widely used amino-salicylates by producing compounds that promote intestinal health[6].

Efforts to reverse ulcerative colitis through transplants of faecal bacteria have yielded conflicting results. However, there is hope: at least two randomized controlled trials have shown that trans-planting microbes from healthy donors leads to remission in around a quarter of recipients[7,8].

Sources: 1. Ekbom, A., Helmick, C., Zack, M. & Adami, H. O. *N. Engl. J. Med.* **323**, 1228–1233 (1990). 2. Duijvestein, M. *et al. Curr. Treat. Options Gastroenterol.* **16**, 129–146 (2018). 3. Targownik, L. E., Singh, H., Nugent, Z. & Bernstein, C. N. *Am. J. Gastroenterol.* **107**, 1228–1235 (2012). 4. Sandborn, W. J. *et al. Gastroenterology* **154**, S1360–S1361 (2018). 5. Naganuma, M. *et al. Gastroenterology* **154**, 935–947 (2018). 6. Kruis, W. *et al. Gut* **53**, 1617–1623 (2004). 7. Moayyedi, P. *et al. Gastroenterology* **149**, 102–109 (2015). 8. Paramsothy, S. *et al. Lancet* **389**, 1218–1228 (2017).