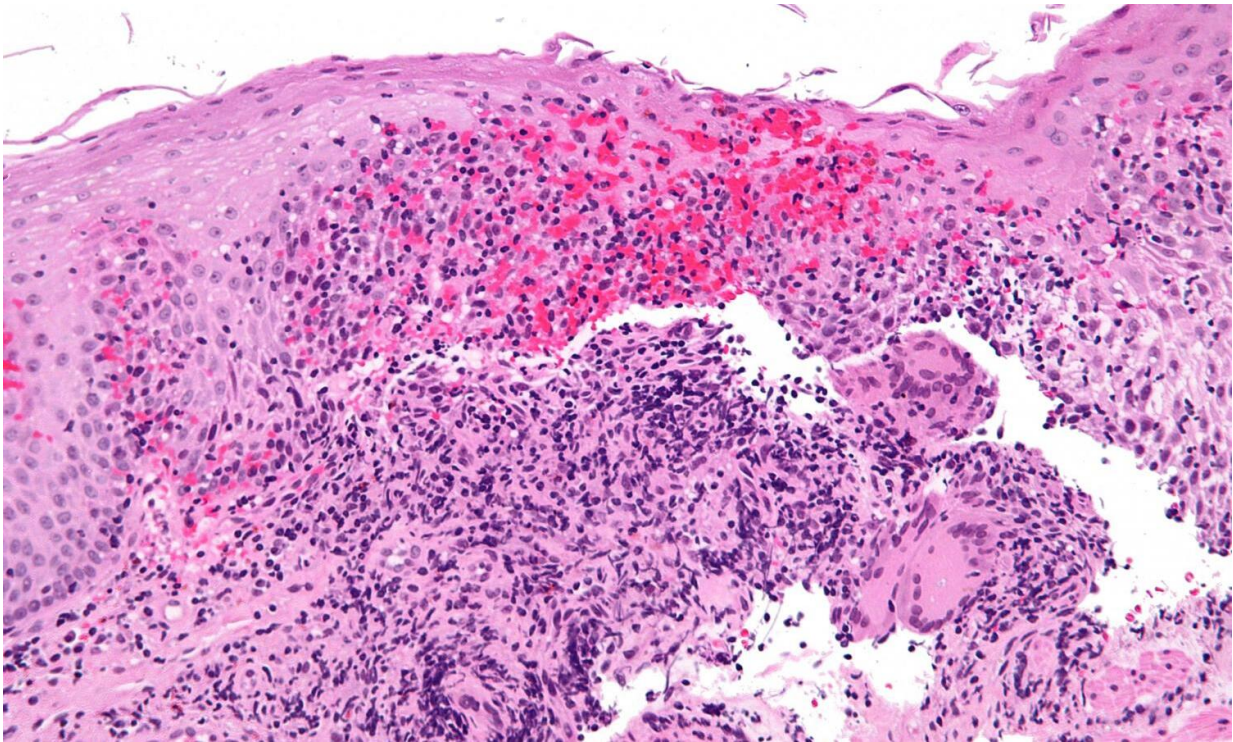


Potential preventative treatment demonstrated for Crohn's disease

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High magnification micrograph of Crohn's disease. Biopsy of esophagus. H&E stain. Credit: Nephron/Wikipedia

A potential preventative treatment for Crohn's disease, a form of inflammatory bowel disease, has been demonstrated in a mouse model and using immune-reactive T cells from patients with Crohn's disease.

This research, led by University of Alabama at Birmingham researcher Charles O. Elson, M.D., professor of medicine, focused on a subset of T [cells](#) known as T memory, or T_m cells. The UAB researchers used a triple-punch treatment to remove T_m cells and increase the number of T regulatory, or T_{reg}, cells. Both of these results were able to prevent colitis in a T cell transfer [mouse model](#), and they had similar inhibitory effects on immune-reactive CD4-positive T cells isolated from Crohn's disease patient blood samples.

These results, Elson says, support a potential immunotherapy to prevent or ameliorate inflammatory bowel disease.

Some background is needed to understand how and why the triple-punch treatment, which was reported in the journal *Science Immunology*, works.

Inflammatory bowel diseases result from an over-activation of the immune response against gut microbes in genetically susceptible hosts. One specific microbial antigen causing this over-reaction by short-lived T effector cells is flagellin, the protein-subunit of bacterial flagella, the long tail-like structures that twirl like a propeller to make some bacterial motile.

One group of immuno-dominant flagellins are those from the Lachnospiraceae family, including CBir1; more than half of Crohn's disease patients have elevated serological reactivity to CBir1 and related flagellins.

Unlike the short-lived T effector cells that act like soldiers to help fight infections, T memory cells serve as sentinels that remember a previous encounter with flagellins. They are long-lived and quiescent, with a low level of metabolism. If reactivated by a fresh encounter with flagellin antigens, they undergo a profound metabolic transition and quickly

expand into large numbers of pathogenic T effector cells.

This metabolic switch is controlled by a signaling protein, mTOR, located in the T_m cell.

Thus, activation of mTOR is necessary for T cell expansion, making it an inescapable metabolic checkpoint to create activated T_m cells. It is also the checkpoint for T naïve cells that are encountering flagellin for the first time.

So, Elson and colleagues hypothesized that activation of CD4-positive T_m or T naïve cells by flagellin antigens, while at the same time shutting down the metabolic checkpoint through the use of mTOR inhibition, would result in the death or an absence of the normal immune response to an antigen, which is called anergy. These effects comprise two parts of the triple-punch treatment, with the third being induction of Treg cells.

The activation was prompted by a synthetic peptide that had multiple repeats of one CBir1 epitope. Such a peptide can selectively stimulate memory cells without activating an innate immune response.

To shut down the metabolic checkpoint, the UAB researchers used two existing drugs, rapamycin and metformin. Rapamycin directly inhibits mTOR, and metformin adds to that inhibition by activating a kinase called AMPK that negatively regulates mTOR activity.

Elson calls this treatment cell activation with concomitant metabolic checkpoint inhibition, or CAMCI.

Parenteral application of CAMCI in mice successfully targeted microbiota flagellin-specific CD4-positive T cells, leading to significant antigen-specific CD4-positive T cell death, impaired development and

impaired reactivation of CD4-positive memory responses, and substantial induction of a CD4-positive Treg cell response. It prevented colitis in the mouse model and had similar inhibitory effects on microbiota-flagellin-specific CD4-positive T cells isolated from patients with Crohn's disease.

For a potential future treatment of patients with Crohn's disease, only targeting a single flagellin is unlikely to have much effect, Elson says. "Instead, we anticipate the future use of a synthetic multi-epitope peptide containing multiple CD4-positive T cell flagellin epitopes to target many microbiota-flagellin-reactive CD4-positive Tm cells," Elson said. "Depending on the serologic or CD4-positive T cell response to certain microbiota antigens, this CAMCI approach could be tailored to individuals with different combinations of epitopes as a personalized immunotherapy."

Elson says he envisions this CAMCI approach as an intermittent pulse therapy to maintain remission in patients with Crohn's disease. "And with autoantigen epitopes better studied in the future," he said, "this approach could be expanded to treat other inflammatory or autoimmune diseases such as Type 1 diabetes or multiple sclerosis."

In developed countries, three of every 1,000 people have inflammatory bowel disease. Its major forms, Crohn's [disease](#) and ulcerative colitis, have substantial morbidity and large medical care costs, and no current therapy alters the natural history of these diseases.

More information: Qing Zhao et al, CD4+ T cell activation and concomitant mTOR metabolic inhibition can ablate microbiota-specific memory cells and prevent colitis, *Science Immunology* (2020). [DOI: 10.1126/sciimmunol.abc6373](https://doi.org/10.1126/sciimmunol.abc6373)

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