

Spotting a molecular warhead for disease in the human gut

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Credit: AI-generated image ([disclaimer](#))

Yale scientists are using new chemical tools to identify and understand molecules in the human gut that alter DNA and regulate inflammatory bowel diseases and colorectal cancers.

In an article published April 6 in the journal *Nature Chemistry*,

researchers describe the chemical structures of 32 such [molecules](#) from the bacterial colibactin pathway, found in select strains of E. coli in the gut. One of those molecules, containing the colibactin warhead, is shown to append and cross-link DNA, indicating new models for the pathway's activities.

In this case, "warhead" refers to the structural feature responsible for the molecule's activity and toxicity to cells.

"These molecules are at the heart of diverse chemical signaling events between man and microbe," said Jason Crawford, an assistant professor of chemistry and microbial pathogenesis at Yale, and co-author of the paper. "In the last decade, we have come to appreciate humans as being 'superorganisms,' consisting of an amalgamation of interacting human and microbial cells. In contrast to our heritable human genome, the genetic instructions for our environmentally derived microbes—the microbiome—can more readily be altered and encode many more genes, representing a vast, unknown landscape for the synthesis of structurally diverse and [biologically active molecules](#)."

Building on its prior work, Crawford's group conducted an interdisciplinary study to identify the molecules. The team used a combination of metabolomics, nuclear [magnetic resonance spectroscopy](#), bacterial genetics, and bioinformatics.

"A collaborative Yale team is now moving forward on how these types of molecules and their activities more specifically regulate IBDs and cancers at the mechanistic level and how these insights could be repurposed for pre-clinical IBD and cancer treatments," Crawford said.

More information: The colibactin warhead crosslinks DNA, *Nature Chemistry*, [DOI: 10.1038/nchem.2221](https://doi.org/10.1038/nchem.2221)

Provided by Yale University

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