Andrew Goodman, PhD, C. N. H. Long Professor of Microbial Pathogenesis and Director of the Microbial Sciences Institute at Yale West Campus, studies the abundant flora in the gut, but he initially trained in ecology and sees many parallels. "I think of the microbiome as an ecosystem," he said, "and the members of the ecosystem are bacteria."

Lately he has been looking into the connections between that ecosystem and cancer patients' responses to therapeutics. Patients often react differently to the same therapy, showing different side effects or outcomes. These differences are usually ascribed to variants in people's genomes, but Dr. Goodman doubted that was the whole story.

"People have enormous differences in their gut microbes," he said, "far greater than the differences within their genomes. We wondered whether differences in drug responses could be affected not only by activities of the liver—the primary organ for drug metabolism—but also by differences in people's microbiomes."

To test their hypothesis, Dr. Goodman and his lab settled on the interaction between a widely used chemotherapy drug named 5-fluorouracil (5-FU) and an antiviral drug often given with it named brivudine. In some patients this combination had proven to be extremely toxic, even lethal. Researchers determined that brivudine can interfere with the metabolic processing of 5-FU, itself a toxin. It turned out that 80 percent of 5-FU gets cleared from the body through a specific chemical pathway, but if that pathway is blocked and 5-FU isn't expelled, patients can overdose on it. Further research revealed the cause: In some patients, brivudine produces a toxic metabolite that blocks the pathway.

"This was a case where not understanding the microbiome and the microbial contribution was a huge problem," explained Dr. Goodman.

The problem wasn't brivudine itself, but its metabolite, which interfered with chemotherapy. Dr. Goodman knew that gut bacteria can make this toxic molecule, but not how. He also knew that the liver was capable of making the same toxic molecule. Since both the microbiome and the liver can make the molecule, which one was the main actor when combining brivudine and 5-FU to cause a toxic reaction?

First, the scientists determined the bacterial chemistry that transformed the drug into a toxic molecule. Next, they altered the microbiomes in mice to include or exclude the responsible bacterial enzyme. That allowed the team to study how much of the toxic molecule came from the liver and how much from the microbes.

"We learned that even though the liver is capable of doing this," said Dr. Goodman, "about 70 percent of this toxic metabolite that interferes with chemotherapy is coming from what the microbes are doing."

Equally significant, the toxicity sometimes showed up in the liver, where 5-FU accumulated if it wasn't eliminated. "We could see that changing just one microbial enzyme in the gut can impact how toxic the drug is in the liver. So, what the microbes are doing in the gut can reach far beyond the gut itself."

He sees implications for the management of chemotherapy's side effects, which can limit a patient's dosage and affect outcomes. "What's new is that we found there is another player to the story. It's not only what drugs you are taking, but it can be what microbes you have, because some of them can interfere with chemotherapy." These findings were published in 2019 in the journal *Science*.

In another major paper published in *Nature*, they tested about 75 bacterial species typically found in the gut against hundreds of drugs currently in use, some for cancer and some not. The surprising result: two-thirds of the drugs were altered by at least one of the gut bacteria.

"So we think the example of bacteria that can change a drug like brivudine into something that interferes with chemotherapy or causes some other harm isn't an exception. It's much more common than we had previously appreciated."

He notes that this isn't necessarily bad news. Bacterial activity can enhance the efficacy of a drug, not just corrupt or negate it. The point is that microbes are dynamic agents that should be considered in medical care. "We're just starting to understand this," said Dr. Goodman, "and the work we're doing is very basic research, but we think there will be translational implications."

In the future, he envisions being able to predict how patients might respond to a particular drug based on their microbiome. He can imagine changing people's microbes to avoid a dangerous drug reaction, or replacing certain microbes with others that would diminish poor side effects.

"That's very different from the way we think about personalized medicine today, which holds that if we understand a person's genome, we can choose which drugs to give them," he said. "We don't think about changing people's genomes in order for them to respond to a drug, but it's not crazy to think we could change people's microbes to do that, to maximize the chances for the best response."

Andrew Goodman, PhD

The Microbiome and Cancer Treatment