



Microbiome Engineering

Synthetic biology may lead to the creation of smart microbes that can detect and treat disease

By Justin L. Sonnenburg

In the not too distant future each of us will be able to colonize our gut with genetically modified “smart” bacteria that detect and stamp out disease at the earliest possible moment. This scenario may sound like the premise for a sci-fi flick, but it is a very real possibility. Microbiome engineering holds great promise because of advances in the field of synthetic biology, which strives to create and rewire biological organisms so they perform desired tasks. Synthetic biologists are attempting to turn bacterial cells into the biological equivalent of the silicon wafer. These principles have been primarily applied to organisms for biofuel production, but the resulting techniques and genetic tool kit, when applied to our resident microbes, will have profound consequences for human health.

These resident microbes are adept at sensing what food is present, whether any pathogens are lurking and what the inflammatory state of the gut is—their survival depends on it. The model gut-resident bacterial species that we are using in our laboratory for initial tests, *Bacteroides thetaiotaomicron*, possesses more than 100 genetic circuits, each responsive to a different cue within the gut. If *B. thetaiotaomicron* “sees” pectin from an apple you recently ate, one circuit is triggered. If you eat a poached egg teeming with *Salmonella*, the resulting intestinal damage triggers a different circuit in *B. thetaiotaomicron*. Each of these circuits can be rewired so that the environmental cue elicits a designed response. Our early tests are focused on

optimizing a DNA memory device for *B. thetaiotaomicron* so that we can record this bacterium’s experiences as it transits through the gut. Invertible pieces of DNA are designed to flip, like switches, depending on what the bacterium detects. The two possible orientations (forward or flipped) of the DNA piece are akin to binary computer bits, which record a 1 or 0. Reading a genetic memory chip of a bacterium after it exits the gut will reveal fundamental principles about a single cell’s journey through the digestive tract.

We are also working to design bacteria that secrete anti-inflammatory molecules when inflammation is detected, providing site-specific drug delivery within the intestine that automatically shuts off when the inflammation is eliminated. In addition to recording memories and treating inflammation, these smart bacteria may ultimately help combat invading pathogens, diagnose early stages of cancer, correct diarrhea or constipation, and regulate mood or behavior.

It is also important to develop safety mechanisms that ensure these organisms can be controlled. We are working to engineer a “kill switch” for eliminating engineered microbes if necessary.

The gut microbiota guides our immune system, metabolism, and even our moods and behavior. As we learn more about the specifics of our relationship with our resident microbes, we will be able to genetically manipulate them in a variety of ways to improve human health.

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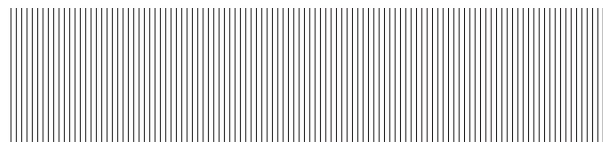


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