New synthetic bacteria could be a ‘paradigm shift’ for biotechnology

By Miles Martin
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By completely reengineering the genetic code of E. coli bacteria, researchers have created a strain that is virtually invincible to viral infection, a development with wide implications for synthetic biology — the redesigning of organisms to meet practical needs.

The study, published June 3 in *Science*, makes the research team the first to successfully incorporate multiple synthetic sense codons into bacterial DNA. These sense codons are small units of DNA that tell the cell which amino acids to use to create proteins.

Reengineering the bacterial genome with these synthetic codons is akin to overhauling the language of their DNA. And since viruses infect cells by reading and hijacking the host cell's DNA, the viruses are incapable of infecting these newly engineered bacterial cells. The new research represents a major leap over current efforts to engineer bacteria for viral resistance. It also has the potential to reshape biotechnology by massively expanding the scope of molecules E. coli can produce in the lab.

"Imagine if you had paragraph, and you're removing letters entirely; [with] these codons representing letters,

then the virus can't really read the paragraph at all," said lead author Wesley Robertson, a postdoctoral researcher at the Medical Research Council Laboratory of Molecular Biology. "By reassigning these codons to unnatural amino acids, now you have a new paragraph with new letters and a totally new meaning."

While outbreaks of pathogenic strains of E. coli bacteria regularly make headlines, this species is generally nonpathogenic in the lab. In fact, it has proved crucial to modern biotechnology, where the bacteria are routinely used as a cellular factory for proteins and DNA. One immediate application of this research is making current applications of biotechnology less susceptible to viral contamination.

"E. coli is the most common microbiology workhorse in labs, both academic and industrial, throughout the world," Robertson said. "[About] 30% of protein-based pharmaceuticals are made with E. coli." Some of these include insulin, human growth hormone and certain cancer drugs.

Previous studies with E. coli have successfully incorporated synthetic stop codons — units of DNA that tell the cell to stop adding amino acids. However, the process of replacing each individual stop codon with a synthetic version was laborious, and doing so was possible only because E. coli does not have many stop codons to begin with.

"There are only 321 instances [of stop codons], and that's enough that we can do it individually. It doesn't require a whole genome synthesis," Robertson said.

However, when it came to sense codons, the researchers faced the challenge of replacing 18,000 different codons with synthetic counterparts, a herculean task when working on one codon at a time. So instead, the team used a combination of CRISPR gene-splicing and current DNA synthesis techniques to build a whole new genome incorporating the team's synthetic sense codons.

"You can't make those individually. [Instead], you make the whole thing from scratch. You redesign it. And that's what we did," Robertson said.

Robertson and his colleagues first published their genome synthesis in a 2019 study in *Nature*, but in the present study, they put their bacterial strain to the test against viral infection. They found that because the synthetic amino acids behave functionally like their natural counterparts, the bacteria can still grow and reproduce normally while being all but immune to infection by viruses, which cannot read the new DNA.

And while the immediate applications for improving biotechnology processes are striking enough, these are just the "tip of the iceberg," according to Abhishek Chatterjee, an associate professor of chemistry at Boston College, who co-authored a perspective article published alongside the new research.

Chaterjee suggests that the ability to add synthetic codons to bacterial DNA opens the possibility of using bacteria like E. coli to produce polymer compounds beyond regular proteins, such as plastic, relying on bacteria to do the synthesis work instead of using industrial chemical methods, which can be inefficient and inaccurate.

"You're basically operating at the level of proteins to create material that simply did not exist before, formed out of non-natural building blocks, with the same kind of efficiency as our natural polymers," Chaterjee said.

And while these applications are not within our grasp just yet, both Chaterjee and Robertson are confident that we will begin to see these developments within the decade. Robertson and his team are currently working on getting their engineered E. coli to form different types of bonds between amino acids, which could yield new classes of molecules that are "genetically encoded but beyond just protein-based structures," as he put it.

More broadly, Robertson hopes that their discovery will be a "paradigm shift" for biotechnology, making manufacturing and biosynthesis more efficient and sustainable in the long term.

"A lot of crude-oil extracts are used to make plastics, so if we can avoid something like that and make it with cells, and then develop approaches to degrade these as well," he said, "that can get us to a circular bioeconomy, as we call it. That's one big vision."

The study, "Sense codon reassignment enables viral resistance and encoded polymer synthesis," published June 3 in Science, was authored by Wesley E. Robertson, Louise F.H. Funke, Daniel de la Torre, Julius Fredens, Thomas S. Elliott, Martin Spinck, Yonka Christova, Daniele Cervettini, Franz L. Böge, Kim C. Liu, Salvador Buse, Sarah Maslen and Jason W. Chin, Medical Research Council Laboratory of Molecular Biology; and George P.C. Salmond, University of Cambridge.