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A bacterium has been engineered to make ‘unnatural’ proteins

Life but different
Andrew Brookes/Plainpicture

By **Aylin Woodward**

THE genetic alphabet just got 50 per cent bigger. A bacterium has been engineered not only to have two more “letters” in its DNA, but to use them to make new proteins that have never existed in nature.

The genes carried on DNA are instruction manuals for making proteins, which do essential jobs like digesting food and fighting infection. The letters that make up the genetic code are molecules called bases. All known living things use the same four letters: A, C, G and T.

The new bacterium has two more synthetically engineered bases, called “X” and “Y”.

Floyd Romesberg at the Scripps Research Institute in La Jolla, California, and his team have been working on X and Y for 13 years. In 2014, they moved them from a test tube into an *E. coli* bacterium. The cell was able to copy the DNA with X and Y in it, and pass that DNA to its daughter cells.

Now they have gone a step further and used the altered DNA to make new proteins (*Nature*, DOI: 10.1038/nature24659).

“Every protein ever translated has been decoded using a four-letter alphabet, but now we’ve decoded proteins using a six-letter one,” says Romesberg.

Cells make proteins by stringing together smaller molecules called amino acids. They do this in factories called ribosomes, which use the letters from the DNA as instructions.

“Every protein ever made was built using a four-letter alphabet. We’re using a six-letter one”

The letters are read in groups of three, such as “ACG”, called codons. There are 64 possible codons, which is more than enough to specify the 20 amino acids used in nature. But Romesberg’s bacterium is far more versatile. Thanks to the extra two letters, the number of possible three-letter codons jumps to 216.

The 152 new codons can be assigned to amino acids beyond the original 20. New amino acids mean new proteins, which might be able to do different things from their counterparts found in nature.

“Work such as this shows that the genetic code… is malleable and subject to expansion,” says Farren Isaacs at Yale University in Connecticut.

It is a “landmark development”, says Alex Deiters at the University of Pittsburgh in Pennsylvania. It is doubly significant because the new bases are linked by a different type of chemical bond not previously used in DNA.

In the short term, Romesberg says it could lead to new protein-based drugs, improving therapies used to treat cancers and autoimmune disorders. But in the longer term, he wants to make new types of life that can do things that natural organisms can’t. He suggests creating microorganisms that can target specific cells or organs in our bodies for therapies, or clean up oil spills by breaking down pollutants into safer chemicals.

"What proteins can do must somehow be limited by the building blocks they can use," says Romesberg. "If we give them new building blocks, there must be something new they can do."

Romesberg says the study is also evidence that life could have evolved in many ways, and that life on another planet could be genetically different to anything on Earth. "It's been a question for hundreds of years: are we the way we are because we're the only solution, or a solution?" he says. "In the smallest possible way, but for the first time, we have data that suggests we are merely a solution."

Romesberg's study is the latest to expand the existing genetic code. Last year, another team reported they were part way through recoding an *E. coli* bacterium with an alternate genetic code, so that it could make proteins with up to four artificial amino acids.

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