How scientists redesign DNA codes

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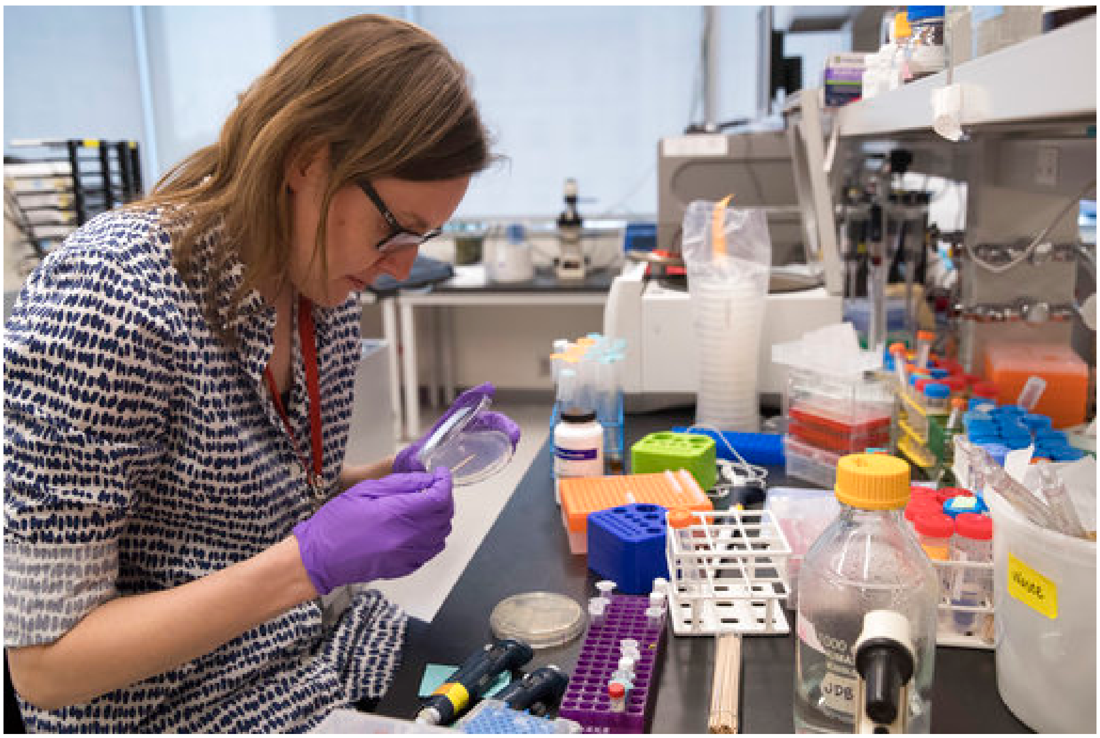

In this Tuesday, April 25, 2017 photo, post doctoral fellow Leslie Mitchell, works at her bench at a New York University lab in the Alexandria Center for Life Sciences in New York, where researchers are attempting to create completely man-made, custom-built DNA. Mitchell says it took her a couple months to build her chromosome but longer to debug. "The tiniest change in the code can have dramatic effect on growth," she said. "We are learning new rules about how cells operate by building from scratch." (AP Photo/Mary Altaffer)

Scientists are working to create yeast that operates with custom-made DNA.

They have long been able to make specific changes in an organism's DNA. Now, they're pushing into the more radical step of starting over, and building redesigned versions from scratch.

Their work is part of a bold and controversial pursuit aimed at creating custom-made DNA codes to be inserted into living cells to change how they function, or even provide treatments for diseases. It could also someday help give scientists the profound and unsettling ability to create entirely new organisms.

The genetic code is like a book written with an alphabet of only four letters: A, C, G, and T. Chemical building blocks that correspond to these letters line up in DNA molecules like links in a chain; genes are made up of specific sequences of those building blocks. These sequences tell the yeast cell how to build particular proteins.

The complete DNA code for yeast, called its genome, contains about 12 million letters. An international scientific team aims to add, delete or alter about a million of the DNA letters.

Yeast DNA is spread across 16 large chunks called chromosomes, which were parceled out among the team's labs to tackle.

So how do you redesign and build a chromosome? We asked Leslie Mitchell, a researcher at New York University. She created a 240,000-letter synthetic yeast chromosome, starting while she was at Johns Hopkins University in Baltimore.

Here's the recipe:

1. On a computer, start with the natural DNA sequence of the letters across a chromosome.

2. Tell the computer to make specific alterations, such as:

— Every time it sees the letter series TAG at the end of a gene, change it to TAA. Both triplets deliver the same message to the yeast's machinery for making protein, so the change doesn't affect the yeast. But the TAG triplet could be used in a different place to make the yeast produce a protein from building blocks not found in nature, for example.

— Delete a class of genes called 'tRNA genes' from their normal positions, where they can impair the process of duplicating the genome before a yeast cell divides. These genes will be relocated to their own, new chromosome, where they can do their jobs without causing trouble.

— Insert bits of DNA code that will let researchers rearrange the order of genes on the chromosomes, like shuffling a deck of cards. This way, scientists can experiment with many different reshufflings to see which one makes yeast grow best, or perform best in some other way.

3. Once the alterations are done, break the redesigned code into lengths of about 10,000 letters apiece and have a company create chunks of DNA that reflect each of these segments. Chunks of that size can be easily manipulated in a laboratory.

4. In the test tube, use a chemical reaction to glue three to six of these chunks together into a "megachunk."

5. Take ordinary yeast and use this 30,000-60,000-letter megachunk to replace the corresponding segment of natural DNA. Yeast will do this without much coaxing.

6. If the yeast doesn't grow normally, identify and fix the problem in the megachunk. This is called debugging. If it's fine, add the next megachunk.

7. Repeat steps 4-6 until the entire chromosome has been replaced with megachunks of synthetic DNA.

Mitchell said it took her a couple months to build her chromosome but longer to debug. "The tiniest change in the code can have dramatic effect on growth," she said. "We are learning new rules about how cells operate by building from scratch."