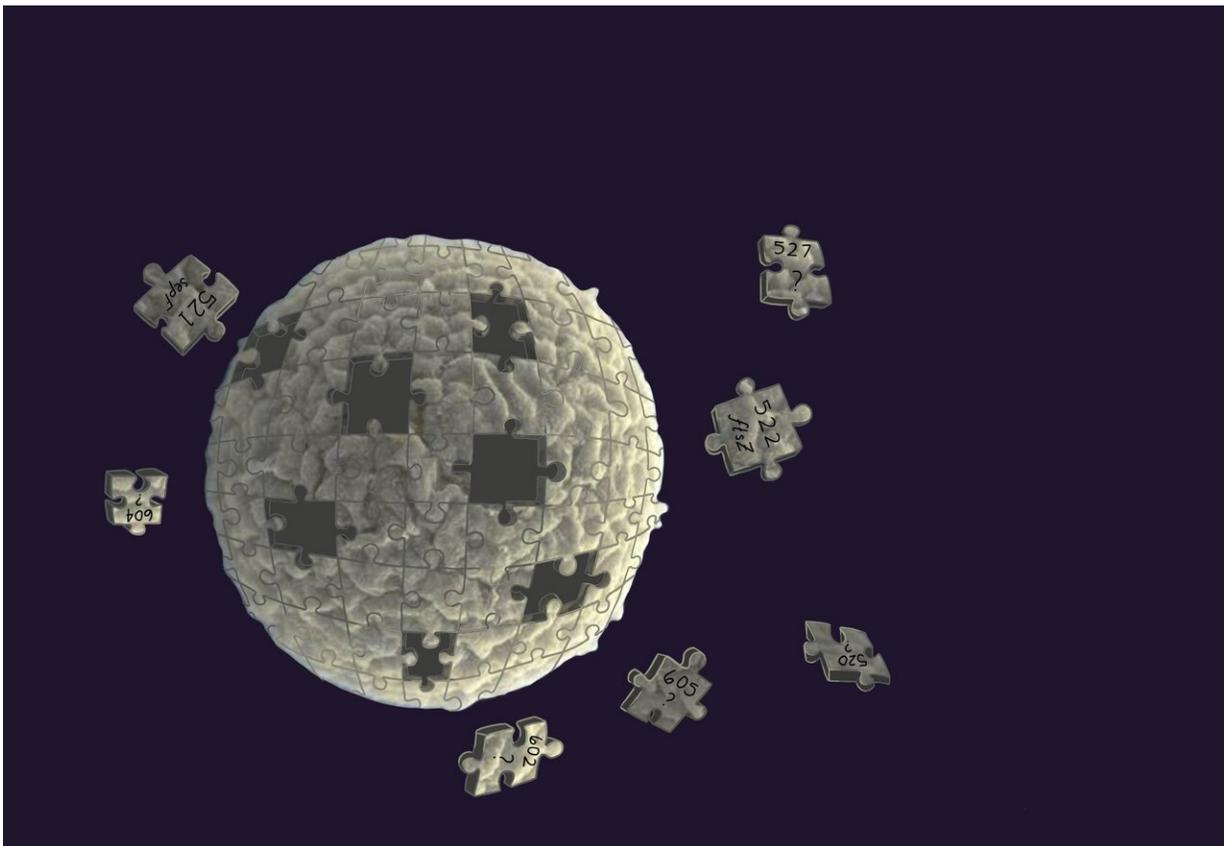


Scientists create simple synthetic cell that grows and divides normally

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An illustration of the simple synthetic cell JCVI-syn3A. Credit: © Emily Pelletier

Five years ago, scientists created a single-celled synthetic organism that, with only 473 genes, was the simplest living cell ever known. However,

this bacteria-like organism behaved strangely when growing and dividing, producing cells with wildly different shapes and sizes.

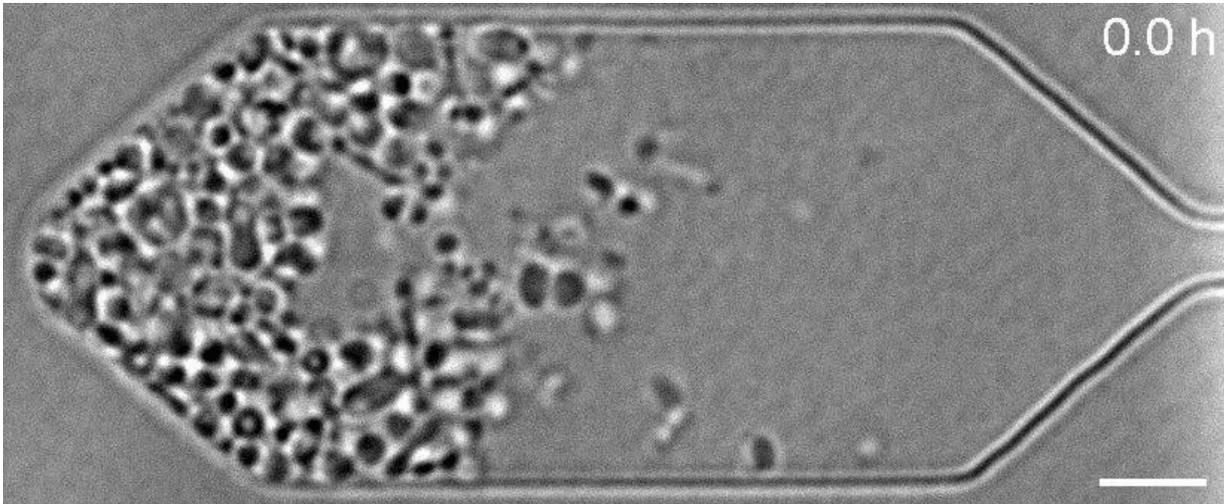
Now, scientists have identified seven [genes](#) that can be added to tame the cells' unruly nature, causing them to neatly divide into uniform orbs. This achievement, a collaboration between the J. Craig Venter Institute (JCVI), the National Institute of Standards and Technology (NIST) and the Massachusetts Institute of Technology (MIT) Center for Bits and Atoms, was described in the journal *Cell*.

Identifying these genes is an important step toward engineering [synthetic cells](#) that do useful things. Such cells could act as small factories that produce drugs, foods and fuels; detect disease and produce drugs to treat it while living inside the body; and function as tiny computers.

But to design and build a cell that does exactly what you want it to do, it helps to have a list of essential parts and know how they fit together.

"We want to understand the fundamental design rules of life," said Elizabeth Strychalski, a co-author on the study and leader of NIST's Cellular Engineering Group. "If this cell can help us to discover and understand those rules, then we're off to the races."

Scientists at JCVI constructed the first cell with a synthetic genome [in 2010](#). They didn't build that cell completely from scratch. Instead, they started with cells from a very simple type of bacteria called a mycoplasma. They destroyed the DNA in those cells and replaced it with DNA that was designed on a computer and synthesized in a lab. This was the first organism in the history of life on Earth to have an entirely synthetic genome. They called it JCVI-syn1.0.



A time lapse video showing cells of the synthetic organism JCVIsyn3.0 growing and dividing under a light microscope, from a research collaboration between the J. Craig Venter Institute, the National Institute of Standards and Technology and the Massachusetts Institute of Technology Center for Bits and Atoms. The scale bar represents 50 micrometers. Credit: NIST/MIT

Since then, scientists have been working to strip that organism down to its minimum genetic components. The super-simple cell they created five years ago, dubbed JCVI-syn3.0, was perhaps too minimalist. The researchers have now added 19 genes back to this cell, including the seven needed for normal cell division, to create the new variant, JCVI-syn3A. This variant has fewer than 500 genes. To put that number in perspective, the *E. coli* bacteria that live in your gut have about 4,000 genes. A human cell has around 30,000.

Identifying those seven additional genes took years of painstaking effort by JCVI's synthetic biology group, led by co-author John Glass. Co-lead author and JCVI scientist Lijie Sun constructed dozens of variant strains by systematically adding and removing genes. She and the other researchers would then observe how those genetic changes affected cell

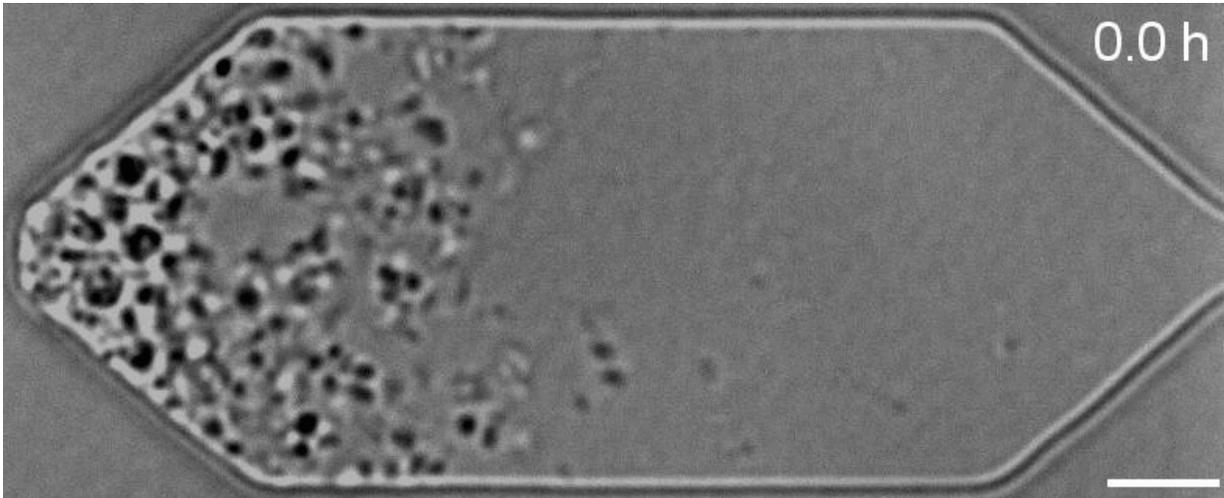
growth and division.

NIST's role was to measure the resulting changes under a microscope. This was a challenge because the cells had to be alive for observation. Using powerful microscopes to observe dead cells is relatively easy. Imaging [live cells](#) is much harder.

Holding these cells in place under a microscope was particularly difficult because they are so small and delicate. A hundred or more would fit inside a single E. coli bacterium. Tiny forces can tear them apart.

To solve this problem, Strychalski and MIT co-authors James Pelletier, Andreas Mershin and Neil Gershenfeld designed a microfluidic chemostat—a sort of mini-aquarium—where the cells could be kept fed and happy under a light microscope. The result was stop-motion video that showed the synthetic cells growing and dividing.

One video shows JCVI-syn3.0 cells—the ones created five years ago—dividing into different shapes and sizes. Some of the cells form filaments. Others appear to not fully separate and line up like beads on a string. Despite the variety, all the cells in that video are genetically identical.



A time lapse video showing cells of the synthetic organism JCVI-syn3A growing and dividing under a light microscope, from a research collaboration between the J. Craig Venter Institute, the National Institute of Standards and Technology and the Massachusetts Institute of Technology Center for Bits and Atoms. The scale bar represents 50 micrometers. Credit: NIST/MIT

Another video shows the new JCVI-Syn3A cells dividing into [cells](#) of more uniform shape and size.

These videos and others like them allowed the researchers to observe how their genetic manipulations affected the [cell growth](#) and division. If removing a gene disrupted the normal process, they'd put it back and try another.

"Our goal is to know the function of every gene so we can develop a complete model of how a cell works," Pelletier said.

But that goal has not been reached yet. Of the seven genes added to this organism for normal cell division, scientists know what only two of them do. The roles that the other five play in cell division are not yet known.

"Life is still a black box," Strychalski said. But with this simplified synthetic cell, scientists are getting a good look at what's going on inside.

More information: James F. Pelletier et al. Genetic requirements for cell division in a genomically minimal cell, *Cell* (2021). [DOI: 10.1016/j.cell.2021.03.008](https://doi.org/10.1016/j.cell.2021.03.008)

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