Synthetic genome resets biotech goals

The assembly of a genome that can 'reboot' cells of a closely related species is one step in a much longer path.

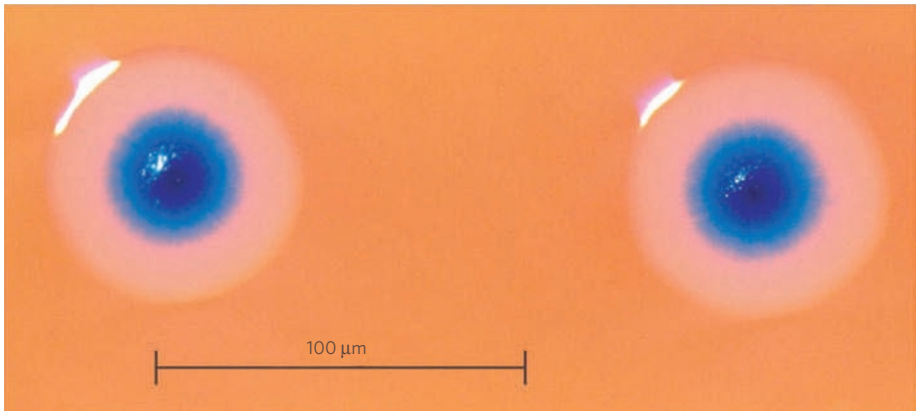
Synthetic biology is a field with an audacious but ultimately utilitarian goal: to redesign the building blocks of life to serve the needs of humanity. It is also an endeavour that challenges clear-cut definitions of natural versus artificial life.

Last week's announcement by researchers in the United States that they have created a synthetic copy of a bacterial genome and used it to commandeer the cell of a closely related species is a landmark on both fronts (D. G. Gibson *et al. Science* doi:10.1126/science.1190719; 2010). The group's success, much-anticipated by the scientific community, provides tools for manipulating the genome on a significantly larger scale than has previously been possible. "I think this is an important technique towards the ultimate goal of completely redesigning genomes," says Ron Weiss, a synthetic biologist at the Massachusetts Institute of Technology in Cambridge. The achievement also demonstrates just how challenging a road synthetic biologists have embarked on.

Daniel Gibson at the J. Craig Venter Institute in Rockland, Maryland, and his colleagues began with a highly accurate genome sequence they had made of the bacterium *Mycoplasma mycoides*. Using this as a template, they ordered a set of short DNA strands called 'cassettes', each about 1,000 base pairs long, from a DNA-sequencing company, then inserted the cassettes into a yeast cell, where the yeast's own genetic machinery strung them together into a copy of the natural *M. mycoides* genome. Finally, the researchers transplanted the 1.1-million-base-pair-long synthetic genome into cells of a closely related bacterial species, *Mycoplasma capricolum*. Although only the genome of the new cell was custom-built, the researchers refer to the entire cell as "synthetic" because its molecular contents quickly took on the characteristics of *M. mycoides*. "By changing the chromosome in the cell, it completely changes the cell from one form to another," Venter said in a press briefing last week.

The group encountered many stumbling blocks. In the final stages of the project, months of attempts to transplant the synthetic genome failed to yield living cells because of errors in the DNA sequence. The culprit proved to be the deletion of a single base pair in a gene involved in chromosome copying.

Finally, the genome worked, and recipient cells were transformed into viable, replicating bacteria, exhibiting the characteristics encoded by the synthetic DNA. "It's the pinnacle to date of genome-scale synthetic biology," says James Collins, a biomedical engineer at Boston University in Massachusetts.



SCIENCE/AAAS

A blue chemical marker shows colonies formed from a single cell containing the synthetic genome.

Potential applications for the technology include developing innovative ways to produce energy, creating novel sensors to monitor the environment or building bacterial factories to churn out medicines. The next challenge will be working out how to build genetic circuits — artificial sequences of genes that interact with each other in complex patterns to produce desired traits. So far, researchers can reliably design gene circuits about 15,000–25,000 base-pairs long, a sequence that contains about six to ten gene promoters. Anything larger, Weiss says, and "nobody right now will be able to give you a design that works". It's difficult to define an interesting property controlled by a larger number of genes, and combining those genes into a single network is harder still. "Getting new genes to work together is actually a major challenge," he says.

"Getting new genes to work together is a major challenge."

Weiss says he is convinced that the field will ultimately get there, but not everyone believes that embedding these circuits in an artificial genome will prove more effective than simply modifying natural genomes. Geneticist George Church of Harvard University in Boston agrees. "I think the jury is still out whether for synthetic biology you want to synthesize whole genomes or just synthesize the parts you want to change," he says.

Some observers worry that the ability to recreate an organism using only sequence data could allow bioterrorists to synthesize harmful microbes in the lab. However, this would require a high degree of technical prowess. A more likely problem, says Mildred Cho, a bioethicist at Stanford University in California, is that lab-created organisms could escape by accident, making it crucial for researchers to do as the Venter group did and insert 'watermark' DNA sequences distinguishing natural from hand-built organisms. In response to the Venter group's announcement, US President Barack Obama charged his bioethics advisory council with exploring the implications of the research in a report to be completed in six months.

Beyond utility, the technique allows researchers to pursue fundamental problems, including a longstanding goal of Venter's: synthesizing a genome with the least number of genes possible for the cell housing it to live. Christopher Voigt, a synthetic biologist at the University of California, San Francisco, notes that the technique might one day also allow researchers to remake extinct organisms, or catalogue species diversity simply by storing sequences.

That possibility is still a long way off. So far, few labs have the capability to sequence whole genomes, and Gibson, Venter and their colleagues can work with only simple organisms. The authors took advantage of yeast's cellular machinery to assemble their synthetic genome, but it is unlikely that the yeast, whose largest chromosome is only about two million base pairs long, could be used to assemble genomes of greater length. "But two million base pairs is definitely within reach," says Gibson, "and there are a lot of bacterial organisms out there that are useful and are within that range." ■

Alla Katsnelson

See also Editorial, page 397.