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First synthetic yeast chromosome revealed

US-based project recruited dozens of undergraduates to stitch DNA fragments together.

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It took geneticist Craig Venter 15 years and US$40 million to synthesize the genome of a bacterial parasite. Today, an academic team made up mostly of undergraduate students reports the next leap in synthetic life: the redesign and production of a fully functional chromosome from the baker's yeast *Saccharomyces cerevisiae*.

As a eukaryote, a category that includes humans and other animals, *S. cerevisiae* has a more complex genome than Venter's parasite. The synthetic yeast chromosome — which has been stripped of some DNA sequences and other elements — is 272,871 base pairs long, representing about 2.5% of the 12-million-base-pair *S. cerevisiae* genome.The researchers, who report their accomplishment in *Science*[1], have formed an international consortium to create a synthetic version of the full *S. cerevisiae* genome within 5 years.

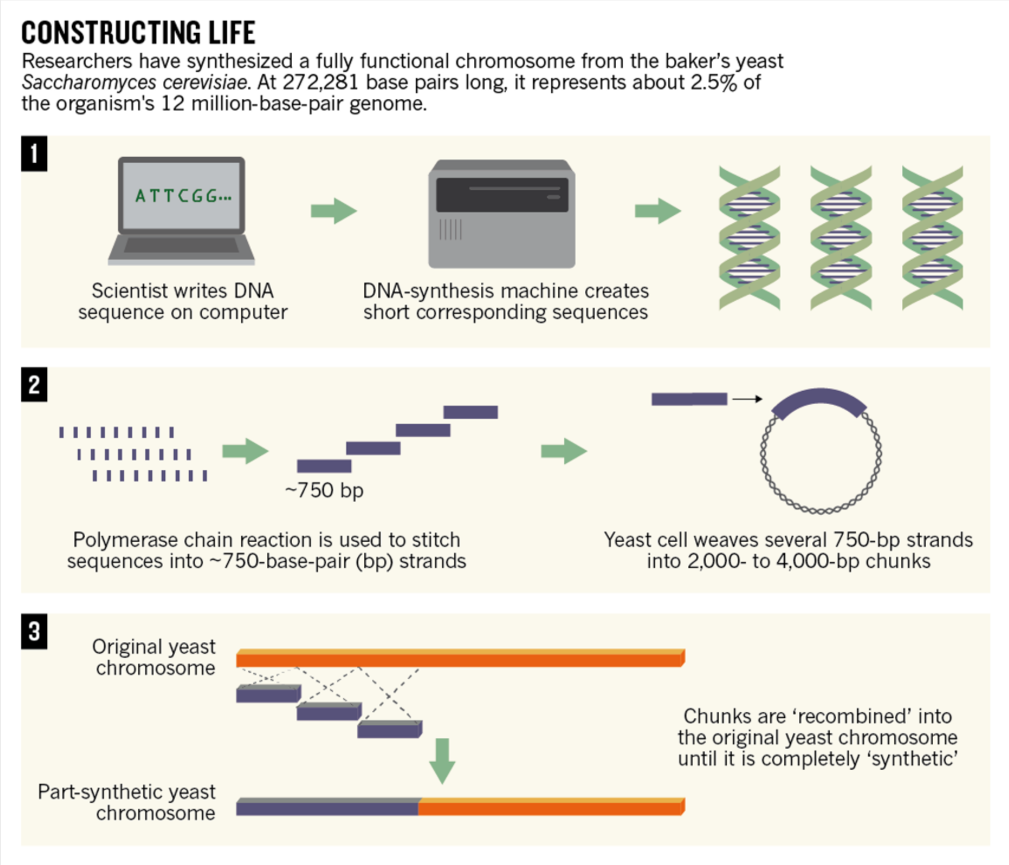
“This is a pretty impressive demonstration of not just DNA synthesis, but redesign of an entire eukaryotic chromosome,” says Farren Isaacs, a bioengineer at Yale University in New Haven, Connecticut, who was not involved in the work. “You can see that they are systematically paving the way for a new era of biology based on the redesign of genomes.”

The project began a few years ago, when Jef Boeke, a yeast geneticist at New York University, set out to synthesize the baker's yeast genome with much more drastic alterations than those demonstrated by Venter and his team in 2010.

The group at the J. Craig Venter Institute in Rockville, Maryland, had chemically synthesized short strands of DNA and stitched them together to create a version of the 1.1-million-base-pair DNA genome of the bacterium *Mycoplasma mycoides*, which was then inserted into a recipient cell[2]. Venter's team wrote a few coded 'watermarks' into the genome sequence, which spelled out the names of the team members, as well as several famous quotes. But besides these tweaks and a few other changes, the synthetic *M. mycoides* genome was identical to its blueprint.

By contrast, Boeke and his team thought that by stripping the genome of certain features to test their importance, they could justify the enormous cost and effort of synthesizing whole yeast chromosomes.

“I wasn't sceptical about whether it could be done,” Boeke says. The question, he explains, was: “How can we make this different from a normal chromosome and put something into it that's really going to make it worthwhile?”



'Build-a-genome'

The scientists decided to omit certain DNA sequences from their synthetic chromosome, such as elements with the ability to move around the genome, known as transposons, and sections within genes that do not encode proteins, called introns. They also inserted a 'scrambling' system — which shuffles and removes genes — to provide a way of testing whether a given gene is essential to survival.

The initial plan was to contract commercial DNA-synthesis companies to create large chunks of the yeast genome to Boeke's specifications. But the first order, a 90,000-base-pair chunk of DNA corresponding to a portion of the *S. cerevisiae* chromosome IX[3], cost roughly US$50,000 and took a year to arrive.

"I'll be dead long before this project will ever be finished," Boeke remembers thinking. So he turned his mind to thinking up other ways of assembling chromosome-length stretches of DNA.

He realized that university campuses were full of undergraduate students interested in dabbling in research. In the summer of 2007, he taught the first "build-a-genome" course at Johns Hopkins University in Baltimore, Maryland, and the classes have been offered most terms since.

Each student makes their own stretch of the yeast genome, which involves stitching together very short lengths of DNA created by a DNA-synthesis machine into ever-larger chunks. These chunks are then incorporated into the yeast chromosome, a few at a time, through a process called homologous recombination. Eventually, this results in an entirely synthetic chromosome. Many of the students are co-authors on Boeke's *Science* paper, which details the synthesis of *S. cerevisiae*'s chromosome III.

Despite all its alterations, yeast cells containing the synthetic chromosome grew just as well as normal yeast. "What's amazing about it is that there are over 50,000 base pairs that were either deleted, inserted or changed in that chromosome of 250,000 base pairs, and it works. That's kind of a remarkable effect," Boeke says.

Global push

The team has grander experiments in mind — including many that depend on creating an entirely synthetic yeast genome. "We'll really be able to explore the depth of what can be done to a genome and still come out with viable cells that are recognizable as yeast," Boeke says.

To make an entire yeast genome from scratch, Boeke has enlisted collaborators — including undergraduate students — from around the world. A build-a-genome class at Tianjin University in China is tackling one of *S. cerevisiae*'s 16 chromosomes, as are teams at BGI-Shenzhen in China, Imperial College London and a few US institutions. Boeke says that half the DNA sequences have already been made.

“This work is another remarkable example of how synthetic biology can be used to rewrite chromosome sequences at a sizable scale,” Venter and his colleagues say in a written statement. “This work is a prelude to and demonstrates the feasibility of extensive refactoring or streamlining of the other chromosomes.”

Tom Ellis, a synthetic biologist at Imperial College London who is leading the effort to synthesize *S. cerevisiae* chromosome XI, sees the project as a riposte to factory-scale synthetic biology. “This shows that the academic, open-source reply to what Venter did is: let's set up some labs with undergraduates, and they can do the same. They can make chromosomes as well.”

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References

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2. Gibson, D. *et al*. *Science* **329**, 52–56 (2010).
3. Dymond, J. S. *et al*. *Nature* **477**, 471–476 (2011).