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In a first, scientists manufacture genome of a bacteria

By Andrew Pollack
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Taking a significant step toward the creation of man-made forms of life, researchers reported Thursday that they had manufactured the entire genome of a bacterium by painstakingly stitching together its chemical components.

While scientists had previously synthesized the complete DNA of viruses, this is the first time it has been done for bacteria, which are much more complex. The genome is more than 10 times as long as the longest piece of DNA ever previously synthesized.

The feat is a watershed for the emerging field called synthetic biology, which involves the design of organisms to perform particular tasks, such as making biofuels. Synthetic biologists envision being able one day to design an organism on a computer, press the "print" button to have the necessary DNA made, and then put that DNA into a cell to produce a custom-made creature.

"What we are doing with the synthetic chromosome is going to be the design process of the future," said Dr. J. Craig Venter, the boundary-pushing gene scientist. He assembled the team that made the bacterial genome as part of his well publicized quest to create the first synthetic organism. The work was published online Thursday by the journal Science.

But there are concerns that synthetic biology could be used to make pathogens, or that errors by well-intended scientists could produce organisms that run amok. The genome of the smallpox virus can in theory now be synthesized using the techniques reported on Thursday, since it is only about one-third the size of the genome manufactured by Dr. Venter's group.

In any case, there are many hurdles to overcome before Dr. Venter's vision of "life by design" is realized. The synthetic genome made by Dr. Venter's team was not designed from scratch, but rather was a copy, with only a few changes, of the genetic sequence of a tiny natural bacterium called Mycoplasma genitalium.

Moreover, Dr. Venter's team, led by a Nobel laureate, Hamilton Smith, has so far failed to accomplish the next - and biggest - step. That would be to insert the synthetic chromosome into a living microbe and have it "boot up" and take control of the organism's functioning.

If that happened, it would be considered by some to be the creation of the first synthetic organism. The failure to achieve that so far has tempered the reception of some outside scientists.

"No matter how they praise the quality of the synthetic DNA, they have no idea whether it is biologically active," said Eckard Wimmer, a professor at Stony Brook University who created live polio virus in 2002 using synthetic DNA and the publicly available genome sequence.

George Church, a professor of genetics at Harvard Medical School, said, "Right now, all they've done is shown they can buy a bunch of DNA and put it together." Dr. Venter's team reported successfully doing such a chromosome transplant last year, but it involved the natural genome of one type of Mycoplasma being put into another species of that bacterium.

Dr. Venter said each pair of donor genome and recipient cell presents unique problems. The scientists also think they interrupted the functioning of one crucial gene by their assembly process, a correctable problem.

"It's not a slam dunk, or we would be announcing it today," he told reporters. Still, he expressed confidence, saying, "I will be equally surprised and disappointed if we can't do it in 2008."

The bacterial genome that was synthesized consisted of 582,970 base pairs, the chemical units of the genetic code that are represented by the letters A, C, G, and T. The longest stretch of synthetic DNA previously reported in a scientific paper was about 32,000 bases long, though some gene synthesis companies say they can attach about 50,000 bases.

The machines that can string together bases make lots of errors, so it is not practical to make a string of more than 50 to 100 bases at a time. But some companies - the foundries of the biotechnology era -

now make genes thousands of bases long by splicing those shorter strings together.

The Venter team ordered 101 such sequences, each 5,000 to 7,000 bases long, from these companies. They then joined them together into bigger pieces and still bigger pieces. In the final step, four big pieces were put into yeast, which hooked them together using a natural gene-repair mechanism.

The process was started in late 2002, Dr. Venter said, and undoubtedly cost millions of dollars. That led some scientists to question why someone would want to synthesize an entire organism. Scientists can already make useful organisms - including some that are now starting to be make biofuels - by modifying existing ones using genetic engineering.

"It's not entirely clear to me what the immediate purpose of doing something like this is," said Jeremy Minshull, chief executive of DNA 2.0, a company that supplied some of the DNA stretches to the Venter team. "To some extent, it's something that was driven by 'I want to be the first person to do it.' " Right now, Minshull said, scientists do not know enough about how living things work to design an entire genome: "Now our synthetic capability way outpaces our understanding of what we want to do."

For now, that is the case, Dr. Venter concedes. He has a company, Synthetic Genomics, that is using genetic engineering to produce biofuels. It is using organisms other than Mycoplasma genitalium, which was chosen for the synthetic genome project because its genome is tiny, one-tenth the size of the genomes of some other bacteria. But Mycoplasma is not suited to industrial production.

Still, Dr. Venter and some other scientists say that DNA synthesis is following the path of computer chips, with capability rising rapidly and cost - now about $1 per base - falling swiftly. At some point, they say, it will become faster and cheaper for scientists to design and synthesize an organism from scratch rather than cut and paste genes from one organism to another, just as it is sometimes easier for a writer to type a fresh draft rather than edit an existing one.

The ability to synthesize genomes would allow for more scientific experimentation. Dr. Venter said he would now be able to create organisms missing dozens of genes to answer the initial question that sparked the research ten years ago: What is the minimum set of genes needed for life?

Dr. Venter, who runs the nonprofit J. Craig Venter Institute in Rockville, Maryland, has been a pioneer in genomics. He is best known for sequencing the human genome in a race with the publicly funded Human Genome Project. The method his team used was novel at the time, but is now widely accepted. It turned out that the genome his team sequenced was his own, making Dr. Venter the first person to have his complete DNA sequence published.

Some activist groups say Dr. Venter is going too far, too fast, this time, and that the entire field of synthetic biology needs outside regulation to prevent the introduction of dangerous organisms, created either by evil intent or by innocent error.

"The fact that he's pushing ahead with this without any societal oversight is very worrying," said Jim Thomas, a program manager at the ETC Group, an activist group based in Canada. He also said it was worrisome that Dr. Venter was applying for very broad patents that could give him a near monopoly over the field of synthetic organisms.

Dr. Venter said the synthetic biology field has been discussing ethics and safety steps since it started and that his work had been reviewed by ethicists.

In the new genome, he said, one gene was changed to make any resulting organism non-infective. (Mycoplasma genitalium, which can be transmitted sexually, is associated with inflammation, though its exact role in causing disease is not well understood.) The team also added some DNA segments to the genome to serve as "watermarks," allowing scientists to distinguish the synthetic genome from the natural one.

That raises new possibilities of using microbes as a method of communication. Dr. Venter said the watermarks contain coded messages. Sleuths will have to determine the amino acid sequence coded for by the watermarks, in order to decipher the message. "It's a fun thing that has a practical application," he said.

Correction:

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