Researchers Take Step Toward Synthetic Life

By ANDREW POLLACK

Taking a significant step toward the creation of synthetic forms of life, researchers reported Thursday that they had manufactured the entire genome of a bacterium by stitching together its chemical components.

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

The feat is a watershed for the emerging field called synthetic biology, which involves the design of organisms to perform particular tasks, like making biofuels. Synthetic biologists envision being able 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 J. Craig Venter, the boundary-pushing gene scientist.

Dr. Venter 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 natural bacterium called Mycoplasma genitalium.

Moreover, Dr. Venter’s team, led by a Nobel laureate, Hamilton O. Smith, has yet 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 functions.

If that happened, it would be considered by some to be the creation of the first synthetic organism.
The failure to achieve that tempered the reaction of some outside scientists to the announced achievement.

“Right now, all they’ve done is shown they can buy a bunch of DNA and put it together,” said George M. Church, a professor of genetics at Harvard Medical School.

Dr. Venter’s team last year reported successfully doing such a chromosome transplant, but it was with the natural genome of one type of Mycoplasma transplanted into another species of that bacterium.

Dr. Venter said in a telephone news conference Thursday that each pair of donor genome and recipient cell presented unique problems. The scientists also think they interrupted the functioning of one crucial gene, a correctable problem.

“It’s not a slam dunk or we would be announcing it today,” Dr. Venter told reporters. Still, he said, “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 represented by the letters A, C, G and T. The longest stretch of synthetic DNA reported in a scientific paper was about 32,000 bases long, though some companies say they have made ones with about 50,000.

The machines that string bases together make many errors, so it is impractical to make a string of more than 50 to 100 bases at once. But some companies — the foundries of the biotechnology era — now make genes thousands of bases long by splicing the shorter strings.

The Venter team ordered 101 such sequences, each 5,000 to 7,000 bases long, from these companies. It then joined them into ever-bigger pieces. Finally, 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 cost millions of dollars. That led some scientists to question why someone would want to synthesize an entire organism when existing organisms can be modified through genetic engineering.

“To some extent, it’s something that was driven by ‘I want to be the first person to do it,’ ” surmised Jeremy Minshull, chief executive of DNA 2.0, a company that supplied some of the DNA stretches to the Venter team.

Dr. Minshull said that scientists did not yet know enough about how living things work to design an entire genome. “Our synthetic capability way outpaces our understanding of what we want to do,” he said.

For now, that is the case, Dr. Venter concedes. He runs a company, Synthetic Genomics, that is
using genetic engineering to produce biofuels. But he and other scientists say that DNA synthesis is following the path of computer chips, with capability rising rapidly and costs — now about $1 per base — falling swiftly. At some point, they say, it will become faster and cheaper for scientists to synthesize an organism from scratch rather than cut and paste genes from one organism to another.

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 inspired the research in 1995: What is the minimum set of genes needed for life?

Dr. Venter, who runs the nonprofit J. Craig Venter Institute in Rockville, Md., is most known for sequencing the human genome in a race with the publicly financed Human Genome Project.

Some activist groups say that Dr. Venter is going too far, too fast, this time, and that synthetic biology needs outside regulation to prevent the introduction of dangerous organisms, created 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, a technology watchdog group based in Canada. He also said it was worrisome that Dr. Venter was applying for very broad patents in synthetic biology.

Dr. Venter said that the field had discussed ethics and safety 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 noninfective. (Mycoplasma genitalium, which can be transmitted sexually, is associated with inflammation.)

The team also added some DNA segments to serve as “watermarks,” allowing scientists to distinguish the synthetic genome from the natural one.

These watermarks, Dr. Venter noted, contain coded messages. Sleuths would have to determine the amino acid sequence coded for by the watermarks to decipher the message.

“It’s a fun thing that has a practical application,” he said.