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Life after the synthetic cell

Nature asked eight synthetic-biology experts about the implications for science and society of the "synthetic cell" made by the J. Craig Venter Institute (JCVI). The institute's team assembled, modified and implanted a synthesized genome into a DNA-free bacterial shell to make a self-replicating *Mycoplasma mycoides*.

The power and the pitfalls

Mark Bedau
Professor of philosophy and humanities, Reed College, Oregon

The "synthetic cell" created by Craig Venter and his colleagues (D. G. Gibson *et al. Science* doi:10.1126/science.1190719; 2010) is a normal bacterium with a prosthetic genome. As the genome is only about 1% of the dry weight of the cell, only a small part of the cell is synthetic. But the genome is pivotal because it contains the hereditary information that controls so much of a cell's structure and function.

The ability to make prosthetic genomes marks a significant advance over traditional genetic engineering of individual genes. The prosthetic genome contains all the information in the natural genome that it supplants, except for a few minor differences (for example, some 'watermarks' were added). There is no technical reason to stop there; any of the information in a prosthetic genome can be changed. Tomorrow's synthetic cell could be radically unlike anything encountered in the history of life.

Putting prosthetic genomes into bacteria raises important scientific and societal issues, beyond those raised by biotechnology in general and genetic engineering in particular. I will mention just four.

First, we now have an unprecedented opportunity to learn about life. Having complete control over the information in a genome provides a fantastic opportunity to probe the remaining secrets of how it works.

Second, even the simplest forms of life have unpredictable, emergent properties. These properties are often useful and we want to control them, but their unpredictability presents a conundrum for traditional engineering. We must develop and perfect methods for engineering emergence.

Third, these new powers create new responsibilities. Nobody can be sure about the consequences of making new forms of life, and we must expect the unexpected and the unintended. This calls for fundamental innovations in precautionary thinking and risk analysis.

Finally, a prosthetic genome hastens the day when life forms can be made entirely from non-living materials. As such, it will revitalize perennial questions about the significance of life — what it is, why it is important and what role humans should have in its future. Although these questions are controversial and difficult to resolve, society will gain from the effort.

Now let's lower costs

George Church
Geneticist, Harvard Medical School

This milestone and many like it should be celebrated. But has the JCVI created 'new life' and tested vitalism? Not really. The semi-synthetic mycobacterium is not changed from the wild state in any fundamental sense. Printing out a copy of an ancient text isn't the same as understanding the language. We already had confidence in our ability to make synthetic DNA and get it to function in cells. The grand challenge remains understanding the parts of cells that help the DNA to function. This will be addressed by genetics, biochemistry and three-dimensional structures of the core life processes of biopolymer synthesis.

Synthetic life does tell us a few things about natural life. Trimming down genomes reveals whether we've missed anything essential for speed, efficiency and robustness. From this viewpoint, starting with rapid replication and high tolerance for chemical production makes *Escherichia coli* the industry standard over slower and more fragile *Mycoplasma*. DNA-synthesis milestones are also important in getting people to dream of projects only doable at the whole-genome scale — for example, making cells resistant to all viruses, enzymes or predators. If a 'minimal genome' turns out to be only one gene, we may find larger synthetic genomes more edifying. Thus, the jump in the new JCVI paper from their previous 0.58- to current 1.08-million-base-pair genome is very encouraging.

With regard to regulations to prevent the release of hazardous life forms made in ways akin to the new *Mycoplasma* or by other means, there are two scenarios: bioerror and bioterror. For the former, licensing and surveillance, handled by computers, minimally inconvenience researchers, while sensitively detecting deviations from normal practice and smoothly integrating new risk scenarios. For bioterror avoidance, realistic lab ecosystems should be standardized to test the ability of new synthetic genomes to persist or exchange genes in the wild.

What we now need are ways to construct and test billions of genome combinations using protein and RNA biosensors for many or all metabolic intermediates and cell-signalling states. In combination with the sort of techniques that the JCVI has just demonstrated — but at much lower cost — this would enable researchers to select for important products such as pharmaceuticals, fuels, chiral chemicals and novel materials.

'Bottom-up' will be more telling

Steen Rasmussen
Professor of physics, University of Southern Denmark

Implementing a synthetic genome in a modern cell is a significant milestone in understanding life today. But the radical 'top-down' genetic engineering that Venter's team has done does not quite constitute a "synthetic cell" by my definition.

> **"DNA-synthesis milestones get people to dream of projects only doable at the whole-genome scale."**

Both the top-down and bottom-up camps focus on the essence of life. The top-down community seeks to rewrite the genetics program running on the 'hardware' of the modern cell, as Venter and his colleagues have done. Bottom-up researchers, such as myself, aim to assemble life — including the hardware and the program — as simply as possible, even if the result is different from what we think of as life.

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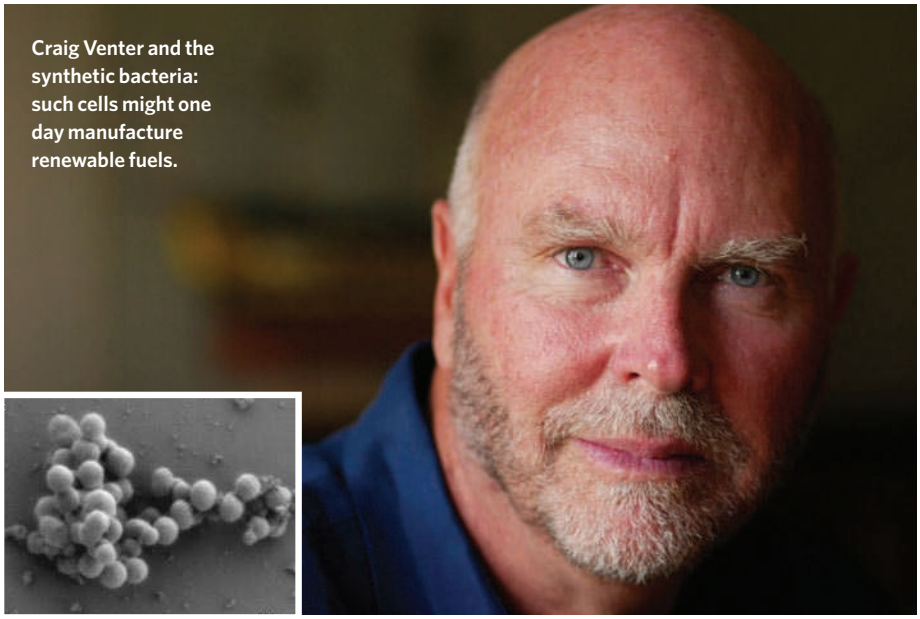

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Craig Venter and the synthetic bacteria: such cells might one day manufacture renewable fuels.

The heritable information (genes) is of course also crucial to the bottom-up approach. But without energy, clearly no life is possible, so a metabolism capable of fuelling the life process is just as necessary. A container also seems unavoidable: the energetics and information need to support each other's production, which can happen most conveniently in some sort of corral, such as a membrane.

So bottom-up scientists believe that constructing life using different materials and blueprints will teach us more about the nature of life than will reproducing life as we know it.

Owing to these different foci and the resulting variations in methods, the two communities have interacted little until recently. They are moving closer — a variety of joint research activities now have team members from both approaches. There is also more overlap because of successes in both camps. The synthetic genome is certainly one such.

The end of vitalism

Arthur Caplan
Professor of bioethics, University of Pennsylvania

Venter and his colleagues have shown that the material world can be manipulated to produce what we recognize as life. In doing so they bring to an end a debate about the nature of life that has lasted thousands of years. Their achievement undermines a fundamental belief about the nature of life that is likely to prove as momentous to our view of ourselves and our place in the Universe as the discoveries of Galileo, Copernicus, Darwin and Einstein.

More than 100 years ago, the French philosopher Henri-Louis Bergson claimed that life could never be explained simply mechanistically. Nor could it be artificially created by synthesizing molecules. There was, he argued, an "*élan vital*" — a vital force that was the ineffable current distinguishing the living from the inorganic. No manipulations of the inorganic would permit the creation of any living thing.

This 'vitalist' view has come in many forms over the centuries. Galen wrote of the 'vital spirit' in the second century; Louis Pasteur in 1862 looked to 'vital action' to explain how life exists; and the biologist Hans Driesch posited an 'entelechy' or essential force as a requisite for life as recently as 1894. The molecular-biology revolution notwithstanding, science has continued to struggle with the reducibility of life to the material. Meanwhile, Christianity, Islam and Judaism, among other religions, have maintained that a soul constitutes the explanatory essence of at least human life.

"The new synthetic technology allows resurrection of ancient bacteria."

All of these deeply entrenched metaphysical views are cast into doubt by the demonstration that life can be created from non-living parts, albeit those harvested from a cell. Venter's achievement would seem to extinguish the argument that life requires a special force or power to exist. In my view, this makes it one of the most important scientific achievements in the history of mankind.

Synthesis drives innovation

Steven Benner
Foundation for Applied Molecular Evolution, Gainesville, Florida

Synthesis is not a field. Rather, it is a research strategy that can be applied to any field in which technology allows scientists to design new subject matter. Such technology has long been available to chemistry, where it allowed theory to develop faster than in fields lacking synthesis, such as planetary science and biology.

The change for biology came in the 1970s, when biotechnology began to deliver synthetic tools. At first, biologists cut and pasted single genes, rearranging what was naturally available. Then, in the early 1980s, synthetic biologists moved away from nature, synthesizing entire genes, artificial genetic systems with extra nucleotides and proteins with more than 20 kinds of amino acid.

To do more than tinker with natural biological parts, however, a synthetic grand challenge must be at the frontier of the possible. If it is, it forces scientists to solve new problems. Should their design strategies be flawed, they will fail in ways that cannot be ignored. Thus, synthesis drives discovery and technological innovation in ways that observation and analysis cannot.

This paper shows how synthesis drives innovation at the frontier of biotechnology. Synthesizing and cloning a genome with 1.08 million base pairs might seem to be a trivial extension of the 1984 synthesis of a gene containing about 300 base pairs (K. P. Nambiar *et al. Science* **223**, 1299–1301; 1984). This paper shows that it was not. The struggle to enhance the power of synthesis just 3,000-fold produced an impressive set of technologies for creating, proofing and manipulating large amounts of genetic material.

The JCVI work may even help to link chemistry to natural history. The sequences of the genomes of extinct ancestral *Mycoplasma* species might be inferred from the sequences of various modern mycoplasmae, including *M. capricolum*, *M. genitalium* and *M. mycoides* — the three that Venter and his colleagues' synthesis started with. The new synthetic technology allows resurrection of such ancient bacteria, whose behaviour should inform us about planetary and ecological environments 100 million years ago. Some day, perhaps even planetary science might benefit from synthesis.

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Nature's limits still apply

Martin Fussenegger
Professor of biotechnology and bioengineering, ETH Zurich, Basel

Researchers at the JCVI have a track record of milestones: transplanting entire genomes between closely related prokaryotes; assembling modified genomes from large stretches of synthetic DNA; and altering engineered chromosomes to dupe the restriction machinery of target cells. Now they are back with another phenomenal achievement: they have put together a synthetic genome with the precision to program an entire organism.

It is a technical advance, not a conceptual one. Chimaeric organisms have long been created through breeding and, more recently, through the transfer of native genomes into denucleated target cells. These methods have shown that nature seems to limit the permissible speed of genetic variation: mules have some desirable features but are sterile, and clones such as Dolly the transgenic sheep inherit the biological age of the genome donor.

Venter's technical tour de force extends advanced genetic engineering to organisms that thus far have been inaccessible to modification. He calls this "going from reading our genetic code to the ability to write it". It may sound scary, but there is no guarantee that what will be written will make sense. It may end up as a fairy tale, a drama, a science-fiction novel or a documentary on new therapies.

Since appearing on the planet, mankind has rarely created something new. Instead, people help themselves to materials that are already present, and produce increasingly complex devices. This latest technology will simply increase the speed with which new organisms can be generated.

It is this speed, and the appearance of a new technology associated with living systems, that trigger discomfort. Such unease accompanies any technological breakthrough, but should a species with a programmed synthetic genome one day become useful, it would probably be contained in specific production environments. If it were ever to face a natural ecosystem, it would be challenged by rivals and would be unprepared for the competition.

Chimaeric organisms with synthetic genomes contain engineered but natural genetic components. They are subject to evolution, a natural law that cannot be tricked. Whether these organisms will face natural limits such as impaired reproduction or a shortened lifespan remains to be seen.

Got parts, need manual

Jim Collins
Professor of biomedical engineering, Boston University

Relax — media reports hyping this as a significant, alarming step forward in the creation of artificial forms of life can be discounted. The work reported by Venter and his colleagues is an important advance in our ability to re-engineer organisms; it does not represent the making of new life from scratch.

The microorganism reported by the Venter team is synthetic in the sense that its DNA is synthesized, not in that a new life form has been created. Its genome is a stitched-together copy of the DNA of an organism that exists in nature, with a few small tweaks thrown in.

Researchers in synthetic biology are designing and constructing non-natural biological circuits out of proteins, genes and other bits of DNA, and are using these circuits to rewire and reprogram organisms. But they are small in scale, consisting of only two to ten genes, which pales in comparison to the hundreds or thousands of genes making up a living cell. It turns out that it is very hard to design even a two-gene network that performs in the way that you would like. Biology is messy and complicated, and often gets in the way of clever engineering.

"Frankly, scientists do not know enough about biology to create life."

Imagine if bioengineers could program genes and cells to grow into a functioning "synthetic" heart that saved a patient in need of a transplant. The recovered patient would not be considered a synthetic organism or a form of artificial life; he or she would be viewed as a lucky individual with a synthesized heart. Venter's microorganism is analogous to the recovered patient, albeit with a transplanted, synthesized genome.

Frankly, scientists do not know enough about biology to create life. Although the Human Genome Project has expanded the parts list for cells, there is no instruction manual for putting them together to produce a living cell. It is like trying to assemble an operational jumbo jet from its parts list — impossible. Although some of us in synthetic biology may have delusions of grandeur, our goals are much more modest.

Origin of life just got closer

David Deamer
Professor of biomolecular engineering, University of California, Santa Cruz

The achievement of the JCVI team is biomolecular engineering of the highest order. But, as the authors point out in their remarkable report, they used pre-existing designs and structures. The cytoplasm of the recipient cell is not synthetic, for example. Therefore, the dictum of seventeenth-century physician William Harvey still holds: *Omne vivum ex ovo* — 'All life from eggs', meaning that all life arises from existing life. But perhaps not for much longer.

Inserting functional genes into bacteria goes back to the early 1970s, when recombinant DNA was 'invented'. A circular bacterial DNA plasmid can be cut open, using an enzyme, and a gene sequence spliced in. Bacteria take up the plasmid, express the gene and make a valuable protein. Genentech, a biotechnology company in South San Francisco, California, pioneered the first commercial application, coaxing *E. coli* to produce human insulin, and in the process spawned a multibillion-dollar industry.

The breakthrough of Venter and his colleagues is to have designed and inserted an entire genome, not just one gene. As an example of the potential of this approach, researchers at the JCVI are exploring ways to construct genomes so that photosynthetic bacteria can use light energy to produce hydrogen gas from water, just as yeast produces ethanol fuel from maize (corn) feedstock. If it works, instead of millions of hectares of farmland given over to inefficient maize production, hydrogen might be harvested from bacterial bioreactors covering thousands of acres of desert.

Now that the JCVI has demonstrated how to reassemble a microbial genome, it may be possible to answer one of the great remaining questions of biology: how did life begin? Using the tools of synthetic biology, perhaps DNA and proteins can be discarded — RNA itself can act both as a genetic molecule and as a catalyst. If a synthetic RNA can be designed to catalyse its own reproduction within an artificial membrane, we really will have created life in the laboratory, perhaps resembling the first forms of life on Earth nearly four billion years ago. ■

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