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## Venter's Build-a-Bug Workshop

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**N**ews reports on May 20, 2010, heralded a new era in scientific research, as well as a new way of thinking about the nature of life. Craig Venter and his team had created a cell controlled by an entirely synthetic genome. So, were the sensational headlines warranted? And just how much of an advance is the latest report from the Venter Institute?

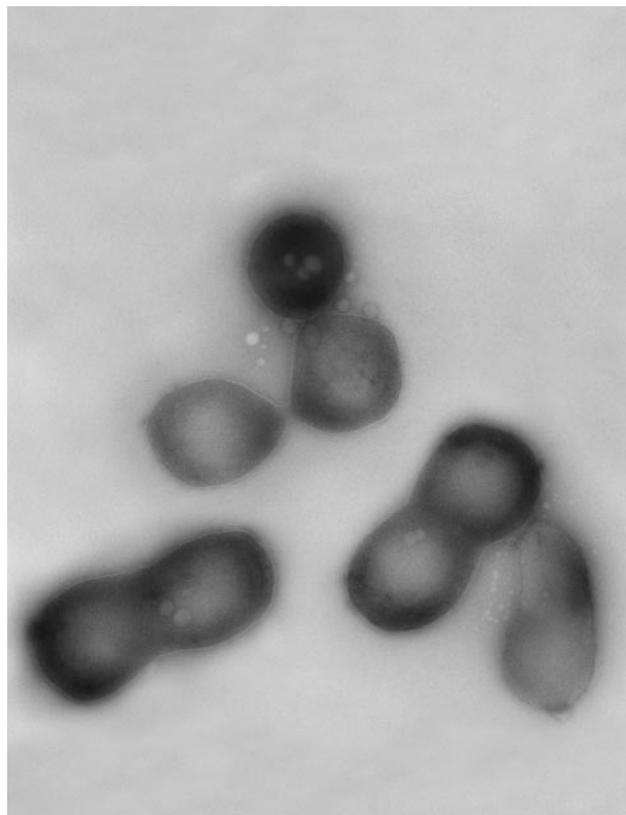
Craig Venter (Chairman and President of the J. Craig Venter Institute, Rockville, Md) always seems to be doing something scientifically brilliant and yet controversial. In the 1990s, he was sequencing the human genome through his then company, Celera, with the aim of owning the information and charging researchers for access. Then, in 2007, he sequenced the first complete diploid human genome of one individual—himself. An impressive, if some might say self-centered, feat. His new article,<sup>1</sup> reporting the first man-made cell, continues the brilliant-yet-controversial theme, with some claiming that Venter is now “playing God.”

The motivation behind Venter's latest work comes from his longstanding interest in deciphering the minimal genetic instructions required for cellular life. This interest was born back in the 1990s, and as a first step toward his goal, Venter chose to study a bacterium thought to have one of the smallest genomes of any replicating cell—*Mycoplasma genitalium*. Through extensive mutational analysis of the microbe, Venter and his team predicted that of its 480 protein-coding genes, only 300 or so were essential.<sup>2</sup>

Armed with this knowledge, Venter envisioned that he might be able to build his own minimal microbial genome from scratch. To show that such a synthetic genome is fully functional, he would then have to insert it into a genome-less cell and demonstrate that it could initiate and continue cell division.<sup>3</sup> The challenge was on.

In 2008, Venter and his team achieved the first step: they showed that they could synthesize an *M. genitalium* genome.<sup>4</sup> This synthetic genome was identical to the naturally occurring one, except for the presence of DNA “watermarks”—DNA sequence changes or insertions that encode a secret message, such as a name or email address, and thus denote the genome's synthetic origin.

Step two—transferring the synthetic genome into a genome-less cell—proved more difficult, however. While figuring out this second step, the team decided to work with *M. mycoides* and *M. capricolum*—two faster replicating cousins of *M. genitalium*. This made each experiment speedier. The team eventually hit the jackpot earlier this year, when



**Figure.** Colonies of the transformed *Mycoplasma mycoides* bacterium. Reprinted with permission from J. Craig Venter Institute. Electron micrographs were provided by Tom Deerinck and Mark Ellisman of the National Center for Microscopy and Imaging Research at the University of California at San Diego.

they managed to synthesize a full-size, DNA-watermarked *M. mycoides* genome, transfer it into an empty *M. capricolum* cell, and show that the genome could drive continuous cell replication.

The *M. mycoides* genome is almost twice the size of *M. genitalium*'s, so the team is still a long way from achieving its ultimate goal—defining and synthesizing a minimal genome. However, they have made an impressive technical step forward, which has triggered equally impressive headlines, philosophical debates, and even a presidential inquiry: as a result of the article, Barack Obama's recently formed bioethics commission has been tasked with investigating the ethical issues of synthetic biology.<sup>5</sup>

“In synthesizing novel organisms from scratch, synthetic biologists are playing God and doing so much more effectively than earlier genetic engineers. They are not just tinkering with life, they are designing and creating it,” reads a blog post by Julian Savulescu, Professor of Practical Ethics, University of Oxford, UK. Savulescu is more tempered on the telephone: “The playing God objection is reasonable as a

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reminder that we often act with inadequate information, that we act prematurely. So, it's a kind of caution," he explains. "The important issue," he insists, "is what are the risks."

Savulescu's main worry is, "the dual use possibility." Not only could the technology be used for creating organisms that benefit mankind, he says, but also, "you will be able to engineer biological super weapons, so you'll be able to engineer organisms that the human immune system hasn't seen. Either the military could do this, or terrorists, or fanatics, and it will be much easier to do than creating nuclear weapon. It gives the possibility to hundreds of thousands of people to kill millions of people in the future. I think that is an important issue."

"Certainly, anything like this is going to add some sort of incremental additional capacity to people who want to do malicious deeds," acknowledges Michelle Garfinkel, Policy Analyst for the Venter Institute. But, she adds, "It's not as if the day before the paper was published, no one could make a bioweapon and the next day everybody could make any bioweapon." Indeed, information on how to synthesize the deadly polio virus has been available since 2002.<sup>6</sup>

"I think all of the hullabaloo, with Obama looking into this, that it is going to change our view of life and everything is a gross exaggeration," says Leroy Hood (Institute for Systems Biology, Seattle, Wash). "It's a technical advance. It isn't an advance in how to do biology. And those are very different things," he continues.

Hood is impressed by the feat: "Being able to synthesize a chromosome that's a megabase and actually demonstrating that it is functional is a real step forward in synthetic biology." But, he adds, it "isn't going to directly lead us to any deep insights into life or anything else, because I think it is much too complicated." To achieve Venter's goal of understanding the minimal requirements of a cell, Hood suggests that it would be better to focus on small networks and pathways first and then piece those together, rather than to tackle an entire cell.

Venter's team is tackling the entire cell anyway. "We have already begun working on our ultimate objective, which has been to synthesize a minimal cell that has only the machinery necessary for independent life," says Daniel Gibson, who was the lead author on the new study. "We can whittle away at the synthetic genome and repeat transplantation experiments until no more genes can be disrupted and the genome is as

small as possible. This will help us to understand the function of every gene in a cell and what DNA is required to sustain life in its simplest form."

This ultimate objective might be many moons away, but in the meantime, the report acts as a springboard for other innovations, says Thomas Caskey (The Brown Foundation Institute of Molecular Medicine, Houston, Tex). "A report like that encourages many scientists to think more broadly about the technology and what the technology might be able to provide for the future." He adds, "If you take ten scientists from different sectors. . .each of those scientists probably would see a different opportunity with this system."

One area that Caskey thinks might soon make use of the technology is vaccine development. "That would be my number one choice, because all you have to do for a vaccine is to have a safe system which delivers a protective epitope." The technology might also be useful for the production of specific proteins or complex molecules, he says, although he concedes that such applications might be more complicated to establish.

Gibson has further suggestions for the technology. "We would like to use available sequencing information and create cells that can produce energy, pharmaceuticals, and industrial compounds and that sequester carbon dioxide," he says.

Currently, building such beasts would probably be much easier to achieve using existing genetic engineering techniques. Perhaps this fact in itself puts the new article and its associated furor into perspective. The cost and complexity of synthetic cell production will only go down, however, and as it does so, we can no doubt expect to see to a growing range of designer microbes becoming available.

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