Playing God with Synthetic Life? Starting with the minimal genome project

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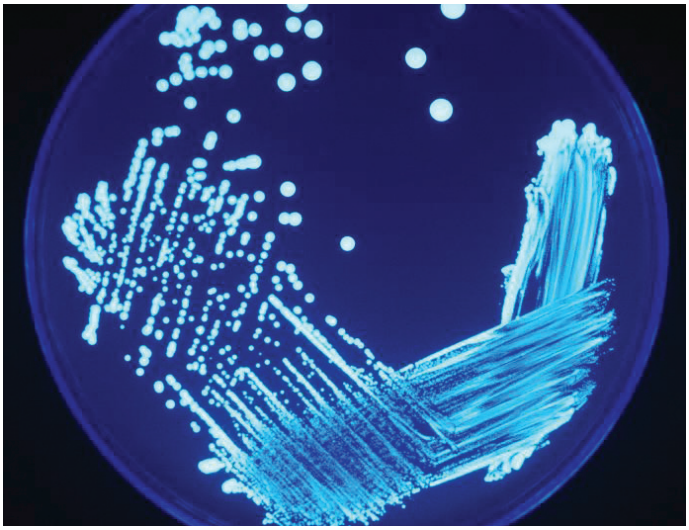
Synthetic life, a term widely connected to the realm of science fiction, is approaching reality as a group of ambitious scientists from the J. Craig Venter Institute in Rockville, Maryland are meticulously completing a series of projects with the main objective being the creation of the first synthetic organism. Unlike genetic engineering, where an organism's genome can be modified with the insertion or deletion of a gene, synthetic biology aims to create a life form entirely by de novo synthesis—the creation of an organism from precursor and foundational components.

However, in order to complete this daunting mission, a series of fundamental facts must first be known. In Venter's case, his team intends to create a synthetic bacterium entirely from its reconstructed genome. Rather than recreating the exact replica of a currently existing genome, the team determined those genes necessary to sustain life for the chosen bacterium *Mycoplasma genitalium*. The synthetic genome will then be transplanted into another, similarly-related bacterial species with the newly inserted genome taking over the functions of the cell, effectively changing the bacterial host into *M. genitalium*. If this research proves to be successful, synthetic organisms can potentially be designed to manufacture a number of useful products—from drugs to ethanol. For instance, great strides in environmental sustainability can be achieved, as researchers will be able to construct and design a genome functional for particular chemical mechanisms used for the production of biofuels.

Dr Craig Venter—the entrepreneur who previously headed a private Human Genome Project—first proposed the creation of a synthetic organism in 1995 and enlisted a group of researchers to conduct primary work at the J. Craig Venter Institute.

The group's first critical paper was published in Science, where the collaborative efforts of the researchers resulted in the genome sequencing and characterization of *Mycoplasma genitalium*, a bacterium containing the smallest known genome of any organism that can be grown in free culture [1]. A subsequent paper, published in 2005, identified 382 essential genes out of the 482 genes characterized in *M. genitalium* [2]. These 382 essential genes defined the minimal genome needed to sustain a free-living cell and represented the first major step in planning the outline of the synthetic genome.



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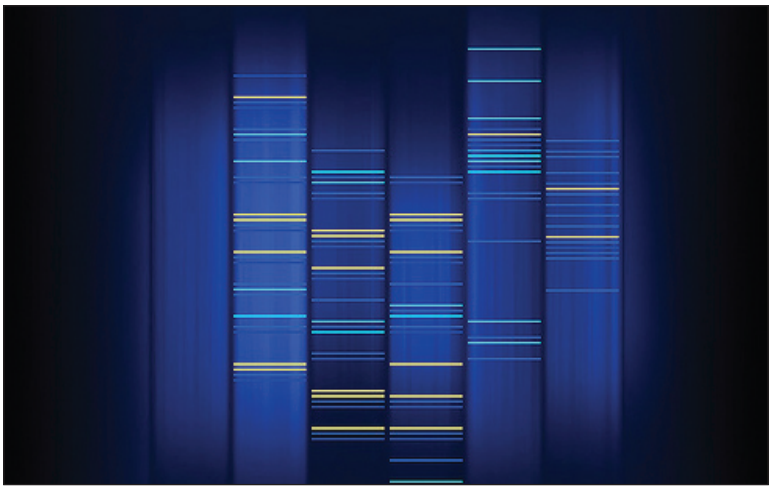
In order to synthesize the first man-made genome and reinsert it into an *M. genitalium* cell, the group needed to determine if the transplanted genome would reprogram the host cell to adopt the characteristics encoded by the replacement genome. In 2007, Venter's research group headed by John Glass successfully transplanted the entire genome of *M. mycoides* into the cell of a similar bacteria *M. capricolum* [3]. Utilizing a tetracycline-resistant strain of *M. mycoides*, a culture of the cells was lysed and proteases were added to digest the proteins [3]. The isolated chromosomes of M. mycoides were then incubated with *M. capricolum* in a polymer substance designed to fuse cell membranes [3]. As several *M. capricolum* cells fuse together, *M. mycoides* chromosomes trapped between the cells will also be enclosed in the fusion. Those cells containing multiple genomes divide, and each daughter cell containing the *M. mycoides* chromosome will have tetracycline-resistant properties, allowing a culture of transplanted cells to be generated. In the study, protein analysis of the transformed cell confirmed complete transformation from *M. capricolum* to *M. mycoides* [3].

> **"Synthetic biologists aim to create a life form entirely by *de novo* synthesis"**

In the most recently published paper by Venter's synthetic bioengineering team, the researchers pushed technology to its limits and succeeded in stringing together an entirely synthetic genome based upon the genome of *M. genitalium* [4]. Dr Hamilton Smith, one of the team's prominent researchers, said the study created 101 DNA fragments or 'cassettes,' each composed of between 5,000 to 7,000 DNA base pairs, covering the entirety of the bacterium's chromosome. The cassettes were first copied, or 'cloned,' inside the cells of living bacteria and then transferred into yeast cells, which stitched together the final, fully-formed chromosome [5]. The resulting synthetic chromosome known as *M. genitalium* JCVI-1.0 consists of 582,000 base pairs and is the longest piece of synthetic DNA ever created, surpassing the previous record, a 32,000 base pair viral genome [6].

With the synthetic genome now at hand, Venter aims

to transplant the synthetic genome *M. genitalium* JCVI-1.0 into the nucleoid of a *M. genitalium* cell to create the first synthetic organism *M. laboratorium* [7]. Although current research is under wraps, members of the scientific community anticipate that successful transplantation will occur within the next year (2008-2009) [6]. The resulting *M. laboratorium* bacterium is expected to be able to replicate itself with its man-made genome, making it the first synthetic organism to date, although the cellular machinery that would allow it to replicate would not be synthetic [7].



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In response to Venter's project, organizations such as Canada's outspoken Action Group of Erosion, Technology and Concentration states concerns about the acceleration of the research and development of synthetic life with an absence of oversight and limited public discussion of the "socio-economic, security, health, environmental and human rights implications" [10]. Because of bacteria's ability to reproduce in diverse conditions, there are unaddressed safety concerns about contamination and unexpected results from pursuing synthetic life before "society has had a chance to properly discuss or assess its implications" [10]. Environmental ethicists are hence asking for a scientific consortium to establish policies before synthetic biology advances to the point of creating organisms that can survive outside of the laboratory. Venter and other synthetic biologists from Massachusetts Institute of Technology, the Venter Institute as well as the Center for Strategic and International Studies in Washington, D.C. have since acknowledged the need to examine ethical and environmental concerns such as creating safeguards to control synthetic life forms [9]. A $570,000 grant from the Alfred P. Sloan Foundation has been allocated for the discussion of these concerns [9].

Dr Venter's reaction to such criticisms is that "[environmental groups] should be ecstatic about what we are doing, since we provide one of the clear alternatives to burning oil and coal" [8]. The potential use of synthetic organisms as the source of renewable energy is the original inspiration that compelled Dr. Venter to pursue this venture. Revealing his motivation for the project, Venter said that the "aim of the research was to make new, artificial life forms that can help to solve the world's most pressing environmental problems. For instance by producing green biofuels, breaking down toxic waste, or even absorbing carbon dioxide from the atmosphere" [8]. In the long term, the team wants to engineer an artificial genome, containing extra sets of genes that can perform useful tasks, such as creating pure hydrogen as a source of biofuel [8].

In a recent lecture at Cornell University covering his latest research, Venter also emphasized that any new microbes created by the process would be made incapable of infecting other organisms—particularly humans—and that they would not be able to survive beyond the confines of a laboratory due to self-destruct mechanisms built into their DNA. For instance, Dr Hamilton Smith, one of the head researchers in Venter's group, notes that having only the essential genes in the synthetic version will make sure that the cell does not survive any mutations of the genome, making them survive only the very specific conditions for which they were engineered [6]. As for the synthetic genome *M. genitalium* JCVI-1.0, it was synthesized with certain modifications to make it innocuous and distinguishable from the wild type genome [8].

If synthetic biology becomes routine, strategically placed bits of DNA to create a unique signature within the chromosome makes the scientist accountable for any potential mishaps [8].

> **"Artificial life forms can help to solve the world's environmental problems"**

Although the practice of marking the synthetic genome may have a more economic appeal, as scientists will presumably patent their creations, doing so also provides geneticists with the ability to determine if a genome is naturally occurring or if it was a synthetic creation. ■

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References:

[1] Fraser CM, Gocayne JD, White O, Adams MD, Clayton RA, Fleischmann RD, Bult CJ, Kerlavage AR, Sutton G, Kelley JM, Fritchman RD, Weidman JF, Small KV, Sandusky M, Fuhrmann J, Nguyen D, Utterback TR, Saudek DM, Phillips CA, Merrick JM, Tomb JF, Dougherty BA, Bott KF, Hu PC, Lucier TS, Peterson SN, Smith HO, Hutchison CA 3rd, Venter JC. The minimal gene complement of Mycoplasma genitalium. Science. 1995 Oct 20;270(5235):397-403.

[2] Glass JI, Assad-Garcia N, Alperovich N, Yooseph S, Lewis MR, Maruf M, Hutchison CA 3rd, Smith HO, Venter JC. Essential genes of a minimal bacterium. Proc Natl Acad Sci U S A. 2006 Jan 10;103(2):425-30.

[3] Lartigue C, Glass JI, Alperovich N, Pieper R, Parmar PP, Hutchison CA 3rd, Smith HO, Venter JC. Genome transplantation in bacteria: changing one species to another. Science. 2007 Aug 3;317(5838):632-8.

[4] Gibson DG, Benders GA, Andrews-Pfannkoch C, Denisova EA, Baden-Tillson H, Zaveri J, Stockwell TB, Brownley A, Thomas DW, Algire MA, Merryman C, Young L, Noskov VN, Glass JI, Venter JC, Hutchison CA 3rd, Smith HO. Complete chemical synthesis, assembly, and cloning of a Mycoplasma genitalium genome. Science. 2008 Feb 29;319(5867):1215-20.

[5] BBC News [Online]. Patent sought on 'synthetic life.' 2007 Jun 8 [cited 2008 Sept 29]; Available from: http://news.bbc.co.uk/2/hi/science/nature/6733797.stm.

[6] Madrigal, A. Scientists build first man-made genome; synthetic life comes next. Wired 2008 Jan 24 2008 [cited 2008 Sept 29]; Available from: http://www.wired.com/science/discoveries/news/2008/01/synthetic_genome

[7] Pilkington, E. I am creating artificial life, declares US gene pioneer. The Guardian 2007 Oct 6[cited 2007 Oct 27]; Available from: http://www.guardian.co.uk/science/2007/oct/06/genetics.climatechange

[8] Angier, N. Pursuing synthetic life, dazzled by reality." New York Times. 2008 Feb 5 [cited 2008 Sept 29]; Available from: http://www.nytimes.com/2008/02/05/science/05angi.html

[9] Pennisi, Elizabeth. Synthetic biology remakes small genomes. Science 2005 Nov 4;310(5749):769-70.

[10] ETC Group. Backgrounder: J. Crai Venter Institute's patent application on World's First Human-Made Species. 2007 June 7 [cited 2008 December 10]; Available from: http://www.etcgroup.org/upload/publication/pdf_file2/631