FAST BREAKING PAPERS - 2009

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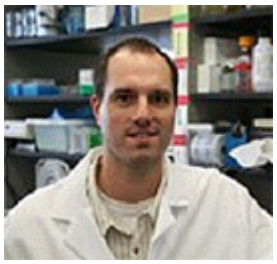
Daniel G. Gibson talks with *ScienceWatch.com* and answers a few questions about this month's Fast Breaking Paper in the Multidisciplinary field.



Article Title: Complete chemical synthesis, assembly, and cloning of a *Mycoplasma genitalium* genome
Authors: 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; Smith, HO
Journal: SCIENCE, Volume: 319, Issue: 5867, Page: 1215-1220 Year: FEB 29 2008
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SW: Why do you think your paper is highly cited?

This paper demonstrates, for the first time, the construction of a synthetic bacterial genome, a critical step in our ambition to create a synthetic cell. The only completely synthetic genomes reported, prior to this work, have been from viruses; the 5.4 kb phiX genome, and the 7.5 kb poliovirus genome. The largest stretch of synthetic DNA that was reported in the literature was only 32 kb. Our synthetic genome is 18 times larger than these examples.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

We describe methods for synthesizing complete bacterial genomes. This work demonstrates that we may soon have the ability to engineer synthetic cells with properties that are defined by the genomes we synthesize. In the meantime, synthetic biologists are metabolically engineering existing organisms, such as *E. coli* and yeast, for the production of biofuels, antibiotics, and industrial compounds. In most cases, this involves constructing large DNA molecules. This paper describes efficient methods for doing so.

"We believe the capacity to synthesize cells will allow researchers to design organisms that have extraordinary properties such as the ability to produce biofuels, pharmaceuticals, and textiles, and the ability to capture carbon from the

SW: Would you summarize the significance of your paper in layman's terms?

This paper describes the synthesis of a bacterial genome. The genome is from a species called *Mycoplasma genitalium* and is 582,970 bp in length. This is the largest chemically defined structure ever synthesized in a laboratory. Complete genome synthesis is an essential step in our goal to construct a synthetic bacterial cell.

SW: How did you become involved in this research, and were there any problems along the way?

atmosphere."

A team led by J. Craig Venter published the sequence of the *Mycoplasma genitalium* genome in 1995. Because of its relatively small size, they began to realize that it would be possible to synthesize the entire genome from overlapping DNA cassettes that could be joined by homologous recombination methods.

By 2003, they improved the methodology of assembling synthetic oligonucleotides into DNA cassettes. All that remained was to learn how to join these DNA cassettes into genome-size molecules.

I was fascinated by this research, and truly understood the significance of creating a synthetic cell. In December 2004, I (Daniel G. Gibson) was hired by the J. Craig Venter Institute (JCVI) as a post-doctoral fellow. I began investigating methods that would allow overlapping DNA fragments to be assembled. Within a year, we had a very good method in place for assembling DNA molecules by *in vitro* recombination.

By this time, we purchased 101 overlapping DNA fragments that were about 6 kb each and began assembling them into the ~582 kb genome. For a very long time, we had the genome assembled in four pieces but could not assemble them any further. We realized that we needed a new method for assembling such large DNA molecules. This was when we found that the yeast *Saccharomyces cerevisiae* can take up these large pieces and join them *in vivo* by using its natural homologous recombination machinery.

SW: Where do you see your research leading in the future?

Experiments are in progress to isolate the synthetic genome from yeast and activate it into a viable synthetic cell. We have already demonstrated that one bacterial species can be converted to another by installing a donor genome into a recipient cell. This work showed that it is the genome that dictates the characteristics of a cell.

We should then be able to transplant the synthetic genome into a recipient cell to create a synthetic cell that was designed by us at the nucleotide level. Once we are able to do this, we will begin designing more useful and complex organisms.

Also, *M. genitalium* has the smallest genome of any known bacterium capable of independent life. This is an excellent starting point for creating a minimal cell, which has only the machinery necessary for life. In a combinatorial fashion we hope to identify a minimal genome in which all genes are essential. This will allow us to better understand life at the cellular level.

SW: Do you foresee any social or political implications for your research?

We believe the capacity to synthesize cells will allow researchers to design organisms that have extraordinary properties such as the ability to produce biofuels, pharmaceuticals, and textiles, and the ability to capture carbon from the atmosphere. Synthetically engineered cells with these properties would offer great benefits to society.

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KEYWORDS: TRANSFORMATION-ASSOCIATED RECOMBINATION; SELECTIVE ISOLATION; HOMOLOGOUS RECOMBINATION; YEAST; DNA; GENE; SEGMENTS; REGIONS; VIRUS; CELLS.

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