

Patenting the parts

Despite hand-wringing over the patenting of a minimized organism, both patents and open-source approaches will be needed to promote innovation and research progress in synthetic biology.

It's been termed the "perfect storm." A fierce controversy is brewing at the intersection of US intellectual property (IP) law and the emerging field of synthetic biology, which aims to build standardized DNA parts that can be mixed and matched to create new types of genetically modified organisms and products. On the one hand, aggressive patenting and licensing could put many of the DNA parts off limits to researchers. On the other, patents are needed to stimulate private sector investment in the development of practical applications of the technology.

The first clouds of this IP storm appeared in recent weeks when a Canadian nongovernmental organization, the Action Group on Erosion, Technology and Concentration (ETC Group), announced it was challenging two patent applications filed by investigators at the J. Craig Venter Institute on "the world's first-ever human-made life form." Since the 1970s, ETC Group (previously known as the Rural Advancement Foundation International) has been fiercely critical of patents on living materials. No surprise, then, that it takes a rather dim view of Venter's patents on a minimal organism.

The patent applications in question (US 2007/0122826A1 and WO2007047148) cover a set of essential genes and a synthetic "free-living organism that can grow and replicate" using those genes. The organism is a stripped-down version of *Mycoplasma genitalium*, a bacterium that lacks cell walls and is one of the smallest self-replicating organisms known, with a 580-kb genome originally sequenced by Venter at the Institute for Genome Research in 1995.

The central claim of the patents are to a "minimal bacterial genome" comprising 381 genes essential for self-replication, identified by sequentially assessing the effect on viability of each of the mycoplasma's 485 protein-encoding genes. The patents also outline how these 381 genes, when stitched together, could be inserted into a "ghost cell" comprising a membrane, ribosomes and DNA/RNA replication machinery, thereby creating an artificial organism.

This artificial organism, which the inventors term *Mycoplasma laboratorium*, is still a theoretical entity. But Venter and his colleagues recently took another step toward making it a reality; just five weeks ago, in a paper published in *Science* (doi:10.1126.1144622, 2007), they described the successful replacement of the genome of one mycoplasma, *Mycoplasma capricolum*, with that of a closely related species (*Mycoplasma mycoides*) engineered with tetracycline resistance. Although the mechanism of transfer is unproven and the efficiency of the process is low (1 in 150,000 times), the paper demonstrates the feasibility of whole-genome engineering.

Apart from its vague objections about mankind meddling with nature, ETC seems to be mainly concerned that the patents' claims are too widely drawn, fencing off a broad swathe of essential (and nonessential) genes. Indeed, US 2007/0122826A1 claims any synthetically constructed organism that lacks at least 55 of the 101 nonessential genes disclosed. According to ETC, with over 100 countries named in the WO2007047148 patent application, Venter's group threatens to become the "Microbesoft" of synthetic biology.

In reality, though, this is less a perfect storm than a tempest in a test tube. First, the Venter patents look shaky in terms of enablement, which requires a sufficiently detailed description of the invention to permit someone else 'skilled in the art' to make or use it. And second, many of the nonessential genes claimed are already in the public domain—the Venter team described 130 of them in a publication in *Science* (286, 2165–2169, 1999).

In any case, it seems unlikely that a mycoplasma-derived organism would be the optimal 'chassis' for expressing the DNA parts being built by the synthetic biology community (<http://parts.mit.edu/>). Mycoplasmas are notoriously fragile, they have a low G+C content (which biases codon usage), they contain atypical termination codons (UGA is read instead as tryptophan) and they have little track record as robust systems for heterologous protein production. Few have the expertise to manipulate them. A mycoplasma-based chassis would thus present several barriers to widespread adoption.

Another patent (US patent 6,989,265) issued in January last year on a minimized *Escherichia coli* genome, however, may be more important. *E. coli* is the type of chassis that could be useful for the synthetic biology community. Based on the work of Fred Blattner at the University of Wisconsin, the patent contains claims that could cover any synthetic cell derived from an *E. coli* genome. Indeed, the IP has already provided the foundation for startup Scarab Genomics, which offers a minimized version of *E. coli* K12 (15% of the genome deleted) with enhanced genetic stability and improved metabolic efficiency for gene cloning and heterologous protein expression applications.

The main take-home message from all this is that ETC is right to raise concerns about patents with sweeping claims to fundamental technology—whether it be DNA parts or the cellular chassis to host them. But contrary to ETC's strident demands for their abolition, patents with reasonable claims are still needed to spur innovation and investment, as it is the private sector that will develop the new generation of synthetic biology products.

At the same time, however, it makes little sense for companies or other institutions to patent individual genes, or DNA parts, especially in a not-so-distant world where a 10-megabase stretch of DNA may be printed in under 24 hours. With this in mind, an important priority for national initiatives, such as SynBERC (the National Science Foundation's Synthetic Biology Engineering Research Center), the BioBricks Foundation (a not-for-profit foundation established by the Massachusetts Institute of Technology, Harvard and the University of California, San Francisco) and EMERGENCE (the Foundation for Synthetic Biology in Europe), should be to push for placing as many of the DNA parts as possible in the public domain. This will encourage sharing of materials unshackled by IP licenses, reduce the cost and time of engineering and encourage the development of biological solutions to our most challenging problems. Most important, it will allow synthetic biology to reach its true power and potential. **IB**