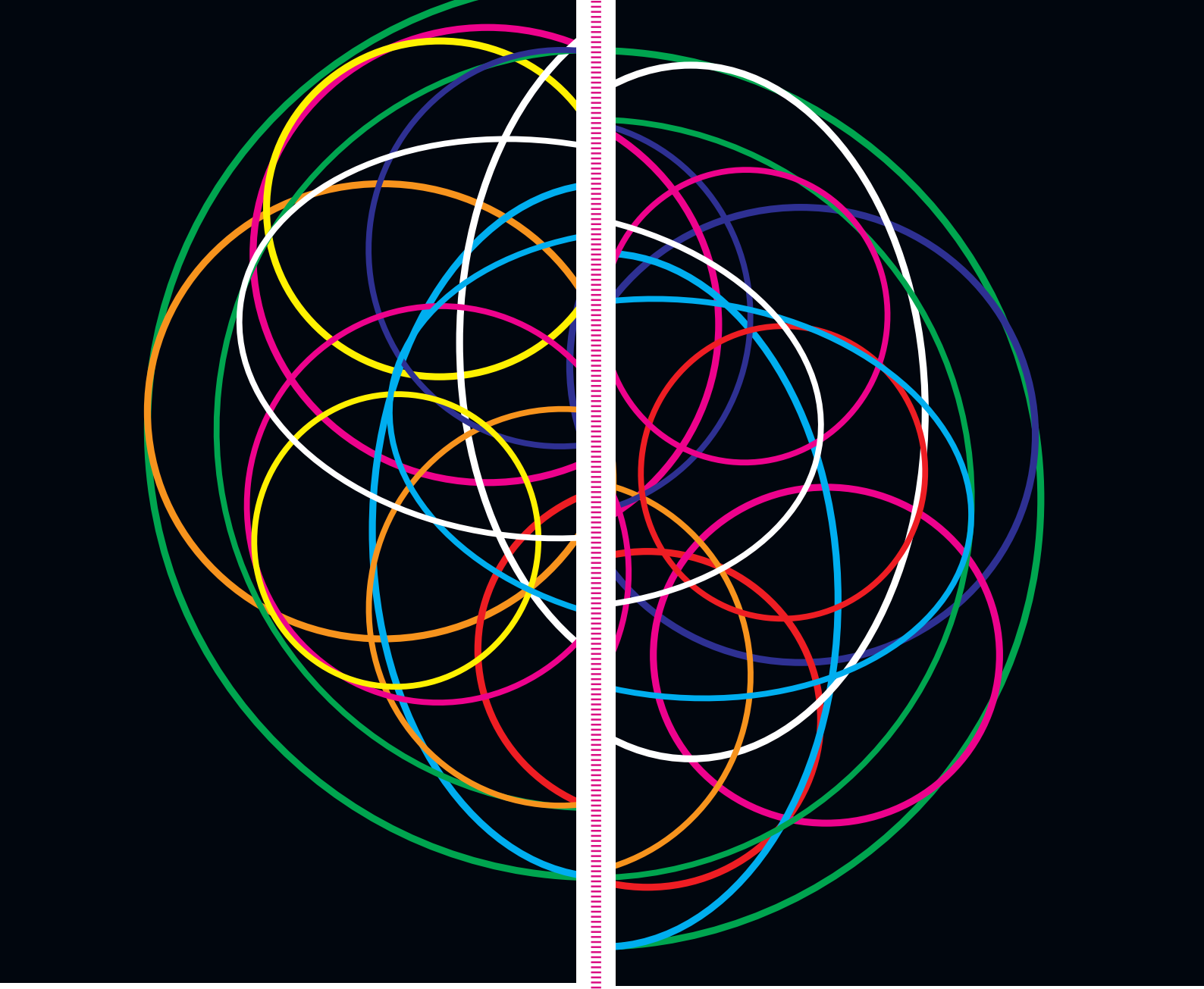

# CULTURAL DIVIDE

*Synthetic biology is facing a tug of war over whether to patent its discoveries or embrace open-source innovation.*

BY BRYN NELSON

A Canadian futurist named Andrew Hessel has an unorthodox idea about how to cure breast cancer. He asks: what if volunteer researchers, working cooperatively from their garages and bedrooms, could rival the efforts of multibillion-dollar pharmaceutical companies?

His crowd-funded venture, the Pink Army Cooperative, is trying to do just that by tapping into open-source tools springing from synthetic biology — an emerging field that designs biological products using engineering principles and a modular approach. Since the cooperative launched in 2009, nearly 600 people have invested in it. The cost to join? A mere US$20.

This radical idea faces considerable hurdles — but even so, it has attracted plenty of attention from industry groups and the media. The cooperative, launched by Hessel and two co-founders, hopes to start

ILLUSTRATIONS BY THOMAS POROSTOCKY

cell-culture studies this year and is considering a therapeutic trial in dogs.

Currently based at the software-design firm Autodesk in San Francisco, California, Hessel represents an increasingly impatient and outspoken faction of synthetic biology that believes that the patent-heavy intellectual-property model of biotechnology is hopelessly broken. His plan relies instead on freely available software and biological parts that could be combined in innovative ways to create individualized cancer treatments — without the need for massive upfront investments or a thicket of protective patents. He calls himself a "catalyst for open-source synthetic biology".

This openness is one vision of synthetic biology's future. Another is more akin to what happens at big pharmaceutical companies such as Pfizer, Merck and Roche, where revenues from blockbuster drugs fund massive research initiatives behind locked doors. For such businesses, the pursuit of new drugs and other medical advances depends heavily on protecting discoveries through patents and restrictive licensing agreements.

Tight controls on intellectual property are necessary to encourage promising medical developments, says the Biotechnology Industry Organization (BIO) in Washington DC, the sector's dominant trade association. On its website, BIO calls intellectual property "imperative for innovation" around the world. "Societies that protect inventors with patents are the world's most advanced — scientifically and technologically," it says.

How synthetic biologists resolve the conflict between open source and patent protection could determine whether the field delivers on its ambitious goal of transforming medicine, agriculture, energy, environmental remediation and other industries through precision engineering. "It's not just return on investment," says Linda Kahl, director of the legal programme at the BioBricks Foundation, a non-profit organization in Cambridge, Massachusetts, that advocates for biological engineering in the public interest. "It's not just commercial applications. It is also about doing good in the world."

## TWO CULTURES

Although its roots extend back to the early twentieth century, synthetic biology started sprouting as an organized field just over a decade ago. In 2003, only 3 peer-reviewed articles listed in Elsevier's Scopus database used the term synthetic biology; in 2013, more than 800 did. Last year, the field also marked one of its biggest developments. Capitalizing on a discovery by biochemical engineer Jay Keasling of the University of California, Berkeley, the Paris-based pharmaceutical firm Sanofi began large-scale production of a partially synthetic form of the malaria drug artemisinin, which is normally derived from plants (see *Nature* **494,** 160–161; 2013). And more big advances are in the pipeline: at the Pacific Northwest National Laboratory in Richland, Washington, for example, researchers are creating synthetic fungal enzymes that can convert sugars from broken-down plant biomass into fuels and other industrially useful chemicals.

From the start, the field has been an amalgam of disparate influences, each with different cultures of intellectual property. On one side sit software design and engineering, which introduced the idea of encoding desired functions in pieces of DNA and joining together a standardized set of biological widgets, much like bricks or Lego pieces. Software engineers also brought with them the philosophy of sharing their work using open, public registries or only lightly restrictive licensing agreements, such as copyrights.

On the other side sit molecular biology and biotechnology, which supplied know-how about messy and unpredictable biological systems. They also brought the practice of patenting genes, molecules and technical processes. Half of the papers published in *Nature Biotechnology* between 1997 and 1999, for example, were linked to a patent. "They came with different perspectives, different goals, and in some cases, different expectations," says Andrew Torrance, a law professor at the University of Kansas in Lawrence who focuses on synthetic biology.

Which intellectual-property culture will come to dominate synthetic biology is still unclear. In June last year, in a case brought by the Association for Molecular Pathology against the company Myriad Genetics, the US Supreme Court ruled unanimously that "products of nature" such as genes and genetic markers are not eligible for patents. But by its very nature, Torrance says, synthetic biology creates DNA that does not occur naturally — and so the court's ruling explicitly allows such human-designed DNA to be patented.

Legally, therefore, synthetic-biology sequences and techniques can be patented, at least in the United States. But the morals and ethics of doing so are vigorously debated by researchers, companies, lawyers and bioethicists.

Patent advocates say that protecting intellectual property is necessary to spur innovation. In a statement after the ruling against Myriad, Craig Venter, founder and chief executive of Synthetic Genomics in La Jolla, California, applauded the court for making a distinction between naturally occurring and human-derived DNA segments. "These man-made genetic constructs are already being used to create new vaccines, biofuels and nutritional products," he said. "And the ability to protect this intellectual property is a necessary component of a vital and robust science and biotechnology industry."

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Many synthetic biologists are indeed patenting their work. Writing in *Systems and Synthetic Biology* last year, a group of researchers in Germany documented a trend towards increasing patent applications in the field — particularly in the energy, medical and industrial sectors (D. van Doren *et al. Syst. Synth. Biol.* **7,** 209–220; 2013). Lead author Davy van Doren, an emerging-technologies researcher at the Fraunhofer Institute for Systems and Innovation Research in Karlsruhe, Germany, concedes that the trend is inferred from a limited number of patents and a short time frame — but says that it is consistent with other areas of biology. "We couldn't find any evidence that patent trends in synthetic biology might be different compared with other domains," he says.

But open-source advocates argue that patents squelch innovation. This opinion is widespread in start-up companies, non-profit organizations, graduate programmes and the wildly popular annual International Genetically Engineered Machine (iGEM) competition, in which university and school students compete to make synthetic systems that work in living cells. These researchers say that if companies and universities can patent key synthetic-biology tools and building blocks, they can charge hefty fees for others to use them, making it prohibitively expensive to create new products building on those discoveries — especially for start-ups and organizations with few resources.

## OUT IN THE OPEN

The free-for-all synthetic-biology movement is advancing its aims by assembling public registries analogous to open-source software registries. The iGEM Registry of Standard Biological Parts, the oldest and biggest, contains samples submitted mainly by teams that have entered the competition. By building up a critical mass of components in repositories dedicated to public use, Torrance says, sharing advocates are creating a commons that future innovators can rely on for synthetic-biology building blocks, dubbed biobricks.

Individual parts from these collections can be incorporated into larger and potentially patentable inventions, but theoretically it is harder to patent the basic parts if they are already in the public commons. The iGEM Registry alone is growing by a few thousand parts per year. But there is a big caveat: no one can say with any certainty how many of these parts are themselves entirely free of patent claims. Not all researchers are willing or able to verify that parts that they label 'open-source' actually are.

To provide some clarity, the BioBricks Foundation has developed a legal tool known as

the BioBrick Public Agreement: a contract for acquiring standardized biological parts on an open-source basis. Contributors agree not to assert any existing or future intellectual-property rights on a biological part that they have developed, in exchange for a promise by users that they will give proper credit to the developer and abide by security regulations.

Although public registries are rapidly expanding, few have the curatorial capacity to verify that every part works as claimed. "You're not getting finished, high-quality pieces of DNA in every case," Torrance says. Some researchers are more blunt. "There's a lot of crap in there," says Keasling. To encourage sharing while weeding out the junk, he favours requirements for authors of journal articles to deposit standardized part-source data and descriptions into a repository — provided that the field can agree on a fair set of rules.

Advocates say that the iGEM Registry has improved vastly in recent years, and point to new collections that are emphasizing quality control. The Synthetic Biology Engineering Research Center in Emeryville, California, is developing an Internet interface called the Web of Registries to stitch multiple databases into a linked system that offers uniform information about parts and their legal status. If the field takes off like open-source software, Torrance says, it may attract a do-it-yourself crowd that will help to verify that parts do what is advertised, just as some software enthusiasts currently spend their free time fixing bugs.

Synthetic biologists on both sides of the debate say that few in the field take an absolutist view on patents. Many are instead homing in on the idea of a 'diverse ecology' — one that includes both intellectual-property protections and public-sharing agreements (J. Calvert *BioSocieties* **7**, 169–187; 2012). Complexity matters here: if the synthetic-biology building blocks are compared to Lego, then in this situation the bricks would be free but a design for a complex rocket ship made of hundreds of Lego pieces would be patentable.

## SHARE AND PROTECT

To give an idea of what a robust and commercially friendly open-source regime might mean for synthetic biology, Hessel points to the Linux computer operating system, the open-source platform that became so popular that it is now among the most widely used in the computer industry. Although the base operating system is free, developers have built proprietary businesses onto it, just like biotech companies might be able to incorporate free synthetic-biology building blocks into more sophisticated and patent-worthy systems.

Ginkgo Bioworks in Boston, Massachusetts — which bills itself as the world's first organism-engineering foundry — is part of an emerging class of synthetic-biology companies that have embraced both public and proprietary models. Among its many projects, Ginkgo is engineering yeast cells to produce chemicals including flavours and fragrances, such as a designer rose extract. The company is not averse to taking out patents on such advanced creations, but it also has a stake in open-source science: Ginkgo sells a $253 kit for assembling biobricks from iGEM's Registry of Standard Biology Parts into a multicomponent genetic system. And in 2011, the company agreed to make publicly available one of its engineered constitutive promoters, a DNA regulatory segment that allows a gene to be continually copied into RNA.

"It's not particularly useful to be patenting individual parts, per se, except in very specific cases," says Ginkgo co-founder Reshma Shetty. "So I think having the commons available to everyone is a good thing for everyone."

Although biobricks and other open-access parts have already shown their potential in research projects, advocates say that it is still too early to predict how much they will be accepted into commercial research and development. Ginkgo co-founder Tom Knight, a computer engineer at the Massachusetts Institute of Technology in Cambridge who is often called the father of synthetic biology, says that the field is shifting away from a focus on handcrafted biology, towards a system in which large-scale foundries create standardized parts en masse. If this shift continues, then companies will want to use small parts interchangeably and without complex patent agreements from every manufacturer. Patents will not disappear entirely, says Knight, but they might have a limited role in an industrial context.

Even if the field evolves towards a middle way, the debate will continue. The biotech industry, for one, worries about liability issues associated with free-for-all biological parts. If a publicly available building block is incorporated into a transgenic seed or medical treatment, for example, it is not obvious who is responsible for tracking down its provenance and demonstrating to regulatory authorities that the part is safe.

## INNOVATE OR DIE

In the tug of war between patents and open-source registries, a nagging question remains: which mechanism is better at driving innovation? In 2003, the US National Research Council issued a report called *Patents in the Knowledge-Based Economy*, which said that the evidence on how patents affected innovation was still "emergent". A decade later, the uncertainty persists.

"There are a lot of people looking into this question," says Torrance. "It is amazing to me that in 2014, it's impossible to point to a definitive study that indicates that the patent system or the copyright system is a net benefit or a net cost to the economy or to innovation. But that's where we are."

It may not matter what the data say, according to Hans Sauer, deputy general counsel for intellectual property at BIO. "For better or worse, we're just committed to a system that depends on the availability of patents, at least to some extent, for greasing the wheels that put the biotech business model in motion." In other words, whether patents actually spur innovation may be trumped by the widespread view of entrepreneurs and investors that they are key to minimizing risk in the start-up phase. "These people, rightly or wrongly, all act on their beliefs and their convictions," says Sauer.

Many in the biotech industry have difficulty imagining a world without patents, he adds. The industry is "a bit spooked" about emerging public hostility to patent rights, and about a legal pendulum that seems to be swinging towards a more restrictive application of patent law, at least in the United States.

The hesitancy is understandable, says Hessel, given the biotech industry's big investments and long lead times. But a new generation of nimbler, leaner open-access types is not bound by such restraints. "What we're seeing is a kind of transition era, where there's this new community emerging and it's in some ways competing intellectually with the current, established industry," he says. The old guard can go on worrying about downstream investment costs and liability, says Hessel, while he and his Pink Army invent a way to cure cancer.

In March, Hessel spoke to pharmaceutical executives and consultants at the Pharma Summit 2014 in London about the Pink Army Cooperative's cancer-therapy work. And BIO has invited him to join a panel discussion about emerging trends in biotechnology at the BIO International Convention in San Diego, California, in June. Although the cultural gap between the two camps remains wide, there are signs that the bridge-building has begun. ■

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