Synthetic Biology and the Marketplace

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Building the new bioeconomy

In a waterfront office building in San Francisco, Twist Bioscience churns out synthetic DNA for companies from Microsoft to Adidas. “We make the fuel for synthetic biology—the DNA,” says CEO Emily LeProust. “Our customers need a lot of DNA to find the [genetic] sequences they want. We bring more DNA faster, cheaper, and higher quality to improve the pace and the productivity.” She has a small silicon plate that holds 1 million oligonucleotides, grouped in 10,000 tiny wells. In contrast, a traditional plastic plate used in DNA synthesis holds 96 wells. On a tour of the small manufacturing facility next door, LeProust shows off the fully automated system that works around the clock.

A privately owned company with 200 employees, Twist has raised more than $190 million in investment funds in 4 years and is growing rapidly. Last year, it shipped 36,000 genes to customers, and 70,000 the first half of this year.

Twist’s customers manufacture tires, vanilla flavoring, soap, and plastic bottles made through synthetic biology. They use it to improve agricultural and industrial processes and to advance biological research. In April, Microsoft announced it was buying 10 million strands of DNA from Twist, part of a collaborative effort between the tech giant, Twist, and the University of Washington to improve high-density digital data storage and perhaps eventually replace magnetic tape.

A new generation of public and private ventures is laying the foundation for synthetic biology, a small but growing part of the twenty-first-century bioeconomy. According to SynBioBeta, the synthetic biology industry has raised $500 million in investment capital the first half of 2017, on track with the $1 billion it raised last year.

For producers, though, turning investment cash into profitable businesses...
is not easy, and many companies are privately held and do not have to reveal sales or profits. “There are various market reports that suggest revenues from synthetic biology will be several billion this year, but I would say that these estimates are problematic because synthetic biology is poorly defined and varies significantly between reports,” says Rob Carlson, managing director of Bioeconomy Capital. Carlson projects that industrial biotechnology as a whole will bring in more than $175 billion in revenues this year, with a portion of that coming from synthetic biology.

What is synthetic biology?

“What distinguishes synthetic biology from recombinant biotechnology was fundamentally the ability to chemically synthesize the parts, the DNA primarily... and reintroduce those that would allow the modulation, the manipulation, of the internal cellular mechanisms,” explains Keith Roper, at University of Arkansas and a former program director at the National Science Foundation’s (NSF’s) Engineering Research Centers program. “Previous to that, biologists [had to] snip DNA out of one organism and modify it using enzymes and then reintroduce it into the same or a second organism to go about changing internal circuitry. Synthetic biology allowed them to synthesize ex vivo, without cutting and pasting, the exact biopolymer constructs they were interested in. That led to this concept of a whole new type of engineering.”

One reason it is hard to measure the field’s economic impact is that there is little agreement on what synthetic biology is or even on what it should be called. “There are no clear definitions between engineering biology, synthetic biology, and metabolic engineering,” says Douglas Friedman, executive director of the not-for-profit Engineering Biology Research Consortium (EBRC). Within the federal government, the Defense Advanced Research Projects Agency (DARPA) uses the term “engineering biology,” the NSF uses “synthetic biology,” and the Department of Energy (DOE) uses “biosystems designs.”

“Those are all top-level headers that fund the same type of research but in different programs,” says Friedman. It is therefore difficult to come up with hard numbers on government spending in the field. A 2015 study by the Wilson Center estimated that the federal government invested $820 million between 2008 and 2014 in synthetic biology.

“[Synthetic biology] is basically the next generation of microbiology,” says Stephen Chambers, CEO of SynbiCITE, the United Kingdom’s national industrial translation center for synthetic biology. “What came out of the development of molecular biology was the growth of the bioeconomy due to recombinant DNA. What we’re experiencing now is another paradigm shift in the way we engineer biology.” His preferred definition (for which he does not claim credit): “engineering biology to make stuff.”

Chambers says that the United States is the recognized global leader in the field, although his country is working hard to catch up. The United Kingdom invested £300 million ($396 million) in synthetic biology between 2009 and 2016, according to a survey released by SynbiCITE in July. The UK government also created a £10 million fund to provide seed money to synthetic biology startups and spinoff ventures. On average, seven British synthetic biology startups a year have gotten off the ground, with private investment of £564 million between 2002 and 2016.

Many other countries are developing their own synthetic biology industries. “The amount of investment China is putting into synthetic biology is quite

Close-ups of Twist Bioscience’s high-throughput silicon plate, which contains 100 additional smaller wells. Each well can produce one oligonucleotide or gene. Photographs: Robert Couto.
staggering,” says Chambers, although the figures are not available. In addition, there is activity in Singapore, Japan, Europe, and South America.

SynbICITE created a UK roadmap in 2012 for moving its industry forward. The NSF has asked EBRC (the successor to NSF’s 10-year Synthetic Biology Engineering Research Center) to create a similar synthetic biology roadmap for the United States. “We’re working on putting together a roadmap in the precompetitive space that both the academic and the industrial communities agree are priority areas for research and investment in synthetic biology,” says Friedman. The roadmap will be updated annually to keep pace with rapid changes in the field.

Bumps along the road
Thanks to CRISPR and other technologies, genetic sequencing has moved ahead far more rapidly than would have seemed possible not long ago. But “DNA synthesis is not growing by the same degree, in terms of lengths and the amount we can synthesize, as sequencing has,” says synthetic biology pioneer Jay Keasling, of the University of California, Berkeley, and senior faculty scientist at the Lawrence Berkeley National Laboratory. “And DNA synthesis is at the core of synthetic biology. I thought we’d have a lot more people engineering completely new bacteria like Craig Venter pioneered.”

In 2010, Venter inserted a synthetic genome inside a bacterium, creating the first self-replicating synthetic life form.

In the early heady days of synthetic biology, everything seemed possible. Synthetic biology would soon create Jurassic Parks from woolly-mammoth DNA, replace gasoline with biofuel, and clean up the environment with engineered bacteria. But reality set in.

GreenFuel Technologies, for example, was one of the earliest and best-funded synthetic biology companies, raising $70 million to turn algae into fuel. But the company closed its doors in 2009. “Petroleum is so darn cheap it’s almost impossible—it is impossible—for biofuels to compete, unless we put a price on carbon,” says Keasling.

Now, “companies that worked on biofuels are turning that attention to higher-value molecules to produce things from sugar in an environmentally friendly way. That’s replacing what we produce from petroleum,” adds Keasling.

Amyris, a successful synthetic biology company cofounded by Keasling, tried its hand at biofuel, “driven by investor interest when oil was $150 a barrel and everyone was predicting the end of oil,” says Joel Cherry, Amyris president for research and development. “We chose farnasene, a molecule that’s an unsaturated hydrocarbon that once it’s hydrogenated makes a great diesel fuel. We had it chemically synthesized and tested, and it’s been produced continuously since 2008. But the fuel market has changed dramatically, and with oil below $50 a barrel, it makes any fuel really difficult to reach in terms of cost targets.” Amyris now sells farnasene on the world market for other applications.

Keasling began his career in bioremediation, and it, too, has lagged. “In the end,” he says, “People would rather have the metal contamination than organisms to clean it up. A lot of people are afraid of recombinant organisms. And companies don’t want to pay a lot to clean things up.”

Still, “no matter what your stance is on petroleum-based products, at some point, [petroleum] will be gone,” says Friedman, “and there needs to be an alternative.” In the meantime, “biobased commodity chemicals can compete, especially as you move to specialty chemicals.”

From cologne to cancer treatment
One of synthetic biology’s selling points is that it can create existing molecules in more sustainable ways. “It gives the power to create things that might be produced in plants in very low quantities, that would take extensive farming, or in some cases from endangered organisms,” says Keasling.

One well-known example is vanillin, the key ingredient in vanilla.
The vanilla bean, grown primarily in Madagascar, is expensive to bring to market. Most of the world’s vanilla is synthetic and, until recently, made from petrochemicals. Since 2014, though, a company called Evolva has marketed an alternative vanillin made from yeast that has been engineered to produce the same chemical. (Critics say synthetic biology will ruin the livelihoods of indigenous farmers such as those in Madagascar.)

The first step in synthetic biology was enhancements such as this, making an existing product in a more sustainable fashion. “The next step in synthetic biology is making new materials we couldn’t make before, like spider silk,” explains Leproust. Researchers have identified the genes in spiders that allow them to make silk. “Spider silk is stronger than steel and ultra lightweight. You can’t farm spiders—but by fermentation, you can use the genes of silk.” Today, consumers can purchase Adidas shoes, Patagonia mountain jackets, and Bolt Threads neckties, all made from spider silk.

Amyris is using farnesene to produce related chemicals that can be used in everything from cosmetics to industrial solvents and car tires. That research led to the engineering of squalane, a cosmetic emollient ingredient once only available in the livers of deepwater sharks. “We purchased a manufacturing facility in North Carolina and launched Biossance,” says Cherry. “Now that product line has six different cosmetic products.... We have about a 30 percent market share worldwide for squalane.”

Another promising area is pharmaceuticals. The poster product for synthetic biology is artemisinic acid, a precursor to artemisinin, an antimalaria drug that Amyris developed early on with research support from the Gates Foundation. Amyris licensed its yeast strains royalty free to Sanofi, which distributes the drug globally. By 2014, more than 120 million treatments had been produced.

Amyris now works with pharmaceutical giants such as Roche and Johnson & Johnson to develop novel molecules for antibiotics and for cancer treatments. “On average, we have between $40 and $60 million annually in collaborative projects funded by external companies to develop products for them,” says Cherry. A publicly traded company, Amyris anticipates $115 million in revenues this year. “We are the closest to profitability of any synthetic biology company and have been around the longest, since 2004,” says Cherry.

Synthetic biology companies are working to develop antibiotics, antivirals, and anticancer drugs, such...
as prostratin, from the bark of the mamala tree in Samoa, to treat AIDS and cancer, and Taxol, from the Pacific yew, to treat breast and other cancers.

Others are developing diagnostics. At Roper’s lab at the University of Arkansas, researchers are working to enable better collection and enrichment of microbes. “If you think about going to the doctor for strep throat, they culture the specimen for 24 to 48 hours,” says Roper. “That culture period is what’s typically required in order to multiply those few individual bacteria that the swab collects to allow a positive identification. The idea would be to develop materials that have the capacity not only to facilitate greater collection but also microbe enrichment. The test results would be much more rapid.”

Roper also received seed funding from the Arkansas Biotechnology Institute to study how to more quickly identify pathogens on food preparation surfaces, an issue of keen interest to restaurants, cruise ships, and supermarkets. In addition, he says, “The medical applications are pretty clear. To analyze pathogens in clinics to minimize the amount of hospitalization necessary and to identify common bacterial infections to much more easily test for antibiotic-resistant organisms would be a really big benefit.”

Moving forward

Much of the action around synthetic biology is happening around developing new technologies to advance the field. Among the leaders in this effort are the nation’s biofoundries, including both public and academic efforts, such as Agile BioFoundry (DOE), the MIT-Broad Foundry (DARPA), and iBioFAB (University of Illinois), and corporate efforts, such as those set up by Amyris, Zymergen, and Ginkgo Bioworks. Biofoundries are also being built in the United Kingdom, Singapore, China, and Denmark.

Agile BioFoundry, a consortium of nine DOE National Laboratories, develops biomanufacturing technologies. “This is trying to boost the

A vial of Twist Bioscience DNA, shown next to a gummy bear for scale. Photograph: Laura Kudritzki.

Further reading.

Growing the next generation of synthetic biologists.

Every year, thousands of students gather in Boston to compete in a synthetic biology contest known as iGEM (International Genetically Engineered Machine). This November, 3000 people are expected at the competition, with more than 300 teams, including high school, undergraduate, and graduate or above—with a sprinkling of retirees. “A lot of team members are in the microbiology world, but there are also a lot in computer science and engineering,” says iGEM Foundation president Randy Rettberg. “We also have artists, design studies, people interested in policy questions, law students. We try to tell the teams to be half biologists and half non-biologists, half female and half male.” This year, forty percent of participants are female, and the teams come equally from Asia, the Americas, and Europe.

Guided by a faculty member, the teams brainstorm an invention and work at full speed throughout the summer to implement it. Teams typically raise about $50,000 for materials, and iGEM sends them the “parts”—BioBricks, standardized DNA sequences that are publicly available. Each team tries to create a product that will both impress the judges and be good for the world.

When iGEM was getting started 13 years ago, Rettberg says, “I was told by some professors at MIT that it was a bad idea. ‘Undergrads don’t know enough to do anything, and summer is way too short.’” Now, companies are actively sponsoring teams and hoping to acquire potential patents.

Although iGEM has not tracked the future careers of team members, Rettberg says that a number have gone on to create synthetic biology startups or to sell their inventions.

“Bento BioWorks is an example,” he says. “The University College London team did a microbiology lab in a box. Now they’re making it as a company in London and offering it as a product.” The 2011 University of Washington team found an enzyme to treat celiac disease. In earlier studies, the results appeared to be superior to current treatment. “PVP Biologics raised $35 million this past year, from work that started at iGEM,” he says.

In 2014, a team from Imperial College London tinkered with bacteria to make cellulose. The result was Aqualose, a bacterial filter paper that can be used in water treatment plants, explains Rettberg. The water filters can also be made to filter out hormone molecules or to bind to heavy metals such as mercury or cadmium. “Imperial is showing it’s not just students; it’s the professors who learn,” he says.

Winners receive recognition (but no money) in a number of categories: presentation, poster, WIKI, public engagement. “The finalist for the top award presents their project in front of the entire community,” says Rettberg. “We want all the teams to see the quality of the winners. The top award is a solid aluminum BioBrick, like a giant Lego, with the team name inscribed.”

To see last year’s winners, visit http://2016.igem.org.
bioeconomy by reducing manufacturing timelines and costs to market,” says Nathan Hillson, principal investigator at Agile and staff scientist at the Berkeley Lab. “If you look at a product, it might typically take 10 years, with $50 million–$100 million for early stage R&D, then the switch to scale up, then having to build an actual plant or go to a large-scale research organization. We’re trying to enable new companies or new products to not have to reinvent the wheel every time.”

As a public biofoundry, Agile shares expertise, microbial organisms, and software infrastructure with companies. “Companies might specialize in the last couple of steps, but we can enable them to get close to where they want to be,” says Hillson. “They can reuse what we’ve learned.”

The DOE has set aside $5 million for companies to write proposals to obtain $500,000 to $2 million over 2 years for product development. Companies put in competitive proposals, as well as commit to a 30-percent in-kind cost-share toward labor costs, materials, or software.

The Advanced Biofuels and Bioproducts Process Demonstration Unit at the Berkeley Lab is a related effort, also funded by DOE. “It’s a competitive process where companies will apply for vouchers to be spent at the national labs,” says Hillson. “Companies can wholly fund R&D, or they can embed their scientists in the national labs.” Companies can learn how the lab is developing its processes and “can take all that learning and knowhow back to their company,” says Hillson.

For the synthetic biology industry to grow more rapidly, Hillson says, biology itself needs to become more nimble and open to change. He argues for a clear division of labor, with researchers buying DNA fragments from companies such as ‘Twist Bioscience and similar vendors rather than building their own. “Your focus should be on what you’re specializing in, as opposed to doing molecular biology,” he says. More open sharing not only of research but also of microbial strains and DNA plasmids would also help, he says.

According to Leproust, her company sells DNA far cheaper than it would cost for an individual researcher to build. In the future, “Biologists will do less cloning and use more of the engineering principles of design, build, test,” she says. “That’s the more intellectual, challenging part.”

Researchers and entrepreneurs say they are optimistic about synthetic biology’s future. Much has been learned in a short time, and the field is in its infancy. “The potential of the field is extraordinary, and it trickles into the technology infrastructure in ways that are not as visible,” says Roper. “The most significant challenge is the inherent complexity of biological systems as a result of continued development or evolution over the past 2.3 billion years here on Earth and the interrelatedness of all the rich information and functional parts of those systems. Our understanding of that is still at a very early stage. In that way, it’s very different from electronics and computing.”

One exciting aspect of synthetic biology is its inherent interdisciplinarity, says Friedman, involving chemistry, molecular and cell biology, bioengineering, computer science, chemical engineering, data-science management, software design, and metrology (measurement science). “I hear people out in the field wondering how the tools of synthetic biology can help the field of ecology,” he says. “The field of synthetic biology is about techniques, tools, and technologies that can create products, but those products can be for the broader scientific community. It’s a whole new world coming.”

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