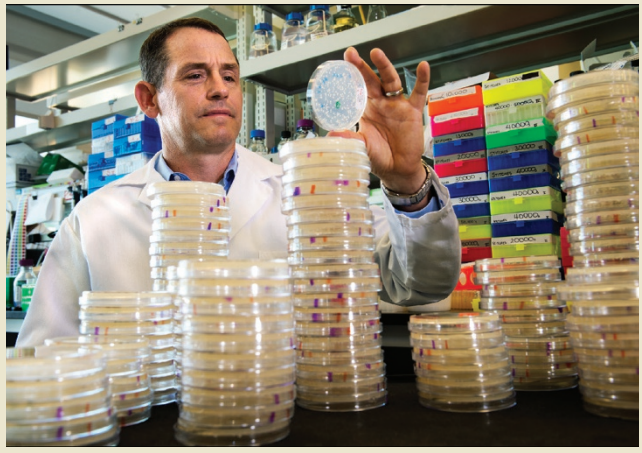
Synthetic biology firms pivot from biofuels to cheap biologics

Amyris's deal with Biogen to deploy its automated strain-engineering system to hunt for highly efficient recombinant protein producer strains could, if successful, have far-reaching consequences for the biopharma industry. The powerful synthetic biology technology Amyris developed for advanced biofuels production has the potential to rewrite the economics of biologic drug manufacturing. Amyris, of Emeryville, California, pivoted away from biofuels, following the oil price crash of 2014, which strangled at birth the nascent market for second-generation biofuels. Synthetic Genomics, of La Jolla, California, is also turning to biopharma production as part of a strategy to deploy its synthetic biology capabilities on a wider range of biobased production opportunities. Both companies face deeply entrenched incumbent biologics production technologies, with billions of dollars of sunk investment and the allegiance of thousands of biotech professionals. Applying strategies originally aimed at low-cost biofuels production to therapeutic protein manufacturing would represent a major shift for the biopharma industry. Given the extensive scientific, technical and regulatory hurdles, it will take time and money to make it happen.



Amyris

Amyris's president of R&D Joel Cherry inspects the firm's factories.

For decades, Chinese hamster ovary (CHO) cell lines have been the mammalian cell factory of choice for the production of recombinant protein drugs, particularly complex proteins. Drug makers and regulators alike have grown accustomed to the system, which reliably produces grams per liter of high-quality recombinant proteins, with appropriate post-translational modifications, such as glycosylation and correct folding. Despite extensive optimization—of genotype, expression vectors, process parameters and growth media—the CHO system remains cumbersome and expensive, however, resulting in long timelines and high production costs. Alternative production platforms, such as transgenic animals or plant-based expression systems, have been used over the last decade to produce protein drugs that reached the clinic (*Nat. Biotechnol.* **34**, 117–119, 2016). So far, these approaches remain minority pursuits. A more generalized shake up in the production of monoclonal antibodies, for example, would reshape the economics of drug production.

Amyris cut its teeth engineering metabolic pathways in yeast to produce advanced biofuels based on isoprenoids, a class of branched hydrocarbons. It also engineered yeast to incorporate the plant mevalonate pathway for manufacturing a precursor of the malaria drug artemisinin. Amyris's automated platform transforms 'artisanal' genetic engineering routines into fully automated, parallel processes.

First, scientists design artificial DNA sequences on a computer and, at the click of a button, have the DNA synthesized and inserted into a host strain. Amyris uses a robotic system to insert up to five different genome fragments, each up to 25 kilobases long, into five different loci simultaneously. "We can do some very radical engineering in a single step, at a single turn of the cycle," says Joel Cherry, president of R&D at Amyris. The system churns out 1,000 heavily engineered strains per month. "Really what this is useful for is looking at combinatorial gene insertions and deletions," he says. The company complements its strain design and selection process with an additional optimization, based on directed evolution. Amyris is not disclosing details of its collaboration with Cambridge, Massachusetts–based Biogen, but the project reaches beyond yeast. "This is built on a perception we can have a significant impact on the cost of production," Cherry says. Industrial biotech offers some clues about what may be possible. "Enzymes can be produced incredibly cheaply. They're still protein products—and they are highly purified," he says.

Synthetic Genomics recently reported on a fast-growing microbe, *Vibrio natriegens* (dubbed 'Vmax'), which can work both as a laboratory strain for gene cloning and as a prokaryotic producer strain for making simple proteins, including antigens for incorporation into vaccines (*Nat. Methods* http://dx.doi.org/10.1038/nmeth.3970, 2016). Chief technology officer Todd Peterson says the strain grows "like an absolute weed," but it will need to be industrially hardened before scaling up to larger production volumes. Next month, the company plans to unveil details of complex protein production, including antibodies, in eukaryotic algal strains using a similar, integrated approach. "We have a lot of experience with organisms in that part of the phylogenetic tree," says Peterson. Its performance objectives are high. "We are targeting 10× improvement," he says. "If you save 5–10%, that's not going to get you anywhere. You really need a step change."

A key challenge is to combine high protein expression and secretion in a single strain. "The problem we're trying to solve is the vast majority of biologics production is performed in cells that don't really specialize in folding and secreting antibodies," he says.

An even more radical approach to biologics production, a miniature bioreactor that can be deployed at the point of care, has been described by scientists at the Massachusetts Institute of Technology (*Nat. Commun.* http://dx.doi.org/10.1038/ncomms12211, 2016). Timothy Lu and colleagues engineered a *Pichia pastoris* yeast strain to express two biologic drugs, recombinant human growth hormone and interferon-α2b. A change of media induces a switch from production of one to the other. The prototype device can produce almost a single dose of either protein in less than 24 hours. The project received funding from the Defense Advanced Research Projects Agency (DARPA)—its potential use in military contexts is obvious, but it could also work in low-income regions with limited infrastructure and access to biotech drugs. "The inspiration for a lot of our work is 3D printing," says Lu. Getting the system anywhere near a patient is obviously some way off—but the research demonstrates how novel technologies could disrupt the current monolithic approach to biopharma production.

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