CORE CONCEPTS

Core Concept: Synthetic biology—change, accelerated

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Dr. Jay Keasling has biologically done what no one has been able to do chemically: cheaply and quickly synthesize an effective malaria medication (1).

Many of the 400 million individuals infected with malaria each year suffer because of a lack of effective, affordable therapies, especially after the malaria-causing *Plasmodium* parasite became resistant to often-used chloroquine-based drugs.

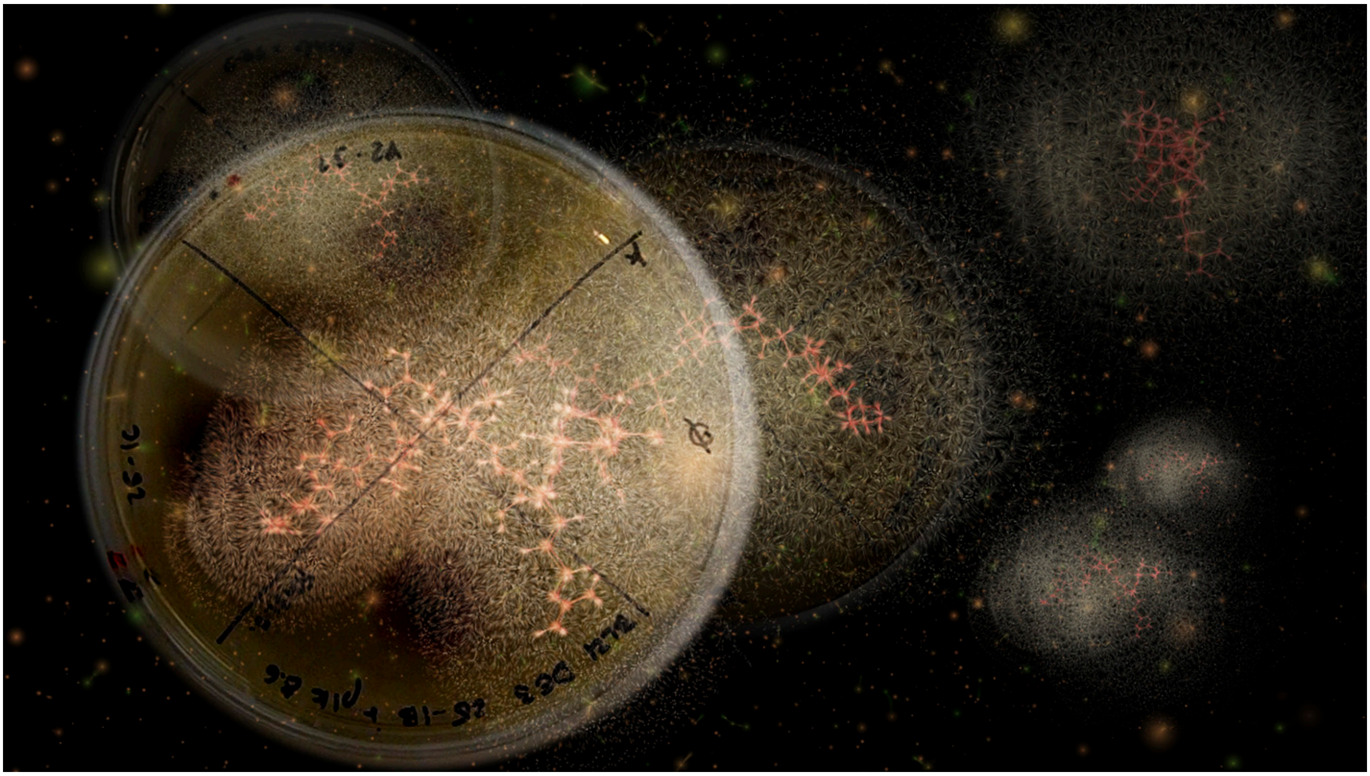
Artemisinin-based drugs are now faster acting and more effective. However, so far, the chemical has been laboriously sourced from the plant *Artemisia annua*, a type of wormwood. It appeared to be too expensive for large-scale use; that is, until Keasling recruited the tools of synthetic biology to coax yeast cells into making the stuff.

Keasling's success is in making what many consider the first bona fide product of synthetic biology, a field which promises new fuels, foodstuffs, industrial materials, and drugs. Defining the sprawling young field has been challenging. This summer, the Scientific Committee on Health and Environmental Risks of the European Union offered a broad definition, whittled down from nearly three dozen working definitions gathered from around the world (2): "Synthetic biology is the application of science, technology, and engineering to facilitate and accelerate the design, manufacture, and/or modification of genetic materials in living organisms to alter living or nonliving materials."

"We have got to the point in human history where we simply do not have to accept what nature has given us," Keasling told *The New Yorker* magazine in 2009 (3).

The field of synthetic biology has more precision than standard genetic engineering methods. Rather than cutting and pasting book chapters, by copying genes from one organism and pasting them into another, synthetic biologists like Keasling are writing and editing at a sentence-and-paragraph level. Instead of, for example, placing existing metabolic pathways into new organisms, they are creating them afresh.

For the project, which began in the early 2000s, Keasling built a metabolic pathway into yeast cells, causing the cells to synthesize a related chemical called artemisinic acid which, after a few chemical tweaks, easily



As part of the 2013 International Genetically Engineered Machine Foundation synthetic biology competition, students were able to reclaim gold from electronic waste with the help of a synthetically derived bacterium, shown here in an artist's conception. Image courtesy of Joanna Hoffman (University of Arts in Poznan, Poznan, Poland).

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transforms into artemisinin. In August Sanofi-Aventis, the company that licensed and optimized Keasling's technology, shipped 1.7 million treatments of semisynthetic artemisinin to Africa (4).

To synthesize the desired attributes, synthetic biologists use toolboxes of defined, standardized genetic parts. Keasling, for example, uses BioBricks; a sort of DNA-based Lego set for biological tinkerers. Each BioBrick is composed of defined sections that can be fit together interchangeably, allowing the tinkerer to design made-to-order biological circuits. Several thousand BioBricks are housed in the Registry of Biological Parts, managed by the Massachusetts Institute of Technology (parts.igem.org/Main_Page).

Using synthetic biology techniques, scientists can potentially both elucidate and manipulate the mechanisms of the cell itself. For example, one group recently devised a way to regulate genome transcription by engineering regulators that modulate chromatin, the packages of DNA and proteins in the cell's nucleus that help facilitate to transcription (5). Other work has used synthetic biology to show how the cell's molecules organize themselves to allow for proper cell function; researchers have devised regulatory networks from the bottom up to investigate (6).

But some in the field hope synthetic biology will have a more global impact. Researchers are working to create microorganisms that will eat carbon dioxide and produce biofuel in hopes of simultaneously combatting global warming and generating cleaner energy (7).

And some biologists are proposing something more radical: the release of designed organisms with the ability to spread their genes through wild populations (8). The idea is to take advantage of "gene drives," which have more than a 50% chance of being inherited by offspring. If these were synthesized to imbue new genetic traits, they could make it harder for mosquitoes to carry malaria and dengue fever, or be used to suppress populations of invasive species, such as Asian carp.

"It's the perfect case to be thinking about how you regulate synthetic biology," says Oye, noting that much of the field remains unregulated (8).

Oye says it doesn't take too much imagination to envision how synthetic biology, and gene drives in particular, could be used for malicious ends. If mosquitoes can be engineered so that they don't carry a disease, they could also be engineered so that they do. If populations of invasive species can be suppressed, so too can populations of crucially important species, such as pollinators.

"It's time now to start examining the [regulatory] gaps," says Oye, "before you end up with a problem."

1 Sanders R (April 11, 2013) Launch of antimalarial drug a triumph for UC Berkeley, synthetic biology. UC Berkeley News Center. Available at newscenter.berkeley.edu/2013/04/11/launch-of-antimalarial-drug-a-triumph-for-uc-berkeley-synthetic-biology/.

2 Scientific Committee on Health and Environmental Risks, Scientific Committee on Emerging and Newly Identified Health Risks, Scientific Committee on Consumer Safety of the European Commission (June 4, 2014) Preliminary opinion on synthetic biology I. Available at ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_044.pdf.

3 Specter M (September 28, 2009) A life of its own. *The New Yorker*. Available at www.newyorker.com/magazine/2009/09/28/a-life-of-its-own.

4 University of California at Berkeley College of Chemistry (August 15, 2014) Semisynthetic artemisinin anti-malarials reach African children. Available at chemistry.berkeley.edu/publications/news/2014/artemisinin_reaches_african_children.php.

5 Keung AJ, Bashor CJ, Kiriakov S, Collins JJ, Khalil AS (2014) Using targeted chromatin regulators to engineer combinatorial and spatial transcriptional regulation. *Cell* 158(1):110–120.

6 Chau AH, et al. (2012) Designing synthetic regulatory networks capable of self-organizing cell polarization. *Cell* 151(2):320–332.

7 de Morsella C (2012) 12 synthetic biology biofuel & biochemical companies to watch. *Green Economy Post*. Available at greeneconomypost.com/synthetic-biology-biofuel-biochemical-company-17244.htm. Accessed September 17, 2014.

8 Oye K (August 19, 2014) Proceed with caution: A promising technique for synthetic biology is fraught with risks. *MIT Technology Review*. Available at m.technologyreview.com/view/530156/proceed-with-caution/.