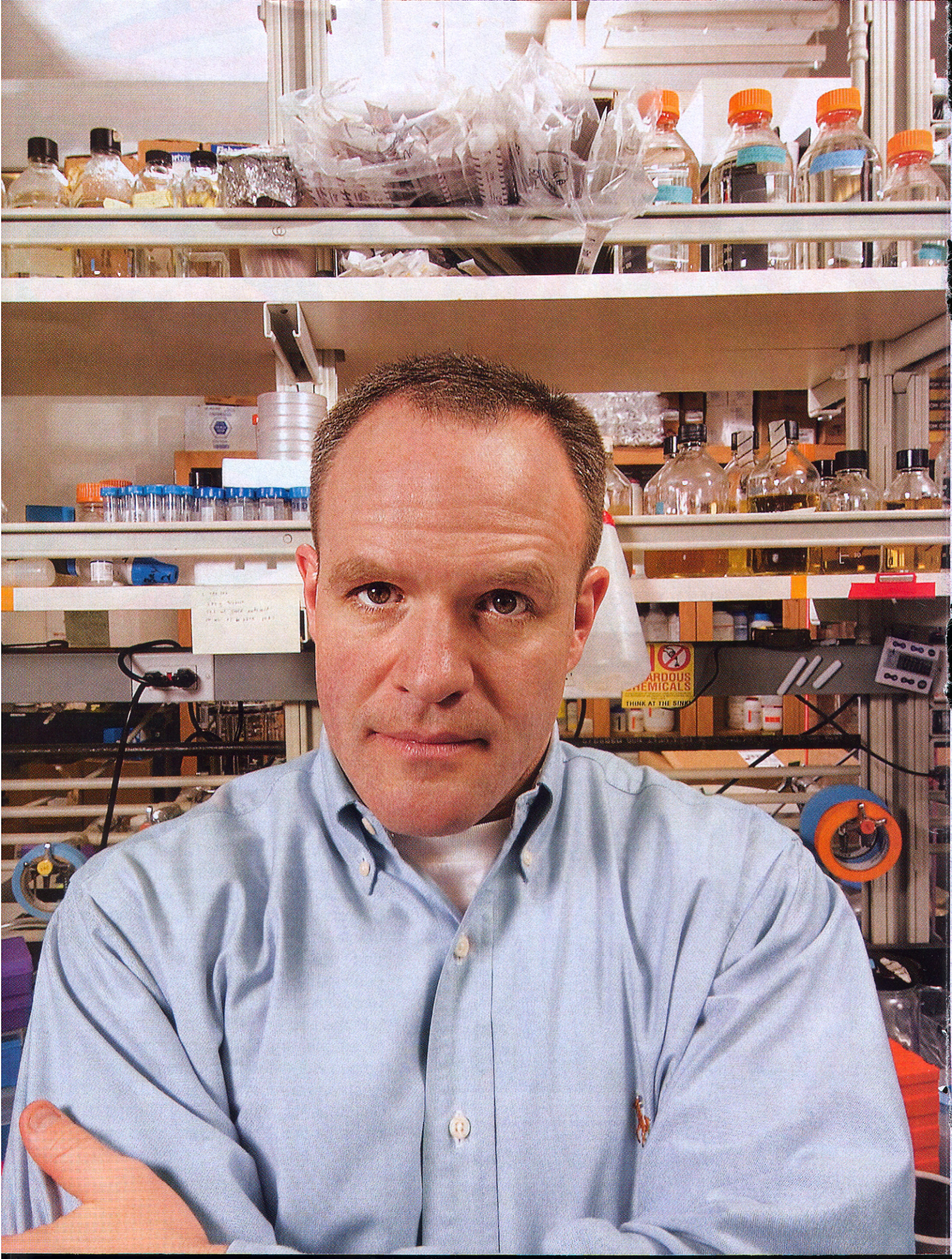






2006 SCIENTIST OF THE YEAR

JAY KEASLING

CHEMICAL ENGINEER AT THE UNIVERSITY OF CALIFORNIA AT BERKELEY

BY CARL ZIMMER

It's easy to be amazed by 21st-century feats of genetic engineering. Genes can be moved from one species to another, creating, say, goats that secrete drugs in their milk or bacteria that make human insulin. But that's not enough for Jay Keasling. Instead of the simple manipulation of single genes, he wants to engineer many genes to work together, like transistors wired in a circuit.

This new approach to manipulating life—along with explorations of artificial DNA, the creation of novel amino acids, and controlled evolution in the lab—has been dubbed synthetic biology, and Keasling, 42, is one of its chief engineers. As a nascent science, synthetic biology must prove itself through practical application, and Keasling is now close to providing just that: He is attempting to integrate genes from different species into a microbe to fabricate a drug for malaria. It is not just a technical tour de force but a humanitarian one. Keasling's microbes will churn out the drug for a fraction of its current cost, making it accessible to much more of the world. Properly harnessed, these microbes could save millions of lives.

Keasling spent his childhood immersed in the practical end of biology, chemistry, and engineering—he was raised on a farm. This background eventually led him to the burgeoning field of biotechnology. In the early 1980s, genetic engineering had just made the leap from the laboratory to the boardroom, as corporations made small fortunes inserting genes into *Escherichia coli* to produce insulin, growth hormones, and other valuable molecules. In Keasling's eyes, however, genetic engineering hadn't harnessed the full power of cells. Scientists had simply inserted a single gene into bacteria and coaxed them into churning out as many copies of the same protein as possible.

Often the production of molecules isn't so simple; it requires a complex of several genes. One gene encodes a protein, which then must be reworked by other proteins. Keasling wanted to invent the tools that would allow him

to engineer these kinds of genetic assembly lines. So he pursued his Ph.D. not in biology but in chemical engineering. What goes on in a cell, Keasling surmised, is a lot like what goes on in a chemical plant: Petroleum goes in, and after a whole chain of reactions, plastic comes out.

Keasling spent his first decade at the University of California at Berkeley building the new tools he would need to turn cells into chemical plants. He studied plasmids, tiny ringlets of DNA that genetic engineers use to insert foreign genes into bacteria. He also found ways to coax microbes into producing abundant copies of a particular protein, and he invented powerful chemical switches that allowed him to trigger protein production.

Meanwhile, other scientists were similarly borrowing techniques from engineering and figuring out how to manipulate microbes, an effort they came to call synthetic biology. In 2003 the first synthetic biology conference took place at MIT, and by 2006 the field had become a media darling. *The Economist* heralded it as "Life 2.0"; *Forbes* wrote about the potential "regeneration" of life.

Behind the dazzle lies the tedious reality: Synthetic biology requires a lot of work to do relatively simple things. Take, for example, the bacterial camera. In 2005 scientists from the University of Texas and the University of California at San Francisco reported that they had created a strain of *E. coli* that could produce a photograph-like image. They inserted genes for sensing light and producing pigments into the bacteria and then engineered the microbes so that the genes would work together—striking proof of the principles of synthetic biology, but in practice a very clumsy substitute for a digital camera.

After years of perfecting his biological tool kit, Keasling wanted to find a real-world use for it. In 2002 he learned of the dire need for synthetic artemisinin, a compound derived from the sweet wormwood plant, which is 90 percent effective against the parasite that causes malaria and has few side effects (malaria kills some 3 million people a



year). However, extracting the drug from sweet wormwood is a slow and expensive process that drives up the cost to as much as 20 times the price of other antimalarial drugs.

Keasling figured he could engineer microbes to pump out artemisinin for a lot less. Rather than wait months for sweet wormwood to grow on farms or try to cobble the drug together with artificial chemistry, Keasling wanted to create it simply by pouring sugar in a tank, then using engineered microbes to make the drug via a chemical pathway of his own creation. In 2003 Keasling's team published its first success, the production of a precursor to artemisinin. That result was impressive enough to garner \$43 million from the Bill and Melinda Gates Foundation. To transform the precursor into the real deal, Keasling had to abandon biological manipulations of bacteria and work instead with yeast. Last April his team reported that they had pieced together bacterial, yeast, and wormwood genes and converted yeast into a chemical factory, yielding artemisinic acid.

The final step for Keasling is to figure out how to mass-manufacture artemisinin. Compared with fast-growing bacteria, yeast do a poor job of producing enzymes. So Keasling has two teams of students in a race. One is looking for a way to create the new chemical pathway in *E. coli*; the other, to scale up the production of artemisinic acid in yeast. Keasling is optimistic that one of the routes will work. If it does, he expects to drive down the cost of artemisinin production from a dollar per gram to just 10 cents.

Fighting malaria is just one part of Keasling's larger agenda to explore the staggering potential of synthetic biology. In his laboratory, students are engineering microbes to break down pesticides, make biodegradable plastics, and create ethanol and other fuels from plants. For his achievements, DISCOVER has named Keasling Scientist of the Year. We took the occasion to talk to him about his work and about the future of synthetic biology.

You arrived at Berkeley in 1992 with training as both a chemical engineer and a biologist. What did you hope to do?

I came with the idea that we could make drugs and chemicals inside microbes. If you want to produce a drug, it may take a huge number of chemical steps—so many that it's not economically feasible using just chemistry. And I thought, gosh, we could be doing a lot of this chemistry inside the cell, using enzymes. Enzymes can do in one step what might take many steps using synthetic organic chemistry. What's more, we could start with something cheap like

sugar and end up with something valuable. Once you get one microbe to do it, you can grow that microbe at any scale from a 10-milliliter test tube up to a 100,000-liter fermenter. Unfortunately, when I started we didn't have a lot of tools to manipulate chemistry inside the cell.

Why hadn't anybody tried to engineer cells that way before?

The biotech industry was based on producing a single protein in a cell. For instance, with human growth hormone and human insulin, the first ones to be made by recombinant DNA, you take one gene, put it into *E. coli*, express it at an extremely high level, and produce your protein of interest. That's your drug, and you're finished. You break the cells open and you get your drug out. But something like Taxol [a cancer drug] takes many genes to be expressed. You need very fine control of gene expression. When you're producing human growth hormone, you don't need fine control because you just want to fill up the cells with proteins and then break them open.

What made you think that kind of approach was possible?

Take bacteria, for instance. When they experience a big shift in temperature, they change the genes that are expressed in the cell. They have control systems that do this, just as in your house when the temperature goes down, the thermostat kicks the furnace on. If you understand these controls, you can make the cell do something that it wouldn't necessarily want to do. That's really where I started thinking about this integration of engineering and biology—not to build tanks to grow microbes but actually to go in and reengineer the cell as a chemical reactor. That's how we treat the cell in my lab: It's a chemical reactor. It takes in something very simple and spits out something complicated and valuable.

When did synthetic biology become a part of your life?

I first heard about the area of synthetic biology about three years ago. I had been doing it all along. It just didn't have a name.

How did you get involved in your antimalaria project?

I became acquainted with a group of natural products called isoprenoids. There's a lot of chemistry there, a huge number of valuable products. It just seemed like a great area in which to be doing research. So we started with a focus of building up the basic pathways needed to make those chemicals, and we thought, what are

we going to use this pathway for? We could produce menthol. We could produce beta-carotene. And then a graduate student came to me with an article reporting that the first gene in the pathway for the production of artemisinin had been cloned. I didn't even know what artemisinin was at the time. We thought, gosh, this sounds like a great thing to be working on.

Other than pharmaceuticals, what do you see as some of the most promising near-term developments in synthetic biology?

I think we're going to see it used for fuels. I think that kind of product is not so far off. Unlike pharmaceuticals, it would not have to get FDA approval. I think energy is going to be a really great area. DuPont is making an effort to produce propane diol, which is a precursor to carpet fibers, and they're producing it in *E. coli* that have been genetically engineered. Every year it gets easier and easier to do this stuff because more tools become available, particularly if we have a vibrant synthetic biology industry—or at least a group of people working in this research area producing tools.

What else are you working on in your lab?

Artemisinin is a hydrocarbon, and we have a huge need for hydrocarbons in the fuels area. So while we're still focused on artemisinin, we are starting biofuels projects in the lab that will ramp up even more once the artemisinin project is completed.

So essentially you'd be creating fuels out of sugar?

That's right. Hopefully cellulose.

Do you expect scientists will be able to use similar tools to engineer human cells in the future?

Oh, sure. They could build replacement organs. They could take a stem cell from a person and engineer it to go down a particular path and differentiate into a liver or a kidney or something like that. It's going to be an important area.

Why do you enjoy this work?

I'm an engineer at heart, and I like to be able to manipulate things and to predict a priori what kind of effect it's going to have on the cell. So it's this aspect of being able to design, build your design, and then see how close the result is to the original prediction.

You've helped set up an information-sharing system that the researchers call open-source biology. What is the goal?

It's really taking a lesson from the high-tech industry. They share the patents on the low-level stuff or they don't patent them at all—they just give them away as open source and patent only the high-level stuff, the big stuff. The pharmaceutical industry and the biotech industry patent everything and hold those patents exclusively so that no one else can use those patents. When it takes a billion dollars to develop a drug, you need some assurance that you're going to be able to keep your intellectual property for a while and pay that back. I fully appreciate that. But if you're going to develop drugs for the developing world, you can't afford to pay those royalties. And so we say: "Look, nobody's really going to make any serious money off of

these small components. The money is in the big applications. So let's make a lot of small components and have them available as open source to everyone." People can still patent the big applications—a lot of integrated components—but let's at least have the components available as open source so everybody gets equal access, and that will further the field of engineering biology.

Does that kind of openness create a risk that someone might use synthetic biology to create a biological weapon?

If I wanted to do evil and do harm, I probably would not choose biology to do it. It's damn complicated. Anyone sophisticated enough to know how to use these biological components that we're making freely available would have been able to do it anyway, to some extent. And by making these components available, we will also help those people who are trying to detect evildoers using biology. A lot of people have been thinking about this. Do we need to regulate the industry? Do we need to have a professional licensing organization so we license people essentially to be synthetic biologists? If we choose to regulate the industry, we have to be willing to pay the price for that, which means there won't be cheap antimalarial drugs developed and there won't be potential biofuels developed and other drugs for other diseases and cleaning up the environment and all the things that come from this area.

What would you say to people who think you're playing God, tampering with nature?

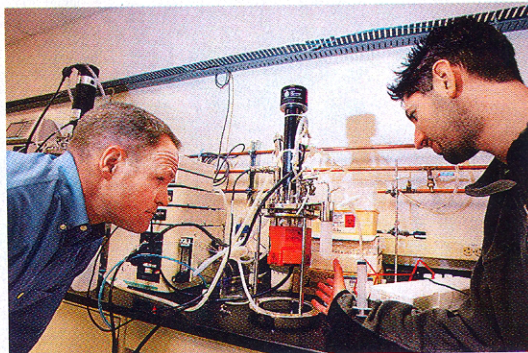
It's easy to say those kinds of things when you don't have malaria.

It's quite another thing when you're ill and don't have the means to come by effective, safe drugs. I was raised on a farm. When I grew up, we didn't have genetically engineered crops. We had hybrids, but those were achieved in the traditional way of just crossing corn, and we used a tremendous number of pesticides on the crops. I mean, this is nasty pollution, right? Roundup Ready corn, for instance, has been genetically engineered to allow farmers to apply far fewer herbicides to the fields. In many ways, it's so much better for the environment. If we use it in the right way, we can actu-

ally make the world a better place. It's the same thing with the kind of chemistry we're trying to do. If we can do this chemistry inside the cell in a vat filled with a medium that you can drink, that's so much better for the environment than using a lot of harmful chemicals that could be spilled.

What are your plans for getting your synthetic artemisinin into mass production and out to the people who need it?

We hope that we can launch this in late 2009 or early 2010. That's a really aggressive timescale, but we are working so hard on this. You know, the really nice thing about getting funding from the Gates Foundation is that once they decide to do something, they put a lot of resources into it and do it right. We have a lot of very smart people working on it, and I'll tell you, they are extremely motivated because it's just the greatest project to be working on. If all goes well, their work will be used in the field to save lives in a very short time.



Keasling (left), here with student Eric Paradise, fused genes from different species to create a chemical pathway in yeast.