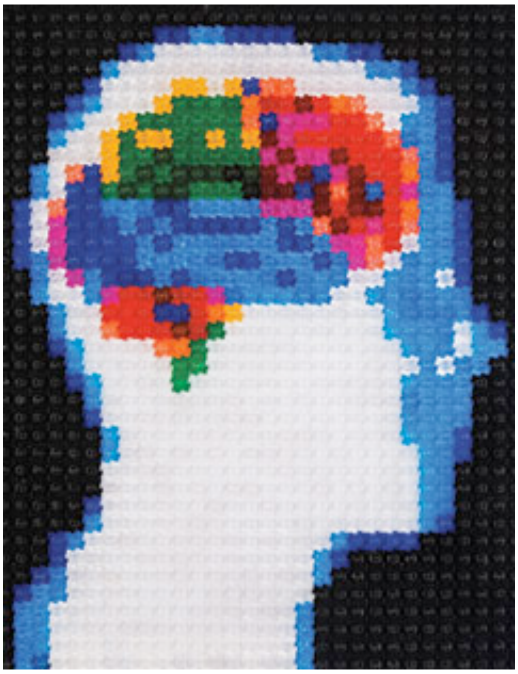
How to Make Life

Drew Endy and a few other pioneers of synthetic biology are starting to intervene in evolution and put it to work for us.



Read more of the Best and Brightest 2007

*****

It's a golden fall day on the MIT campus in Cambridge, Massachusetts, across the water from Boston, and there are sailboats on the river, and white birds and falling leaves are riding the same breeze -- a beautiful, optimistic morning, so sunny and soul warming that you might actually be given to believe the thirty-seven-year-old man sitting cross-legged on the park bench beside you when he announces that he will build houses out of gigantic programmable gourds.

You want to believe him because he will make other promises, too, the sorts of promises that have been made by science and by scientists for the last hundred years, the sorts of promises that would make a four-bedroom, two-bathroom pumpkin seem ordinary.

No more oil rigs.

No more malaria.

No more cancer.

Of course you want to believe him. Someone you love will one day live or die because this man's dreams have or have not come true. And since you believe him, you're also scared. Because so is he.

Drew Endy is, in his heart, a builder, and over the years, he has built many things out of many other things. When he was a child, he was obsessed with Erector Sets, Lincoln Logs, Legos, "all the clichés," he says. Later, because he was driven to make more spectacular things -- buildings that danced like living sculptures, space stations -- he went to school to become a civil engineer. Now, in addition to making music with the drums in his office and cut-glass mosaics on his lab bench (most notably, of a funky-looking virus called phage T7), Endy is learning how to make biological systems -- changing the equipment inside nature's factories so that they do the building for us -- the way other engineers design electronic or computer systems. "Only it's much cooler than electronics or computers," he says. "It's the stuff of life."

First, Endy must help finish building a new scientific field to prop up his imagination: synthetic biology, they're calling it. This past weekend, he gathered together several like-minded engineers, biologists, and professors from across the country to discuss what it is they've been doing, what they can do with it, and how they can do it better.

They held these meetings behind closed doors at MIT, inside Frank Gehry's wonderfully trippy Stata Center. They emerged only for lunch, sitting in the lobby, eating boxed sandwiches that had been piled on top of round tables. There was mop-topped Endy in jeans and sneakers and a brown hooded sweatshirt, looking like the skateboarder he once was. There was Tom Knight, fifty-nine, also from MIT, the burly reformed computer engineer who first began using the term "synthetic biology" to describe his experimental intentions. There was Harvard's George Church, fifty-three, the bearded genetics guru who had been one of the principal forces behind the Human Genome Project. And over there sat Berkeley's Jay Keasling, forty-three, the lab magician who's provided one of the field's first successful applications, having taken $42 million from the Gates Foundation to figure out how to trick *E. coli* into producing the antimalarial drug artemisinin.

Absent was Endy's girlfriend, a scary-smart thirty-two-year-old chemical engineer from Caltech named Christina Smolke. She's pretty, and she likes to run and knit, and she's the one who's going to help cure cancer.

As a couple, they are a world within a world within a universe. Like the rest, they're sleepless. Most of these folks, so driven by the revolution they're starting, grab three or four hours a night, and they look it, red eyed and coffee stained. But unlike most of the rest of them, Endy and Smolke are in love with something in addition to their science. It tells on them in the way they talk, not so much about each other but about each other's possibilities, each making the other sound right and limitless.

"I wouldn't necessarily call what we do work," Smolke says. "It's really something we believe in."

What they believe in is spanning the gulf between where nature is and where they want it to be.

Synthetic biology is so new, it has yet to be perfectly defined. By Endy's count, there are four different camps, including a rap-style ideological divide between the coasts, represented by MIT and Berkeley. What they agree on, though, is that they are all in the construction business: taking life's microchips -- genes from strands of DNA -- refining them, putting them back into cells (not necessarily from the same species), and then watching the cells follow their new and improved instructions, as reliably and robustly as any other engineered machine.

"Fundamentally, biology is a manufacturing technology," Knight says. "The things it builds are more copies of itself. We also use it to make food, to make lumber, lots of products. But it's making the things that biology would make anyway. How can we redirect that mechanism to build the things we would like to have made?"

Take Jay Keasling's goosed-up *E. coli.* Artemisinin is produced in nature by a plant known as sweet wormwood, indigenous only to China, which makes it expensive, which means it makes economic sense for more than a million sub-Saharan Africans to die each year. The plant uses sunlight and carbon dioxide to make artemisinin because a small collection of its genes tells it to. Keasling extracted those genes -- synthetic biologists call them parts, as if to underscore their mechanical worldview -- and transplanted them into *E. coli.* (The host is usually called a chassis; *E. coli* and yeast are today's preferred chassis, because they're easy to work with and reproduce perfect copies of themselves unusually quickly.) What makes the process distinct from genetic engineering, say, is that various tweaks are made and control systems programmed to keep the new machines humming along -- it goes far beyond "gene bashing," the derogatory term that synthetic biologists save for simple cut-and-paste jobs. These reengineered *E. coli,* ever multiplying and doped up on sugar, churn out something called artemisinic acid, a precursor to artemisinin. Keasling will soon contract an outside company to scale up tanks of *E. coli,* strip the acid from the cells, perform some basic chemistry on it, and within two years pack the finished product into pills bound for Africa. "At a tenth the current cost," he says. "It's crazy stuff. It's great stuff."

The possibilities are as diverse, literally, as nature itself. Next in line are biofuels, to which Keasling, George Church, and others have begun turning their attention. Dare to utter the word *ethanol* in their presence and they'll make faces as though they've been served a bitter tea. "Ethanol takes on water very easily, which means that you can't pipe it, because all of our infrastructure is built on pumping," Keasling begins, counting off his fingers. "You can't put it in jet engines, because it's got about two-thirds the energy density of gasoline. It just isn't an ideal molecule. . . ."

In other words? "It's what nature gave us, and we can do better."

The theory is similar to the one that duped all that *E. coli* into thinking that it's sweet wormwood growing in the Chinese hills. Instead of adding genes that produce artemisinin, put in some genes with different instructions, feed the cells sugar or switchgrass or algae, and floating to the top comes synthetic gasoline, diesel, and jet fuel -- close enough to the original that it can run in today's engines but refined during the production process so that it doesn't pollute nearly as much, and all without running pipelines through caribou herds. Church is about a year away from filling his first tank. "Instead of having the infrastructure adapt to biology," he says, "we're using biology to adapt to the infrastructure."

And that includes our own. Christina Smolke lies awake trying to muscle up our built-in immunity systems, T cells in particular. Evolution has given us a pretty good system for fighting off viruses and infections, but there are some significant holes left in its defenses. One of the reasons cancer, for instance, is so insidious is that T cells don't recognize it; cancerous cells are cloaked in a protein that T cells don't have a receptor to read.

Smolke is working to give T cells the antennae they need to spot cancer, the way students in Edinburgh recently engineered a microbe that changes color in the presence of otherwise invisible arsenic. (That's good news for the people of Bangladesh, who will soon have a cheap and easy method for outing their many poisonous wells.) Smolke's hope is to go a step beyond simple recognition, however, programming our T cells to fight cancer the way they fight infections -- she wants to give them swords as well as eyes.

"I'm confident it's doable," she says. "We just need more parts, and we need to get better at putting them together."

Which brings us three thousand miles away, perhaps not coincidentally, to a certain guy sitting cross-legged on a park bench, watching sailboats.

In April 1864, a tool builder named William Sellers gave a presentation at the Franklin Institute in Philadelphia titled "On a System of Screw Threads and Nuts." At the time, there was no American standard for nuts and bolts; threads were unique to the particular machinist who had made them. Sellers argued the need for a uniform system, and he proposed one: threads cut on a 60 degree angle, squared at the top, with a precise number of threads per inch. It didn't take hold right away, but by the 1880s the Sellers Standard had become the United States Standard, and at last engineers had been given the interchangeable parts they needed to design the machines that changed the world.

Drew Endy keeps a copy of Sellers's original paper on his laptop. It's one part inspiration, one part ready analogy, as Endy continues his crusade to make synthetic biology more real -- to make it enginelike. He is happy to see applications such as free-flowing artemisinin. Ultimately, Endy would like to see DNA made from scratch with automated construction, labs spinning out custom-designed strands like ticker tape, each programmed with a specific purpose in mind. But at the moment, he believes it's more important to settle on what he calls the "foundational technology," the nuts and the bolts: reliable parts machined to universal standards, tied together to make devices that can be transplanted easily into a cell. He calls them BioBrick parts. "We're doing the research that, if it works, nobody will care about it, they'll just use it," Endy says. "Like if you're building a transistor radio, you don't have to invent the transistor. You don't even need to know how it works."

Eyes closed now, yet still seeing -- seeing someone like Christina Smolke scanning through a catalog, the way electronics engineers lean on Texas Instruments for switches and microcontrollers, only on the hunt for a device that will help detect and consume cancer cells. Lo, there it will be, already manufactured, boxed up, and ready to be shocked into a fresh batch of T cells, which could be dripped into the bloodstream of a bald-headed child, whose vision will begin to clear as the tumor pinching his optic nerves is eaten away cell by black-hearted cell.

In fact, if Endy is on target -- and it's starting to look as if he probably is (MIT's Registry of Standard Biological Parts currently boasts an open-sourced library of about fifteen hundred components) -- someone not nearly as scary smart as Smolke could do it. "I expect we'll have garage biotechnology sooner or later, because I think it will be that accessible," he says.

Jesus.

Survey the leaders in synthetic biology about the potential good of their chosen field and they can come up with hundreds of remedies, fail-safes, and cures for just about all that ails us. Ask them about the potential bad and they provide nearly as many answers.

"If we make it easy enough, you could go on the Internet and figure out how to make drug-resistant smallpox from scratch," Church says.

"You can do a ton of bad things with traditional biology, and in time, we're going to be able to do some pretty bad things with synthetic biology," Keasling says.

"People will die," Endy says.

Because of the times we live in, it can sometimes seem as though all our miracles are cursed. What Endy calls the "biosecurity funk" creeps over places like MIT like a fog, filling even the most benevolent labs with shivers. The danger goes far beyond the fear that terrorists will learn how to cook up airborne fevers that make us bleed out our ears. Politics weighs nearly as heavily. Synthetic biologists understand that the Right will seek clamps on the science, lest these modern heathens destroy God's good work. And they're also resigned to getting it from the Left, those same armies who rose up to oppose genetically modified foods. Already projects that seem on the surface indisputably good -- such as biofuels research -- are being targeted for their unintended consequences. What if sugar demand burns up the last acres of rain forest? What if it keeps us from making any real change to the way we commute?

And last, the hardest ill to stomach: Even the most well-meaning engineers make mistakes. A clunky Scottish poem about the collapse of the Tay Bridge in 1879 is read to them early and often, lest they become careless and more bridges fall down. Still, bridges fall down.

Endy, Smolke, Church, Knight, Keasling -- they know better than anyone that all of this is true, and they are too smart to argue otherwise. And they know that the more they come to understand the basic forces of life, the more complex life seems.

"There are some people out there who think we should rename it 'Shiny Happy Biology,' " Endy says. "I'm not comfortable with renaming it. If we use a label that hides these issues, then I think they're more dangerous. Our problems become more dangerous the less we talk about them. We shouldn't just sweep them under the rug."

So he looks out to the river, and he takes a breath.

And you listen -- you really listen, because this is important. Endy recently got an invitation from the Chaos Computer Club in Berlin, a group of kid hackers who fly the pirate flag. They had been thinking that they would like to make the same jump from computers to cells that Tom Knight has made, and they decided that Endy would teach them how to crack into the human genome the way they hack into software. Now, do you think Endy should go? "I think I have to," he says. "I can ignore this stuff, or I can try to kick the snowball in a path that's constructive."

And when you begin to think like an engineer, you understand that Endy believes, more than anything else he knows, that people are good and that it's in us to build. He's decided to trust us. "We live in a culture that celebrates people making things -- beautiful things, practical things," he says. Because he remembers that he played with Erector Sets, Lincoln Logs, and Legos, "all the clichés," as though by instinct, he probably suspects that we've been hardwired to create -- that like the sweet wormwood, we are told by our genes to get busy. And if you believe that, then all of the debate and rancor falls away. We're doing what we were made to do.

And even if you don't believe that -- if instead you believe in God's immutable plan, or if you believe we shouldn't make pumpkins grow spiral staircases, or if you believe that the few who opt for destruction make the risks too many -- you probably still count someone you loved among those who have died from cancer, and if you happen to be from Tanzania or Nigeria, you almost certainly count someone you loved among those who have died from malaria. In that stark moment, watching them die, their last breaths rattling inside their former selves, emptied like bottles, the chances are very high that you would have done anything to save them. Chances are that you announced out loud just that intention, that you would make any deal, pay any price.

And now here you are, sitting on a park bench on a beautiful, optimistic morning beside a good man who has a good girlfriend and who is surrounded by good people who want to do good things, and who finishes by reminding you of what you said. You said any deal, remember? You said any price.

*****

Read more of the Best and Brightest 2007

Find this article at: http://www.esquire.com/features/best-brightest-2007/synthbio1207

Click to Print Close