A LIFE OF ITS OWN

Where will synthetic biology lead us?

BY MICHAEL SPECTER

The first time Jay Keasling remembers hearing the word "artemisinin," about a decade ago, he had no idea what it meant. "Not a clue," Keasling, a professor of biochemical engineering at the University of California at Berkeley, recalled. Although artemisinin has become the world's most important malaria medicine, Keasling wasn't an expert on infectious diseases. But he happened to be in the process of creating a new discipline, synthetic biology, which—by combining elements of engineering, chemistry, computer science, and molecular biology—seeks to assemble the biological tools necessary to redesign the living world.

Scientists have been manipulating genes for decades; inserting, deleting, and changing them in various microbes has become a routine function in thousands of labs. Keasling and a rapidly growing number of colleagues around the world have something more radical in mind. By using gene-sequence information and synthetic DNA, they are attempting to reconfigure the metabolic pathways of cells to perform entirely new functions, such as manufacturing chemicals and drugs. Eventually, they intend to construct genes—and new forms of life—from scratch. Keasling and others are putting together a kind of foundry of biological components—BioBricks, as Tom Knight, a senior research scientist at the Massachusetts Institute of Technology, who helped invent the field, has named them. Each BioBrick part, made of standardized pieces of DNA, can be used interchangeably to create and modify living cells.

"When your hard drive dies, you can go to the nearest computer store, buy a new one, and swap it out," Keasling said. "That's because it's a standard part in a machine. The entire electronics industry is based on a plug-and-play mentality. Get a transistor, plug it in, and off you go. What works in one cell phone or laptop should work in another. That is true for almost everything we build: when you go to Home Depot, you don't think about the thread size on the bolts you buy, because they're all made to the same standard. Why shouldn't we use biological parts in the same way?" Keasling and others in the field, who have formed bicoastal clusters in the Bay Area and in Cambridge, Massachusetts, see cells as hardware, and genetic code as the software required to make them run. Synthetic biologists are convinced that, with enough knowledge, they will be able to write programs to control those genetic components, programs that would let them not only alter nature but guide human evolution as well.

No scientific achievement has promised so much, and none has come with greater risks or clearer possibilities for deliberate abuse. The benefits of new technologies—from genetically engineered food to the wonders of pharmaceuticals—often have been oversold. If the tools of synthetic biology succeed, though, they could turn specialized molecules into tiny, self-contained factories, creating cheap drugs, clean fuels, and new organisms to siphon carbon dioxide from the atmosphere.

In 2000, Keasling was looking for a chemical compound that could demonstrate the utility of these biological tools. He settled on a diverse class of organic molecules known as isoprenoids, which are responsible for the scents, flavors, and even colors in many plants: eucalyptus, ginger, and cinnamon, for example, as well as the yellow in sunflowers and the red in tomatoes. "One day, a graduate student stopped by and said, 'Look at this paper that just came out on amorphadiene synthase,'" Keasling told me as we sat in his office in Emeryville, across the Bay Bridge from San Francisco. He had recently been named C.E.O. of the Department of Energy's new Joint BioEnergy Institute, a partnership of three national laboratories and three research universities, led by the Lawrence Berkeley National Laboratory. The consortium's principal goal is to design and manufacture artificial fuels that emit little or no greenhouse gases—one of President Obama's most frequently cited priorities.

Keasling wasn't sure what to tell his student. "'Amorphadiene,' I said. 'What's that?' He told me that it was a precursor to artemisinin, an effective anti-malarial. I had never worked on malaria. So I got to studying and quickly realized that this precursor was in the general class we were planning to investigate. And I thought, Amorphadiene is as good a target as any. Let's work on that."

Malaria infects as many as five hundred million of the world's poorest people every year and kills up to a million, most of whom are children under the age of five. For centuries, the standard treatment was quinine, and then the chemically related compound chloroquine. At ten cents per treatment, chloroquine was cheap and simple to make, and it saved millions of lives. By the early nineties, however, the most virulent malaria parasite—*Plasmodium falciparum*—had grown largely resistant to the drug. Worse, the second line of treatment, sulfadoxine-pyrimethanine, or SP, also failed widely. Artemisinin, when taken in combination with other drugs, has become the only consistently successful treatment that remains. (Reliance on any single drug increases the chances that the malaria parasite will develop resistance.) Known in the West as *Artemisia annua*, or sweet wormwood, the herb that contains artemisinic acid grows wild in many places, but supplies vary widely and so does the price.

Depending so heavily on artemisinin, while unavoidable, has serious drawbacks: combination therapy costs between ten and twenty times as much as chloroquine, and, despite increasing as-

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"Can I call you back? I've got eight million people in my office right now."

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sistance from international charities, that is too much money for most Africans or their governments. Artemisinin is not easy to cultivate. Once harvested, the leaves and stems have to be processed rapidly or they will be destroyed by exposure to ultraviolet light. Yields are low, and production is expensive.

Although several thousand Asian and African farmers have begun to plant the herb, the World Health Organization expects that for the next several years the annual demand—as many as five hundred million courses of treatment per year—will far exceed the supply. Should that supply disappear, the impact would be incalculable. "Losing artemisinin would set us back years, if not decades," Kent Campbell, a former chief of the malaria branch at the Centers for Disease Control and Prevention, and director of the Malaria Control Program at the nonprofit health organization PATH, said. "One can envision any number of theoretical public-health disasters in the world. But this is not theoretical. This is real. Without artemisinin, millions of people could die."

Keasling realized that the tools of synthetic biology, if properly deployed, could dispense with nature entirely, providing an abundant new source of artemisinin. If each cell became its own factory, churning out the chemical required to make the drug, there would be no need for an elaborate and costly manufacturing process, either. Why not try to produce it from genetic parts by constructing a cell to manufacture amorphadiene? Keasling and his team would have to dismantle several different organisms, then use parts from nearly a dozen of their genes to cobble together a custom-built package of DNA. They would then need to construct a new metabolic pathway, the chemical circuitry that a cell needs to do its job—one that did not exist in the natural world. "We have got to the point in human history where we simply do not have to accept what nature has given us," he told me.

By 2003, the team reported its first success, publishing a paper in *Nature Biotechnology* that described how the scientists had created that new pathway, by inserting genes from three organisms into E. coli, one of the world's most common bacteria. That research helped Keasling secure a $42.6-million grant from the Bill and Melinda Gates Foundation. Keasling had no interest in simply proving that the science worked; he wanted to do it on a scale that the world could use to fight malaria. "Making a few micrograms of artemisinin would have been a neat scientific trick," he said. "But it doesn't do anybody in Africa any good if all we can do is a cool experiment in a Berkeley lab. We needed to make it on an industrial scale." To translate the science into a product, Keasling helped start a new company, Amyris Biotechnologies, to refine the raw organism, then figure out how to produce it more efficiently. Within a decade, Amyris had increased the amount of artemisinic acid that each cell could produce by a factor of one million, bringing down the cost of the drug from as much as ten dollars for a course of treatment to less than a dollar.

Amyris then joined with the Institute for OneWorld Health, in San Francisco, a nonprofit drugmaker, and, in 2008, they signed an agreement with the Paris-based pharmaceutical company Sanofi-Aventis to make the drug, which they hope to have on the market by 2012. The scientific response has been reverential—their artemisinin has been seen as the first bona-fide product of synthetic biology, proof of a principle that we need not rely on the whims of nature to address the world's most pressing crises. But some people wonder what synthetic artemisinin will mean for the thousands of farmers who have begun to plant the wormwood crop. "What happens to struggling farmers when laboratory vats in California replace farms in Asia and East Africa?" Jim Thomas, a researcher with ETC Group, a technology watchdog based in Canada, asked. Thomas has argued that there has been little discussion of the ethical and cultural implications of altering nature so fundamentally. "Scientists are making strands of DNA that

have never existed," Thomas said. "So there is nothing to compare them to. There are no agreed mechanisms for safety, no policies."

Keasling, too, believes that the nation needs to consider the potential impact of this technology, but he is baffled by opposition to what should soon become the world's most reliable source of cheap artemisinin. "Just for a moment, imagine that we replaced artemisinin with a cancer drug," he said. "And let's have the entire Western world rely on some farmers in China and Africa who may or may not plant their crop. And let's have a lot of American children die because of that. Look at the world and tell me we shouldn't be doing this. It's not people in Africa who see malaria who say, Whoa, let's put the brakes on."

Artemisinin is the first step in what Keasling hopes will become a much larger program. "We ought to be able to make any compound produced by a plant inside a microbe," he said. "We ought to have all these metabolic pathways. You need this drug: O.K., we pull this piece, this part, and this one off the shelf. You put them into a microbe, and two weeks later out comes your product."

That's what Amyris has done in its efforts to develop new fuels. "Artemisinin is a hydrocarbon, and we built a microbial platform to produce it," Keasling said. "We can remove a few of the genes to take out artemisinin and put in a different gene, to make biofuels." Amyris, led by John Melo, who spent years as a senior executive at British Petroleum, has already engineered three microbes that can convert sugar to fuel. "We still have lots to learn and lots of problems to solve," Keasling said. "I am well aware that makes some people anxious, and I understand why. Anything so powerful and new is troubling. But I don't think the answer to the future is to race into the past."

For the first four billion years, life on Earth was shaped entirely by nature. Propelled by the forces of selection and chance, the most efficient genes survived, and evolution insured that they would thrive. The long, beautiful Darwinian process of creeping forward by trial and error, struggle and survival, persisted for millennia. Then, about ten thousand years ago, our ancestors began to gather in villages, grow crops, and domesticate animals. That led to stone axes and looms, which in turn led to better crops and a varied food supply that could feed a larger civilization. Breeding of goats and pigs gave way to the fabrication of metal and machines. Throughout it all, new species, built on the power of their collected traits, emerged, while others were cast aside.

By the beginning of the twenty-first century, our ability to modify the smallest components of life through molecular biology had endowed humans with a power that even those who exercise it most proficiently cannot claim to fully comprehend. Human mastery over nature has been predicted for centuries—Bacon insisted on it, Blake feared it profoundly. Little more than a hundred years have passed, however, since Gregor Mendel demonstrated that the defining characteristics of a pea plant—its shape, its size, and the color of the seeds, for example—are transmitted from one generation to the next in ways that can be predicted, repeated, and codified.

Since then, the central project of biology has been to break that code and learn to read it—to understand how DNA creates and perpetuates life. The physiologist Jacques Loeb considered artificial synthesis of life the goal of biology. In 1912, Loeb, one of the founders of modern biochemistry, wrote that there was no evidence that "the artificial production of living matter is beyond the possibilities of science," and declared, "We must either succeed in producing living matter artificially, or we must find the reasons why this is impossible."

In 1946, the Nobel Prize-winning geneticist Hermann J. Muller attempted to do that. By demonstrating that exposure to X rays can cause mutations in the genes and chromosomes of living cells, he was the first to prove that heredity could be affected by something other than natural selection. He wasn't entirely sure that people would use that information responsibly, though. "If we did attain to any such knowledge or powers there is no doubt in my mind that we would eventually use them," Muller said. "Man is a megalomaniac among animals—if he sees mountains he will try to imitate them by pyramids, and if he sees some grand process like evolution, and thinks it would be at all possible for him to be in on that game, he would irreverently have to have his whack at that too."

The theory of evolution explained that every species on earth is related in some way to every other species; more important, we each carry a record of that history in our body. In 1953, James Watson and Francis Crick began to make it possible to understand why, by explaining how DNA arranges itself. The language of just four chemical letters—adenine, cytosine, guanine, and thymine—comes in the form of enormous chains of nucleotides. When they are joined, the arrangement of their sequences determines how each human differs from all others and from all other living beings.

By the nineteen-seventies, recombinant-DNA technology permitted scientists to cut long, unwieldy molecules of nucleotides into digestible sentences of genetic letters and paste them into other cells. Researchers could suddenly combine the genes of two creatures that would never have been able to mate in nature. As promising as these techniques were, they also made it possible for scientists to transfer viruses—and microbes that cause cancer—from one organism to another. That could create diseases anticipated by no one and for which there would be no natural protection, treatment, or cure. In 1975, scientists from around the world gathered at the Asilomar Conference Center, in Northern California, to discuss the challenges presented by this new technology. They focussed primarily on laboratory and environmental safety, and concluded that the field required little regulation. (There was no real discussion of deliberate abuse—at the time, there didn't seem to be any need.)

Looking back nearly thirty years later, one of the conference's organizers, the Nobel laureate Paul Berg, wrote, "This unique conference marked the beginning of an exceptional era for science and for the public discussion of science policy. Its success permitted the then contentious technology of recombinant DNA to emerge and flourish. Now the use of the recombinant DNA technology dominates research in biology. It has altered both the way questions are formulated and the way solutions are sought."

Decoding sequences of DNA was tedious. It could take a scientist a year to complete a stretch that was ten or twelve base pairs long. (Our DNA consists of three billion such pairs.) By the late nineteen-eighties, automated sequencing had

simplified the procedure, and today machines can process that information in seconds. Another new tool—polymerase chain reaction—completed the merger of the digital and biological worlds. Using PCR, a scientist can take a single DNA molecule and copy it many times, making it easier to read and to manipulate. That permits scientists to treat living cells like complex packages of digital information that happen to be arranged in the most elegant possible way.

Using such techniques, researchers have now resurrected the DNA of the Tasmanian tiger, the world's largest carnivorous marsupial, which has been extinct for more than seventy years. In 2008, scientists from the University of Melbourne and the University of Texas M. D. Anderson Cancer Center, in Houston, extracted DNA from tissue that had been preserved in the Museum Victoria, in Melbourne. They took a fragment of DNA that controlled the production of a collagen gene from the tiger and inserted it into a mouse embryo. The DNA switched on just the right gene, and the embryo began to churn out collagen. That marked the first time that any material from an extinct creature other than a virus has functioned inside a living organism.

It will not be the last. A team from Pennsylvania State University, working with hair samples from two woolly mammoths—one of them sixty thousand years old and the other eighteen thousand—has tentatively figured out how to modify that DNA and place it inside an elephant's egg. The mammoth could then be brought to term in an elephant mother. "There is little doubt that it would be fun to see a living, breathing woolly mammoth—a shaggy, elephantine creature with long curved tusks who reminds us more of a very large, cuddly stuffed animal than of a T. Rex.," the *Times* editorialized soon after the discovery was announced. "We're just not sure that it would be all that much fun for the mammoth."

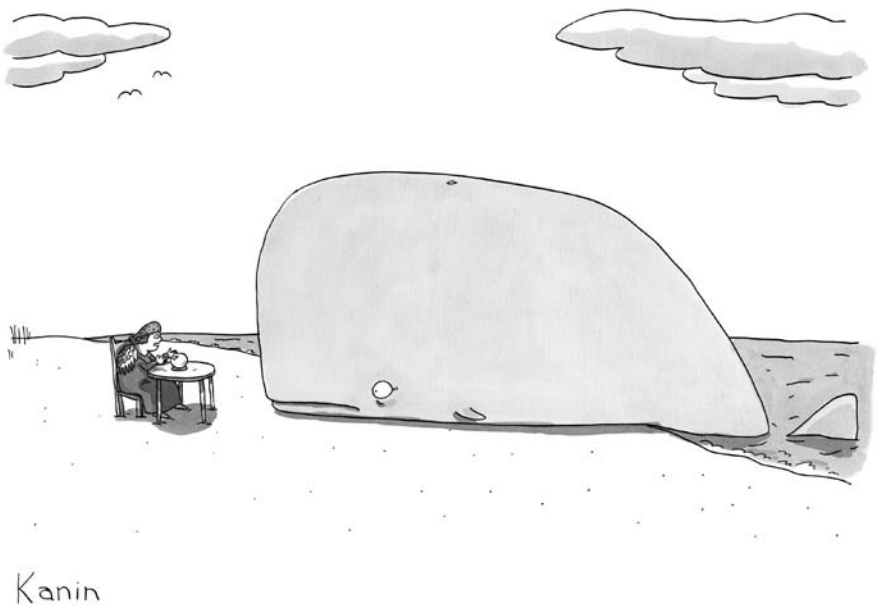
The ultimate goal, however, is to create a synthetic organism made solely from chemical parts and blueprints of DNA. In the mid-nineties, Craig Venter, working at the Institute for Genomic Research, and his colleagues Clyde Hutchison and Hamilton Smith began to wonder whether they could pare life to its most basic components and then use those genes to create such an organism. They began modifying the genome of a tiny bacterium called *Mycoplasma genitalium*, which contained four hundred and eighty-two genes (humans have about twenty-three thousand) and five hundred and eighty thousand letters of genetic code, arranged on one circular chromosome—the smallest genome of any cell that has been grown in laboratory cultures. Venter and his colleagues then removed genes one by one to find a minimal set that could sustain life.

Venter called the experiment the Minimal Genome Project. By the beginning of 2008, his team had pieced together thousands of chemically synthesized fragments of DNA and assembled a new version of the organism. Then, using nothing but chemicals, they produced from scratch the entire genome of *Mycoplasma genitalium*. "Nothing in our methodology restricts its use to chemically synthesized DNA," Venter noted in the report of his work, which was published in *Science*. "It should be possible to assemble any combination of synthetic and natural DNA segments in any desired order." That may turn out to be one of the most understated asides in the history of science. Next, Venter intends to transplant the artificial chromosome into the walls of another cell and then "boot it up," thereby making a new form of life that would then be able to replicate its own DNA—the first truly artificial organism. (Activists have already named the creation Synthia.) Venter hopes that Synthia and similar products will serve essentially as vessels that can be modified to carry different packages of genes. One package might produce a specific drug, for example, and another could have genes programmed to digest carbon in the atmosphere.

In 2007, the theoretical physicist Freeman Dyson, after having visited both the Philadelphia Flower Show and the Reptile Show in San Diego, wrote an essay in *The New York Review of Books*, noting that "every orchid or rose or lizard or snake is the work of a dedicated and skilled breeder. There are thousands of people, amateurs and professionals, who devote their lives to this business." This, of course, we have been doing in one way or another for millennia. "Now imagine what will happen when the tools of genetic engineering become accessible to these people."

It is only a matter of time before domesticated biotechnology presents us with what Dyson described as an "explosion of diversity of new living creatures. . . . Designing genomes will be a personal thing, a new art form as creative as painting or sculpture. Few of the new creations will be masterpieces, but a great many will bring joy to their creators and variety to our fauna and flora."

Biotech games, played by children "down to kindergarten age but played with real eggs and seeds," could produce entirely new species—as a lark. "These games will be messy and possibly danger-

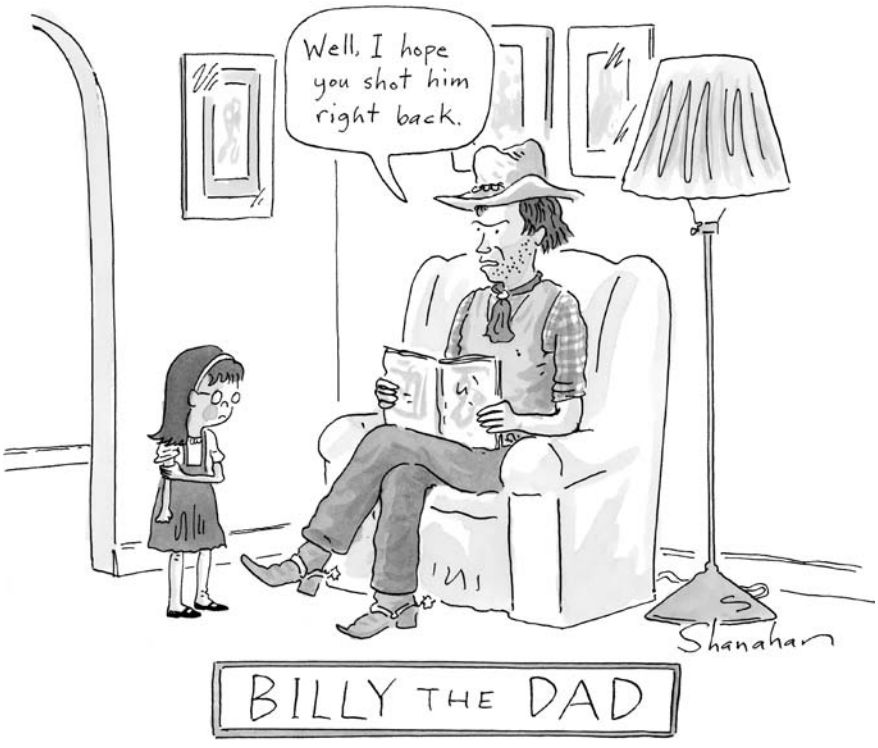


"I get the sense that there's some large body of water you're longing to return to—not a lake, maybe a sea? Is it an ocean?"

ous," Dyson wrote. "Rules and regulations will be needed to make sure that our kids do not endanger themselves and others. The dangers of biotechnology are real and serious."

Life on Earth proceeds in an arc—one that began with the big bang, and evolved to the point where a smart teenager is capable of inserting a gene from a cold-water fish into a strawberry, to help protect it from the frost. You don't have to be a Luddite—or Prince Charles, who, famously, has foreseen a world reduced to gray goo by avaricious and out-of-control technology—to recognize that synthetic biology, if it truly succeeds, will make it possible to supplant the world created by Darwinian evolution with one created by us.

"Many a technology has at some time or another been deemed an affront to God, but perhaps none invites the accusation as directly as synthetic biology," the editors of *Nature*—who nonetheless support the technology—wrote in 2007. "For the first time, God has competition."



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"What if we could liberate ourselves from the tyranny of evolution by being able to design our own offspring?" Drew Endy asked, the first time we met in his office at M.I.T., where, until the summer of 2008, he was assistant professor of biological engineering. (That September, he moved to Stanford.) Endy is among the most compelling evangelists of synthetic biology. He is also perhaps its most disturbing, because, although he displays a childlike eagerness to start engineering new creatures, he insists on discussing both the prospects and the dangers of his emerging discipline in nearly any forum he can find. "I am talking about building the stuff that runs most of the living world," he said. "If this is not a national strategic priority, what possibly could be?"

Endy, who was trained as a civil engineer, spent his youth fabricating worlds out of Lincoln Logs and Legos. Now he would like to build living organisms. Perhaps it was the three well-worn congas sitting in the corner of Endy's office, or the choppy haircut that looked like something he might have got in a tree house, or the bicycle dangling from his wall—but, when he speaks about putting together new forms of life, it's hard not to think of that boy and his Legos.

Endy made his first mark on the world of biology by nearly failing the course in high school. "I got a D," he said. "And I was lucky to get it." While pursuing an engineering degree at Lehigh University, Endy took a course in molecular genetics. He spent his years in graduate school modelling bacterial viruses, but they are complex, and Endy craved simplicity. That's when he began to think about putting cellular components together.

Never forgetting the secret of Legos—they work because you can take any single part and attach it to any other—in 2005 Endy and colleagues on both coasts started the BioBricks Foundation, a nonprofit organization formed to register and develop standard parts for assembling DNA. Endy is not the only scientist, or even the only synthetic biologist, to translate a youth spent with blocks into a useful scientific vocabulary. "The notion of pieces fitting together—whether those pieces are integrated circuits, microfluidic components, or molecules—guides much of what I do in the laboratory," the physicist and synthetic biologist Rob Carlson writes in his new book, "Biology Is Technology: The Promise, Peril, and Business of Engineering Life." "Some of my best work has come together in my mind's eye accompanied by what I swear was an audible click."

The BioBricks registry is a physical repository, but it is also an online catalogue. If you want to construct an organism, or engineer it in new ways, you can go to the site as you would one that sells lumber or industrial pipes. The constituent parts of DNA—promoters, ribosome-binding sites, plasmid backbones, and thousands of other components—are catalogued, explained, and discussed. It is a kind of theoretical Wikipedia of future life forms, with the added benefit of actually providing the parts necessary to build them.

I asked Endy why he thought so many people seem to be repelled by the idea of constructing new forms of life. "Because it's scary as hell," he said. "It's the coolest platform science has ever produced, but the questions it raises are the hardest to answer." If you can sequence something properly and you possess the information for describing that organism—whether it's a virus, a dinosaur, or a human being—you will eventually be able to construct an artificial version of it. That gives us an alternate path for propagating living organisms.

The natural path is direct descent from a parent—from one generation to the next. But that process is filled with

"Don't forget to pay the cashier on your way down."

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errors. (In Darwin's world, of course, a certain number of those mutations are necessary.) Endy said, "If you could complement evolution with a secondary path, decode a genome, take it off-line to the level of information"—in other words, break it down to its specific sequences of DNA the way one would break down the code in a software program—"we can then design whatever we want, and recompile it," which could permit scientists to prevent many genetic diseases. "At that point, you can make disposable biological systems that don't have to produce offspring, and you can make much simpler organisms."

Endy stopped long enough for me to digest the fact that he was talking about building our own children. "If you look at human beings as we are today, one would have to ask how much of our own design is constrained by the fact that we have to be able to reproduce," he said. In fact, those constraints are significant. In theory, at least, designing our own offspring could make those constraints disappear. Before speaking about that, however, it would be necessary to ask two essential questions: What sorts of risk does that bring into play, and what sorts of opportunity?

The deeply unpleasant risks associated with synthetic biology are not hard to imagine: who would control this technology, who would pay for it, and how much would it cost? Would we all have access or, as in the 1997 film "Gattaca," which envisaged a world where the most successful children were eugenically selected, would there be genetic haves and have-nots and a new type of discrimination—genoism—to accompany it? Moreover, how safe can it be to manipulate and create life? How likely are accidents that would unleash organisms onto a world that is not prepared for them? And will it be an easy technology for people bent on destruction to acquire? "We are talking about things that have never been done before," Endy said. "If the society that powered this technology collapses in some way, we would go extinct pretty quickly. You wouldn't have a chance to revert back to the farm or to the prefarm. We would just be gone."

Those fears have existed since humans began to transplant genes in crops. They are the central reason that opponents of genetically engineered food invoke the precautionary principle, which argues that potential risks must always be given more weight than possible benefits. That is certainly the approach suggested by people like Jim Thomas, of ETC, who describes Endy as "the alpha Synthusiast." But he also regards Endy as a reflective scientist who doesn't discount the possible risks of his field. "To his credit, I think he's the one who's most engaged with these issues," Thomas said.

The debate over genetically engineered food has often focussed on theoretical harm rather than on tangible benefits. "If you build a bridge and it falls down, you are not going to be permitted to design bridges ever again," Endy said. "But that doesn't mean we should never build a new bridge. There we have accepted the fact that risks are inevitable." He believes the same should be true of engineering biology.

We also have to think about our society's basic goals and how this science might help us achieve them. "We have seen an

example with artemisinin and malaria," Endy said. "Maybe we could avoid diseases completely. That might require us to go through a transition in medicine akin to what happened in environmental science and engineering after the end of the Second World War. We had industrial problems, and people said, Hey, the river's on fire—let's put it out. And, after the nth time of doing that, people started to say, Maybe we shouldn't make factories that put shit into the river. So let's collect all the waste. That turns out to be really expensive, because then we have to dispose of it. Finally, people said, Let's redesign the factories so that they don't make that crap."

Endy pointed out that we are spending trillions of dollars on health care and that preventing disease is obviously more desirable than treating it. "My guess is that our ultimate solution to the crisis of health-care costs will be to redesign ourselves so that we don't have so many problems to deal with. But note," he stressed, "you can't possibly begin to do something like this if you don't have a value system in place that allows you to map concepts of ethics, beauty, and aesthetics onto our own existence.

"These are powerful choices. Think about what happens when you really can print the genome of your offspring. You could start with your own sequence, of course, and mash it up with your partner, or as many partners as you like. Because computers won't care. And, if you wanted evolution, you can include random-number generators." That would have the effect of introducing the element of chance into synthetic design.

Although Endy speaks with passion about the biological future, he acknowledges how little scientists know. "It is important to unpack some of the hype and expectation around what you can do with biotechnology as a manufacturing platform," he said. "We have not scratched the surface. But how far will we be able to go? That question needs to be discussed openly, because you can't address issues of risk and society unless you have an answer."

Answers, however, are not yet available. The inventor and materials scientist Saul Griffith has estimated that powering our planet requires between fifteen and eighteen terawatts of energy. How much of that could we manufacture with the tools of synthetic biology? Estimates range between five and ninety terawatts. "If it turns out to be the lower figure, we are screwed," Endy said. "Because why would we take this risk if we cannot create much energy? But, if it's the top figure, then we are talking about producing five times the energy we need on this planet and doing it in an environmentally benign way. The benefits in relation to the risks of using this new technology would be unquestioned. But I don't know what the number will be, and I don't think anybody *can* know at this point. At a minimum, then, we ought to acknowledge that we are in the process of figuring that out and the answers won't be easy to provide.

"It's very hard for me to have a conversation about these issues, because people adopt incredibly defensive postures," Endy continued. "The scientists on one side and civil-society organizations on the other. And, to be fair to those groups, science has often proceeded by skipping the dialogue. But some environmental groups will say, Let's not permit any of this work to get out of a laboratory until we are sure it is all safe. And as a practical matter that is not the way science works. We can't come back decades later with an answer. We need to develop solutions by doing them. The potential is great enough, I believe, to convince people it's worth the risk."

I wondered how much of this was science fiction. Endy stood up. "Can I show you something?" he asked, as he walked over to a bookshelf and grabbed four gray bottles. Each one contained about half a cup of sugar, and each had a letter on it: A, T, C, or G, for the four nucleotides in our DNA. "You can buy jars of these chemicals that are derived from sugarcane," he said. "And they end up being the four bases of DNA in a form that can be readily assembled. You hook the bottles up to a machine, and into the machine comes information from a computer, a sequence of DNA—like T-A-A-T-A-G-C-A-A. You program in whatever you want to build, and that machine will stitch the genetic material together from scratch. This is the recipe: you take information and the raw chemicals and compile genetic material. Just sit down at your laptop and type the letters and out comes your organism."

We don't have machines that can turn those sugars into entire genomes yet. Endy shrugged. "But I don't see any physical reason why we won't," he said. "It's a question of money. If somebody wants to pay for it, then it will get done." He looked at his watch, apologized, and said, "I'm sorry, we will have to continue this discussion another day, because I have an appointment with some people from the Department of Homeland Security."

I was a little surprised. "They are asking the same questions as you," he said. "They want to know how far is this really going to go."

Scientists skipped a step at the birth of biotechnology, thirty-five years ago, moving immediately to products without first focussing on the tools required to make them. Using standard biological parts, a synthetic biologist or biological engineer can already, to some extent, program living organisms in the same way a computer scientist can program a computer. However, genes work together in ways that are staggeringly complex; proteins produced by one will counteract—or enhance—those made by another. We are far from the point where scientists might yank a few genes off the shelf, mix them together, and produce a variety of products. But the registry is growing rapidly—and so is the knowledge needed to drive the field forward.

Research in Endy's Stanford lab has been largely animated by his fascination with switches that turn genes on and off. He and his students are attempting to create genetically encoded memory systems, and his current goal is to construct a cell that can count to two hundred and fifty-six—a number derived from the mathematics of Basic computer code. Solving the practical challenges will not be easy, since cells that count will need to send reliable signals when they divide and remember that they did.

"If the cells in our bodies had a little memory, think what we could do," Endy said the next time we talked. I wasn't quite sure what he meant. "You have memory in your phone," he explained. "Think of all the information it allows you to store. The phone and the technology on which it is based do not function inside cells. But if we could count to two hundred, using a system that was based

on proteins and DNA and RNA—well, now, all of a sudden we would have a tool that gives us access to computing and memory that we just don't have.

"Do you know how we study aging?" Endy continued. "The tools we use today are almost akin to cutting a tree in half and counting the rings. But if the cells had a memory we could count properly. Every time a cell divides, just move the counter by one. Maybe that will let me see them changing with a precision nobody can have today. Then I could give people controllers to start retooling those cells. Or we could say, Wow, this cell has divided two hundred times, it's obviously lost control of itself and become cancer. Kill it. That lets us think about new therapies for all kinds of diseases."

Synthetic biology is changing so rapidly that predictions seem pointless. Even that fact presents people like Endy with a new kind of problem. "Wayne Gretzky once said, 'I skate to where the puck is going to be.' That's what you do to become a great hockey player," Endy told me. "But where do you skate when the puck is accelerating at the speed of a rocket, when the trajectory is impossible to follow? Whom do you hire and what do we ask them to do? Because what preoccupies our finest minds today will be a seventh-grade science project in five years. Or three years.

"We are surfing an exponential now, and, even for people who pay attention, surfing an exponential is a really tricky thing to do. And when the exponential you are surfing has the capacity to impact the world in such a fundamental way, in ways we have never before considered, how do you even talk about that? "

For decades, people have invoked Moore's law: the number of transistors that could fit onto a silicon chip would double every two years, and so would the power of computers. When the I.B.M. 360 computer was released, in 1964, the top model came with eight megabytes of main memory, and cost more than two million dollars. Today, cell phones with a thousand times the memory of that computer can be bought for about a hundred dollars.

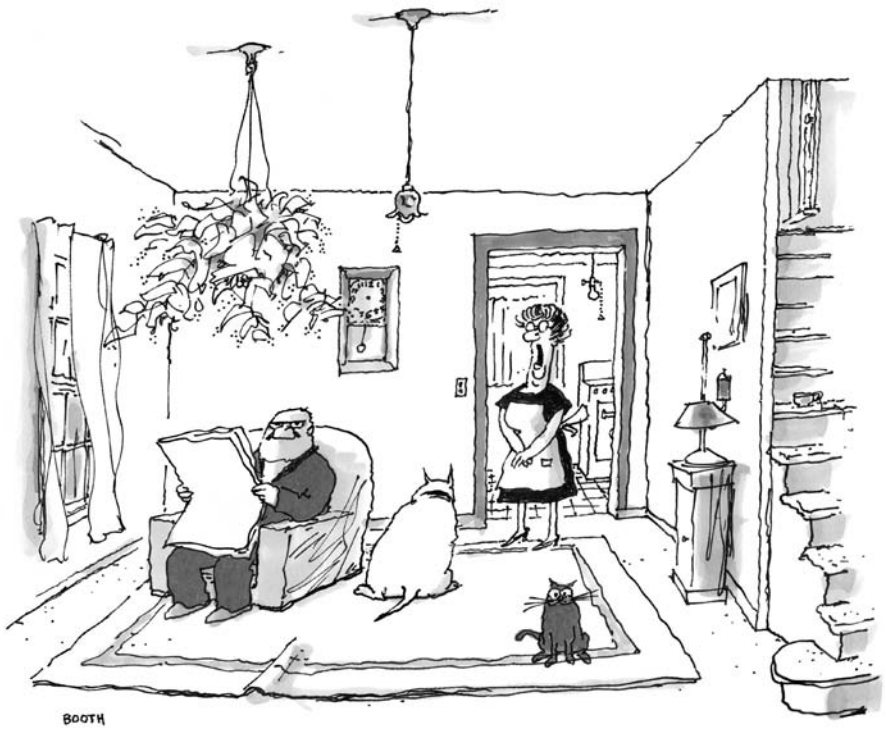
In 2001, Rob Carlson, then a research fellow at the Molecular Sciences Institute, in Berkeley, decided to examine a similar phenomenon: the speed at which the capacity to synthesize DNA was growing. He produced what has come to be known as the Carlson curve, and it shows a rate that mirrors Moore's law—and has even begun to exceed it. The automated DNA synthesizers used in thousands of labs cost a hundred thousand dollars a decade ago. Now they cost less than ten thousand dollars, and, most days, at least a dozen used synthesizers are for sale on eBay—for less than a thousand dollars.

Between 1977, when Frederick Sanger published the first paper on automatic DNA sequencing, and 1995, when the Institute for Genomic Research reported the first bacterial-genome sequence, the field moved slowly. It took the next six years to complete the first draft of the immeasurably more complex human genome, and six years after that, in 2007, scientists from around the world began mapping the full genomes of more than a thousand people. The Harvard geneticist George Church's Personal Genome Project now plans to sequence more than a hundred thousand.

In 2003, when Endy was still at M.I.T., he and his colleagues Tom Knight, Randy Rettberg, and Gerald Sussman founded iGEM—the International Genetically Engineered Machine competition—whose purpose is to promote the building of biological systems from standard parts. In 2006, a team of Endy's undergraduate students used BioBrick parts to genetically reprogram E. coli (which normally smells awful) to smell like wintergreen while it grows and like bananas when it is finished growing. They named their project Eau d'E Coli. By 2008, with more than a thousand students from twenty-one countries participating, the winning team—a group from Slovenia—used biological parts that it had designed to create a vaccine for the stomach bug *Helicobacter pylori*, which causes ulcers. There are no such working vaccines for humans. So far, the team has tested its creation on mice, with promising results.

This is open-source biology, where intellectual property is shared. What's available to idealistic students, of course, would also be available to terrorists. Any number of blogs offer advice about everything from how to preserve proteins to the best methods for desalting DNA. Openness like that can be frightening, and there have been calls for tighter control of the technology. Carlson, among many others, believes that strict regulations are unlikely to succeed. Several years ago, with very few tools other than a credit card, he opened his own biotechnology company, Biodesic, in the garage of his Seattle home—a biological version of the do-it-yourself movement that gave birth to so many computer companies, including Apple.

The product that he developed en-



"Are you ready to pound down some breakfast?"

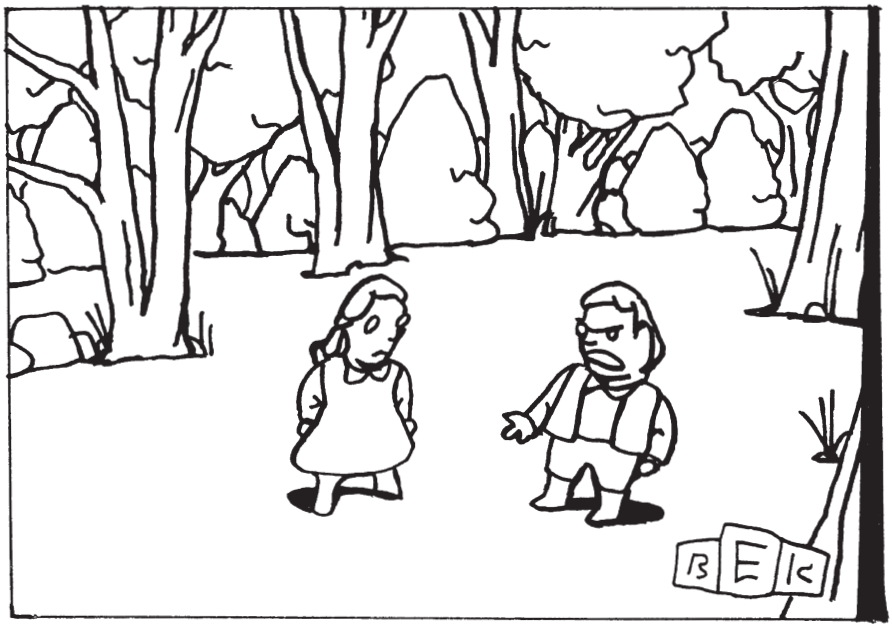
ables the identification of proteins using DNA technology. "It's not complex," Carlson told me, "but I wanted to see what I could accomplish using mail order and synthesis." A great deal, it turned out. Carlson designed the molecule on his laptop, then sent the sequence to a company that synthesizes DNA. Most of the instruments could be bought on eBay (or, occasionally, on LabX, a more specialized site for scientific equipment). All you need is an Internet connection.

"Strict regulation doesn't accomplish its goals," Carlson said. "It's not an exact analogy, but look at Prohibition. What happened when government restricted the production and sale of alcohol? Crime rose dramatically. It became organized and powerful. Legitimate manufacturers could not sell alcohol, but it was easy to make in a garage—or a warehouse."

By 2002, the U.S. government intensified its effort to curtail the sale and production of methamphetamine. Previously, the drug had been manufactured in many mom-and-pop labs throughout the country. Today, production has been professionalized and centralized, and the Drug Enforcement Administration says that less is known about methamphetamine production than before. "The black market is getting blacker," Carlson said. "Crystal-meth use is still rising, and all this despite restrictions." Strict control would not necessarily insure the same fate for synthetic biology, but it might.

Bill Joy, a founder of Sun Microsystems, has frequently called for restrictions on the use of technology. "It is even possible that self-replication may be more fundamental than we thought, and hence harder—or even impossible—to control," he wrote in an essay for *Wired* called "Why the Future Doesn't Need Us." "The only realistic alternative I see is relinquishment: to limit development of the technologies that are too dangerous, by limiting our pursuit of certain kinds of knowledge."

Still, censoring the pursuit of knowledge has never really worked, in part because there are no parameters for society to decide who should have information and who should not. The opposite approach might give us better results: accelerate the development of technology and open it to more people and educate them to its purpose. Otherwise, if Carlson's methamphetamine analogy proves accurate, power would flow directly into the hands of the people least likely to use it wisely.



"Gretel, I don't like living in this culture of fear."

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For synthetic biology to accomplish any of its goals, we will also need an education system that encourages skepticism and the study of science. In 2007, students in Singapore, Japan, China, and Hong Kong (which was counted independently) all performed better on an international science exam than American students. The U.S. scores have remained essentially stagnant since 1995, the first year the exam was administered. Adults are even less scientifically literate. Early in 2009, the results of a California Academy of Sciences poll (conducted throughout the nation) revealed that only fifty-three per cent of American adults know how long it takes for the Earth to revolve around the sun, and a slightly larger number—fifty-nine per cent—are aware that dinosaurs and humans never lived at the same time.

Synthetic biologists will have to overcome this ignorance. Optimism prevails only when people are engaged and excited. Why should we bother? Not just to make E. coli smell like chewing gum or fish glow in vibrant colors. The planet is in danger, and nature needs help.

The hydrocarbons we burn for fuel are believed to be nothing more than concentrated sunlight that has been collected by leaves and trees. Organic matter rots, bacteria break it down, and it moves underground, where, after millions of years of pressure, it turns into oil and coal. At that point, we dig it up—at huge expense and with disastrous environmental consequences. Across the globe, on land and sea, we sink wells and lay pipe to ferry our energy to giant refineries. That has been the industrial model of development, and it worked for nearly two centuries. It won't work any longer.

The industrial age is drawing to a close, eventually to be replaced by an era of biological engineering. That won't happen easily (or quickly), and it will never solve every problem we expect it to solve. But what worked for artemisinin can work for many of the products our species will need to survive. "We are going to start doing the same thing that we do with our pets, with bacteria," the genomic futurist Juan Enriquez has said, describing our transition from a world that relied on machines to one that relies on biology. "A house pet is a domesticated parasite," he noted. "It is evolved to have an interaction with human beings. Same thing with corn"—a crop that didn't exist until we created it. "Same thing is going to start happening with energy," he went on. "We are going to start domesticating bacteria to process stuff inside enclosed reactors to produce energy in a far more clean and efficient manner. This is just the beginning stage of being able to program life." ♦