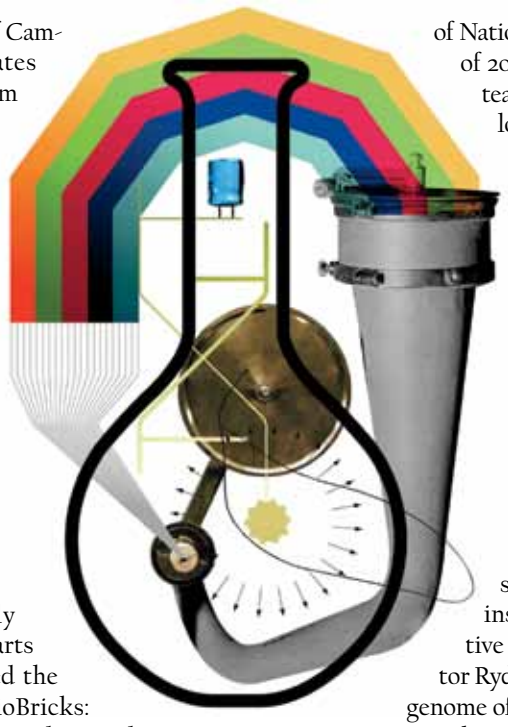
Synthetic Biology's New Menagerie

Life, reengineered



In the summer of 2009, a team of Cambridge University undergraduates built seven strains of the bacterium *Escherichia coli*, one in each color of the rainbow. Red and orange carotenoid pigments were produced by inserting genes from plant pathogen *Pantoea ananatis*; a cluster of genes from *Chromobacterium violaceum* were likewise modified to yield green and purple. The students' technicolor creations, dubbed "E. chromi" in reference to the organisms' scientific name, won the Cambridge team the grand prize at that year's International Genetically Engineered Machines (iGEM) competition, in which high-school and college students engineer biology.

The students' goals were not merely chromatic. Instead, they were building parts for biological machines. They engineered the genes into standardized forms called BioBricks: pieces of DNA that, like genetic Legos, are designed to be mixed and matched at will. Several thousand of these BioBricks, fulfilling various functions, are already housed in the MIT-based Registry of Standard Biological Parts. Some BioBricks detect chemicals like arsenic; others act as "tuners" that determine the threshold level of chemical input needed to turn on a certain gene. By combining the new color-producing genes with existing parts, the thinking went, one might easily construct biosensors that, in the presence of environmental toxins, produce output visible to the naked eye.

"E. chromi" struck a chord with designers Alexandra Daisy Ginsberg, G '06, and James King, who began a collaboration with the iGEM team. In a short video that was named best documentary at the Bio:Fiction synthetic biology film festival in 2011, Ginsberg and King imagined possible futures for living color. Soon, they suggested, scientists might search the natural world for new biological pigments and the genes responsible, revolutionizing dye production. "E. chromi" in probiotic yogurt might monitor human disease while traveling through the gut; microbes in the atmosphere might change color to indicate air quality.

"I think it's a new term to most of the public, *synthetic biology*," mused the host of National Public Radio's *Science Friday* in the fall of 2009 when he interviewed the Cambridge team. "But I guess we're going to be hearing a lot more of it."

How to Build a Biological Machine

Armed with powerful new genetic tools and a penchant for tinkering, synthetic biologists have built a new menagerie. Photographic "E. coliroid" darken in response to light. Sensor bacteria record the presence of a chemical in a mouse's gut by turning on certain genes. There are strains of *E. coli* that count input signals and others that carry out logical operations—steps toward biological computers. Still other strains smell like wintergreen and bananas instead of like the human gut. In 2005, festive researchers "wrote" the first verse of Viktor Rydberg's Christmas poem "Tomten" into the genome of yet another *E. coli* strain, using triplets of DNA nucleotides to represent each letter; the resulting bacterium, they wrote, was "the first example of an organism that 'recites' poetry."

Insofar as a common theme unites these diverse creations, it is the transformation of biology into an engineering discipline. Traditional genetic engineering amounted more or less to biological cut-and-paste: scientists could, for instance, transfer a cold-tolerance gene from an Arctic fish into a tomato. Synthetic biology aims for a more radical reorganization. Its organisms are built to be biological machines, with DNA and proteins standing in for circuit components or lines of computer code. In combination, the biological parts perform functions unknown to nature: processing signals, producing new chemicals, storing information.

"I like to say that biological carbon is the silicon of this century," says Pamela A. Silver, Adams professor of biochemistry and systems biology at Harvard Medical School (HMS; see "Biology in This Century," September-October 2011, page 72). Just as computers revolutionized the past hundred years, she says, biology is poised to transform the next. "The building of biological machines and biological computers—all of that should soon become a reality."

To a certain mind, a cell already resembles a tiny, complex machine. It takes

by Katherine Xue

portraits by Stu Rosner
illustrations by Stuart Bradford

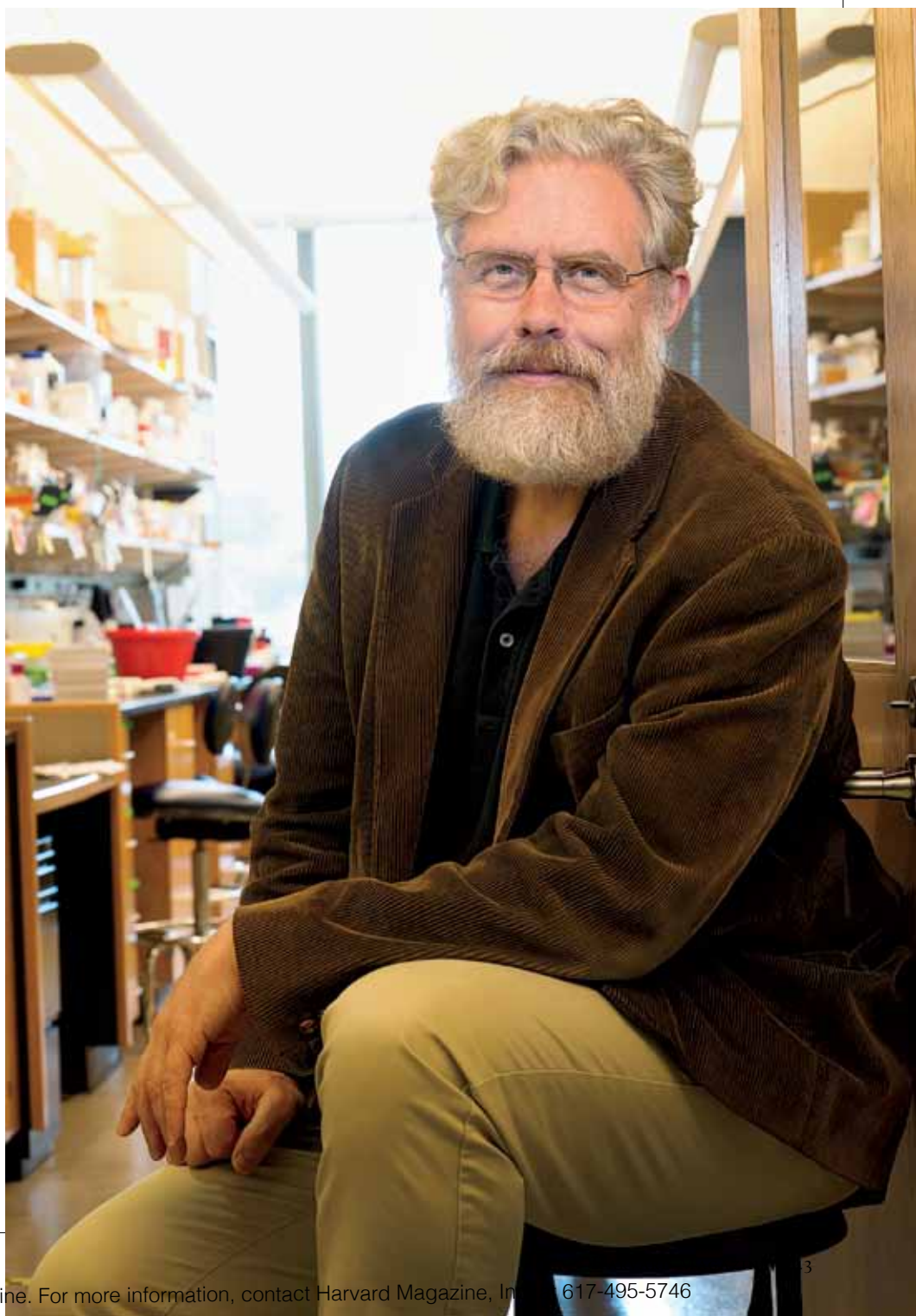
in chemicals from the environment and performs reactions to build new biological parts; it monitors signals and turns genes on and off in response. Cells have been compared to computers, to factories, to automatons. For a synthetic biologist with such complex systems already at hand, the task is to identify and manipulate the appropriate parts. "Many of the biomolecular components we're not building from scratch," says James J. Collins, Warren Distinguished Professor at Boston University and founding core faculty member at Harvard's Wyss Institute for Biologically Inspired Engineering. "We're taking native systems and then modifying them."

Understanding and manipulating this elaborate machinery is a tough job. "I think of it as if some alien intelligence just dropped onto us all their intellectual property without documentation," says George Church, Winthrop professor of genetics at HMS (see "DNA as Data," January-February 2004, page 44). There's no direct biological equivalent of a capacitor or the delete command, and synthetic biologists must creatively recombine existing biological parts in order to build new functions.

Take, for instance, the toggle switch, one of the simplest circuit components. A nonbiological example would be a light switch: it can be flipped between two discrete states, on or off, with nothing in between. In an abstract sense, the toggle switch amounts to a kind of memory, with its two states tantamount to 0's and 1's. Such bistability has some analogues in nature. Venus fly traps, for instance, have structures that alternate between open and shut (see "Leaves That Lunch," May-June 2005, page 14). Specific signals instruct cells whether to remain dormant or divide. Some viruses also toggle between two distinct states of dormancy or active infection.

When Collins's lab built a *bacterial* toggle switch—one of the first pieces of biological circuitry—they made it from two genes. Each encoded a repressor protein for the opposite gene; once one gene was turned on, it turned the other gene off. The switch could be flipped by giving the cell a specific chemical signal, disabling the active repressor protein and allowing the other to take hold. With the second gene now turned on, turning off the first, the switch would stay flipped long after the signal had disappeared. "As a cellular memory unit," wrote Collins when his team published its design in 2000, "the toggle forms the basis for 'genetic applets'—self-contained, programmable, synthetic gene circuits for the control of cell function."

Genetic applets (perhaps more aptly, apps today) are one of synthetic biology's defining goals. Some 40 years after scientists began learning to rearrange DNA, genetic engineering remains something of a cottage industry. In a time-consuming, almost artisanal craft, researchers modify organisms *ad hoc* to suit their particular needs. Synthetic biology was born out of a desire for greater, more versatile control, says Silver, who took part in early meetings of the Synthetic Biology Working Group at MIT. "The question that forms the core of synthetic biology is, 'Why can't biology be easier and more predictable to engineer?'"



George Church's lab has reengineered the genetic code of the bacterium *Escherichia coli* to make it resistant to viral infection.

Indeed, for synthetic biologists, it is not enough to have painstakingly built genetic switches and biological machines. "Right now, people—especially graduate students—just spend an inordinate amount of time making DNA and figuring out how to put DNA together," says Jeffrey Way, senior staff scientist at the Wyss Institute, who is married to Silver. "It's extremely time-consuming."

Early on, he says, synthetic biology took its cues from the computer industry, where early common standards for computer chips allowed multiple circuits to be combined. One of the field's key aspirations is modularity—the ability to mix and match genetic parts. In an article in *Scientific American* in 2006, Church, Collins, and several other researchers outlined principles for what they called a "bio fab," a set of standards and methods to make genetic circuits easier to build and recombine. "Part of the vision was that you should be able to abstract away part of how biology works and not have to worry about the details," says Way, who worked at the Molecular Sciences Institute, an independent research lab in California, where many of synthetic biology's principles were initially conceived. "A computer programmer never worries about how a computer chip works—they don't actually need to know how the commands are executed by the machine."

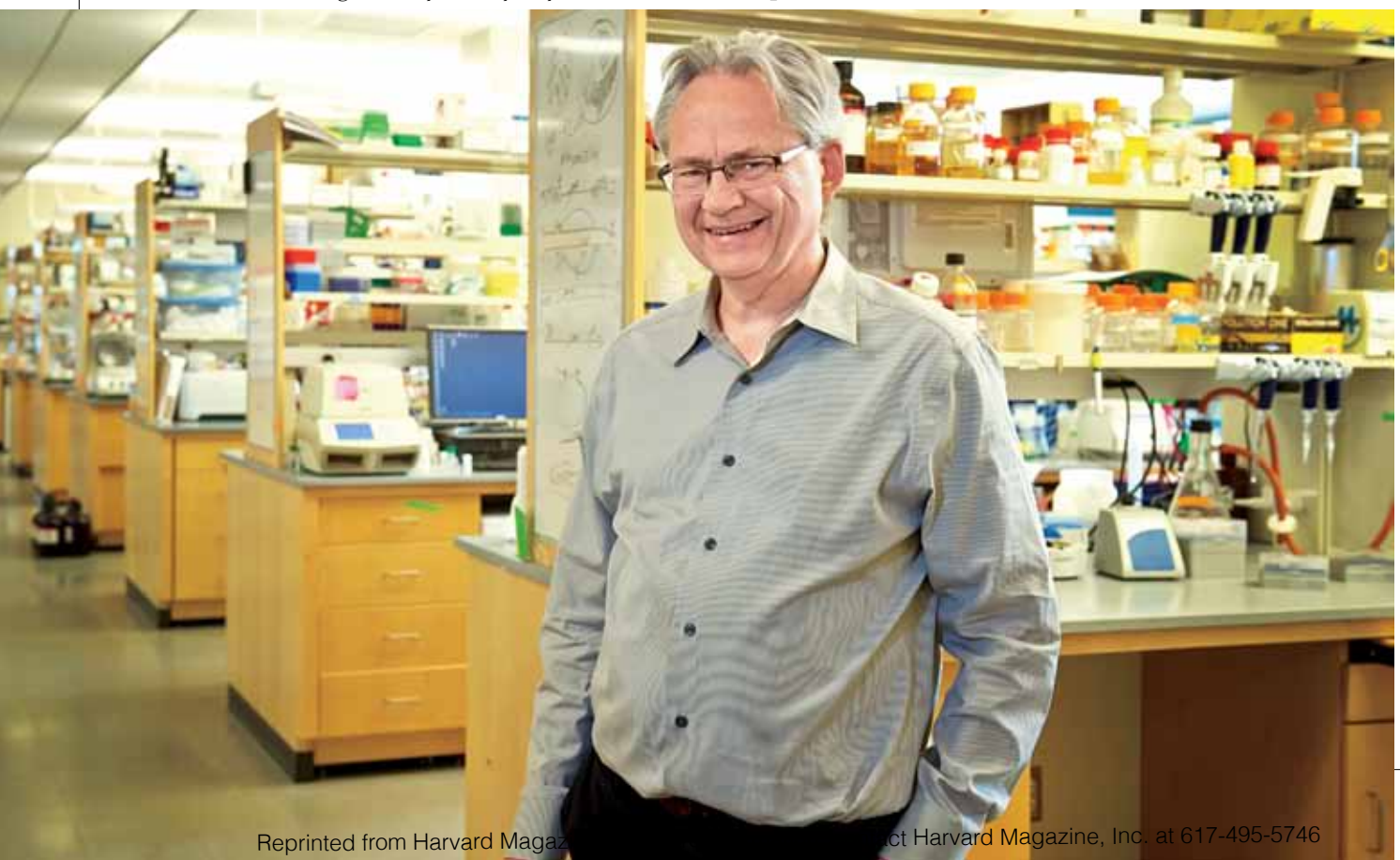
Yet progress toward such abstraction has been mixed, researchers acknowledge. "What do you need to know to use a part?" asks Silver, who is a board member of the nonprofit BioBricks Foundation, which promotes the bio fab vision. "What constitutes a characterization?" Way goes further, questioning the analogy between circuits and living things. "In biology, the key difference is that the equivalent of computer chips—pieces of DNA, proteins, and so forth—those are all made by nature and not by human design," he says. "They may seem modular, but it's an open question as to whether that's the way that biology is, or whether that's an artifact of human understanding."

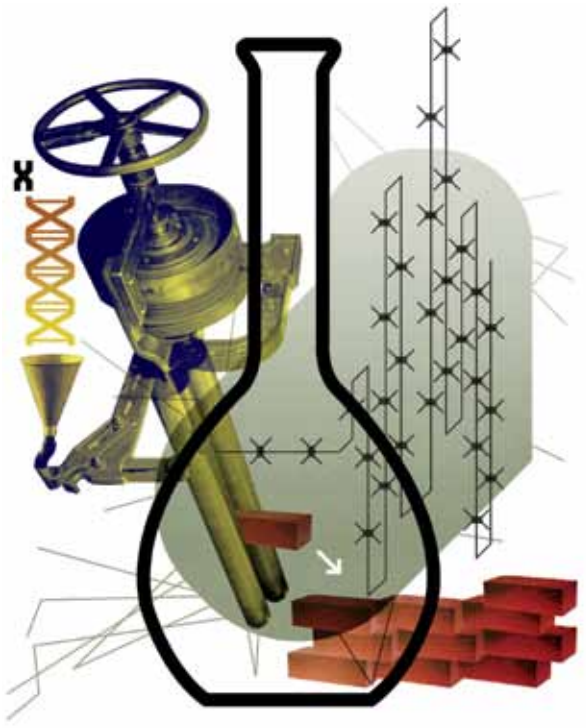
Jeffrey Way is part of a team that engineered cyanobacteria to produce sugars from photosynthesis more efficiently.

For now, says Way, synthetic biologists still must hew tightly to the contours of nature, closely studying biological systems to identify and make use of special properties. For instance, in a project published this spring, he and Silver collaborated with Collins to engineer bacterial "reporters." Once fed to mice, the bacteria take up residence in the gut, where they detect the presence of the antibiotic-like molecule anhydrotetracycline and record it by flipping a genetic switch. Silver and Way, both trained as molecular biologists, made use of a well-studied natural switch from bacteriophage lambda (a virus that infects bacteria) that has two convenient properties. It is extraordinarily stable, maintaining its state through multiple bacterial generations, and it imposes a negligible burden on the bacterial host, helping it survive in the mouse gut. Silver and Way were both present at Harvard in the 1980s when key work on phage lambda was done, giving them deep familiarity with the virus's genetic switch. "Rational design *is* really feasible—provided you know enough about the system," says Way. "Knowing all the quirky stuff about the biology of an organism was critical in making the whole thing work."

Synthetic Biology Remakes Nature

Sometimes life is just too hard to understand. Such was the conclusion of current Stanford professor Drew Endy, then at MIT, after several years spent trying to computationally model the bacteriophage T7. The virus is one of the simplest and most well-studied biological systems, and after 60 years of research, Endy thought, scientists should have T7 down to a T. But this proved far from so: his simulations, which sought to predict how mutations would affect viral development, simply did not match experimental results.





Faced with biological complexity, Endy decided to get rid of it. In 2005, he and collaborators published a report on a virus they dubbed "T7.1," a version of T7 they designed to be easy to understand and manipulate. Evolution may have been responsible for the diversity of biological functions, but to a human scientist, those functions could appear byzantine and impossible to comprehend, let alone engineer. T7, for instance, had multiple overlapping genes, meaning that mutations in one gene could affect others in unpredictable ways. Endy's team built "T7.1," by separating the virus's genes into discrete parts—all the better for rational design. "T7.1" survived its massive genome reordering, though barely. Compared to T7, its fitness was considerably reduced.

"'T7.1' is a perfect example of what makes synthetic biology different from other post-genomic disciplines in the life sciences," says Sophia Roosth, assistant professor in the history of science. As a graduate student at MIT, Roosth conducted an ethnographic study of synthetic biology, doing extensive fieldwork in Endy's lab. In her forthcoming book, *Synthetic: How Life Got Made*, she uses projects like "T7.1" as lenses to examine the concepts of nature and design that motivate synthetic biologists' work. "Instead of trying to rebuild the model, Endy's team wanted to rebuild the phage to be more understandable. That's a symptom of the move to manufacture in the life sciences—comprehensibility becomes a design principle, and making becomes a form of inquiry. Knowledge about how life works is furthered not by experimenting on life, but by making new forms of it."

Indeed, synthetic biology's mission of making biology easier to engineer has occasionally entailed wholescale *remaking*. Unexpected cellular behaviors can still complicate the best-laid plans. The basic design of the toggle switch, for instance, followed a computational model that Collins's lab had developed prior to beginning experiments, but it nevertheless took several months of trial and error to tune the switch so that one gene did not overpower the other. Building a biological circuit remains a much more uncertain endeavor than building its electronic counterpart. "The environment inside cells is very noisy," says Collins. "There are a lot of fluctuations that make it challenging to have genetic circuits that behave reliably. And because cells are dense and highly complex with their host machinery operating, the circuits that we're building are interacting with the host in ways we don't fully understand."

One strand of synthetic biology aims to lessen this unpredictability by creating minimal "chassis" organisms, designed to serve as neutral, well-characterized backgrounds upon which genetic circuits can be built. For example, the J. Craig Venter Institute (JCVI), founded and led by the eponymous genome-sequencing pioneer, has eliminated one gene at a time from *Mycoplasma genitalium*, the bacterium with the smallest known cellular genome, in order to identify the smallest set of genes needed to carry out basic, self-sustaining functions of cell metabolism and replication. Of the organism's 482 protein-coding genes (humans have an estimated 20,000), Venter's team estimated that 265 to 350 are necessary for survival. They plan to synthesize an altered genome consisting of this minimal set and transplant it into *Mycoplasma* cells whose own genomes have been removed, forming an organism they call "Mycoplasma laboratorium."

Other researchers are focusing on building chassis chromosomes. "Imagine if you had a piece of DNA, and you knew everything about it—there were no mysteries," says Silver. Her lab is working with the Venter Institute to design a mammalian artificial chromosome, in which the complex processes of mammalian gene regulation would be more fully characterized and understood. Earlier this year, researchers from New York University and Johns Hopkins announced the creation of an artificial yeast chromosome, with nearly one in six base pairs of the genetic scaffold modified to make genes easier to insert and remove. The artificial chromosome is the first step in building synthetic yeast, whose entire genome is similarly redesigned.

Such massive genome remodeling also lends itself to more radical possibilities. Church's lab, for instance, is working to alter the genetic code. All living things have cellular machinery that interprets DNA instructions, mapping three-nucleotide sequences called codons into the amino acids that make up proteins. In 2011, Church's group reported that it had massively reengineered the *E. coli* genome, replacing each instance of the codon "TAG" with "TAA" (see "Life: The Edited Version," November-December 2011, page 14). Both are stop codons, signaling that a series of genetic instructions is complete, but each codon is interpreted using different cellular machinery. With the "TAG" codon now gone, the researchers deleted the machinery that handled its translation. In its absence, if a virus were to invade the engineered organism—dubbed "rE. coli"—the viral "TAG" codons would be ignored, dooming its attempted infection. Using techniques like those that built "rE. coli," Church says, it might someday be possible to engineer humans to be similarly virus-free.

"Today we are at the point in science and technology where we humans can reduplicate and then improve what nature has already accomplished," wrote Church in the introduction to the popular-science book he coauthored, *Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves.* "We too can turn the inorganic into the organic. We too can read and interpret genomes—as well as modify them. And we too can create genetic diversity, adding to the considerable sum of it that nature has already produced."

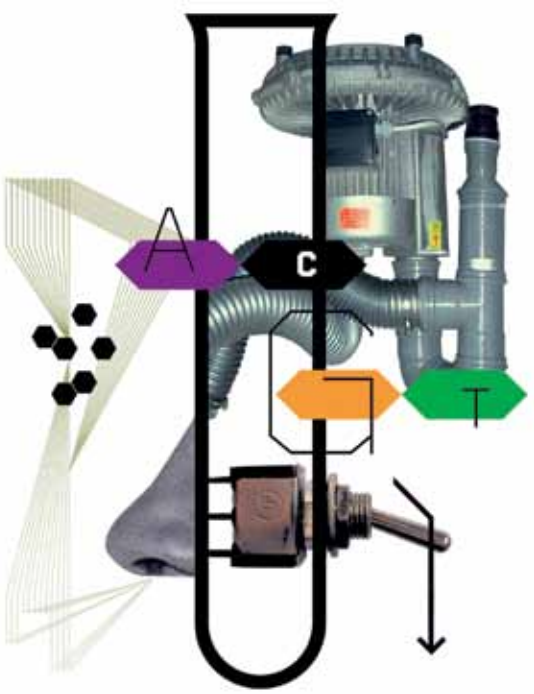
Life on a Leash

Projects of such scope give many observers pause. A mosaic of religious frescoes, reordered and recombined, adorns the cov-

er of Church's *Regenesis*, placing front and center the language and imagery that has frequently dominated public discourse about the field. In her book, Roosth describes how notions of "design," imported into synthetic biology from engineering, sometimes retain religious resonances, especially in connection with terms like "creation." In 2008, *Radiolab* ran a segment on synthetic biology titled "Intelligent Design?"

One of the most disquieting acts of whole-scale biological recreation came in 2002, when researchers were able to produce live, infectious poliovirus by synthesizing its genome. In 2005, researchers at the Centers for Disease Control and Prevention used similar methods to reconstruct the virus responsible for the 1918 pandemic of Spanish flu. In 2006, using private addresses and identities, reporters from *The Guardian* were able to mail-order a small segment of the smallpox genome, though additional equipment and expertise would have been required to assemble the entire genome and bring the virus to life.

Indeed, the logical extreme of making biology easier to engineer is that anyone could do it. In a 2007 essay, "Our Biotech Future," published in the *New York Review of Books*, Nobel Prize-winning physicist Freeman Dyson drew an analogy to the computing industry, predicting a world in which genetic engineering was literally child's play. "The final step in the domestication of biotechnology will be biotech games," he wrote, "designed like computer games for children down to kindergarten age but played with real eggs and seeds rather than with images on a screen."



"There are distinct challenges coming out of synthetic biology," says Kenneth A. Oye, Ph.D. '83, professor of political science at MIT. "Modularity and repurposing potentially decrease barriers to diffusion, and the potential for more artificial organisms renders obsolete regulatory approaches that are based on standardized lists of dangerous wild-type organisms."

Oye works with synthetic biologists to study questions of safety and security raised by new technologies as part of the Synthetic Biology Engineering Research Center, or Synberc, funded by the National Science Foundation (NSF). "I believe that engineers and scientists should accept responsibility for addressing or engaging with risks that are associated with what they're creating," he says. "By 'responsible,' what I mean is taking an active interest in identifying and doing research to identify potential problems, and not just simply responding or reacting to problems that others raise."

Twin concerns of safety and security, the latter focused on preventing malevolent use, have prompted synthetic biologists and policymakers alike to closely examine the opportunities and challenges of the new field. "I think something that both scientists and lay audiences forget is just how much safety engineering goes into a mature field," says Church. "You look at a car, and it doesn't take

Synthetic Biology in the Wild

This July, Wyss Institute fellow Kevin Esvelt and Winthrop professor of genetics George Church coauthored a paper in the journal *eLife* outlining how new technologies containing self-replicating pieces of DNA could potentially be used to genetically reengineer entire species in the wild. A recently discovered bacterial system called CRISPR-Cas, named after the DNA and proteins involved, has allowed scientists to make highly specific genetic modifications with greater ease than ever before (see **harvardmag.com/genomic-14**). As Church and colleagues predicted in the recent paper, certain genetic changes that themselves include a CRISPR-Cas system could copy themselves in a process called a "gene drive," enabling a modification to spread through an entire species during the course of many generations. Scientists might one day be able to alter or even eliminate entire species—reengineering herbicide susceptibility into populations of resistant weeds, for instance, or suppressing malaria mosquitoes or invasive plants.

Church's technical paper was published simultaneously with a policy paper in *Science* that assessed the technology's possible impacts. The environmental and security effects of gene drives are still unclear, wrote the authors, a team of scientific and legal experts that included technologists Church and Esvelt, Ph.D. '10, evolutionary ecologist and former National Science Foundation director for population biology and physiological ecology James P. Collins, and lead author Kenneth Oye, Ph.D. '83, professor of political science at MIT. Moreover, regulatory gaps remain: domestic and international policies, built narrowly around lists of dangerous toxins or organisms, fail to address the uniquely broad character of gene drives. The authors made 10 recommendations for managing environmental and biosecurity risks. Certain types of gene drives might reverse prior genetic changes or immunize organisms from further modification, for instance, and new regulatory structures might adopt broader definitions of biological impact. The authors also called for a public discussion on how the new technology ought to be used. "For emerging technologies that affect the global commons, concepts and applications should be published in advance of construction, testing, and release," they wrote in conclusion. "Lead time will allow for broadly inclusive and well-informed public discussion to determine if, when, and how gene drives should be used."

much reflection to remember that they have seatbelts, air bags, crushable fenders. There are also other things you don't see so much, like licensing, speed traps, and Breathalyzers. It's harder to do in a new field because you don't even *know* what you don't know, and that freaks people out."

Church's lab works actively on both building and testing the biological equivalents of seat belts, which might be designed into future chassis organisms. "We're building genetically modified organisms that can't escape and can't influence the ecosystem because they are genetically and metabolically isolated," he says. "They're on a very short leash." With an altered genetic code, he argues, a synthetic organism could neither give nor receive DNA, since it would process genetic instructions differently from its wild relatives. His lab's genetically recoded "rE. coli" is already unable to live more than a few minutes without an inexpensive compound that is only available in the lab, says Church. Moreover, "we're building more radically recoded organisms that literally can't use natural DNA from their environment, since it must be processed by cellular machinery that these organisms lack." Collins's lab has devised another solution, developing a genetic "kill switch" that responds to certain chemicals by producing toxic proteins that kill the cell.

Other safeguards for synthetic biology are under construction, and many of them are, likewise, self-imposed. After *The Guardian* exposed the ease of ordering pathogens' DNA, DNA-synthesis companies voluntarily created collaborative consortia to screen orders against databases of known pathogens and toxins and to flag suspicious behavior. All competitors in the iGEM bioengineering competition are required to submit their projects for review by a safety committee, which works with teams to modify projects that provoke concern, and several federal agencies have also sponsored educational programs to sensitize competitors to biosecurity issues.

Indeed, says Oye, synthetic biology is on its way to developing what he calls a "culture of responsibility." It aims to augment rather than supplant traditional regulatory measures, he says, and can influence both the nature of regulation and how researchers think about the projects they pursue. For instance, when Silver and Way led a team that engineered cyanobacteria to more efficiently produce sugars via photosynthesis, their team and Oye's group conducted a joint risk-assessment exercise. Ecologists, microbiologists, and regulators from the Environmental Protection Agency came together to discuss the environmental implications of release of the engineered organisms, with attention to competition with wild bacteria, for instance, as well as potential gene transfer and evolution.

"By 'culture of responsibility,' what I mean is the inculcation of a set of values and mores," Oye says. "Over the long term, it makes quite a difference. It makes a difference in the kinds of projects people decide to do. It makes a difference in terms of their willingness to work with others to discourage bad activity and to lean hard on the side of openness and responsible conduct."

Pamela A. Silver and colleagues engineered bacteria that detect and report on the presence of a certain molecule in a mouse's gut.

Imagining the Future

Questions of scientific responsibility featured prominently in the 1970s, when similar concerns arose as scientists began learning how to manipulate organisms' genes. In 1974, researchers

working on genetic engineering undertook a voluntary moratorium to assess the impacts of their work, a moratorium that ended with the convening of the landmark 1975 Asilomar Conference on Recombinant DNA. There, a group of leading molecular biologists discussed safeguards for the new field, designating avenues of research that should not be pursued and settling on a self-imposed strategy of containment to reduce the risk that engineered organisms would escape the lab.

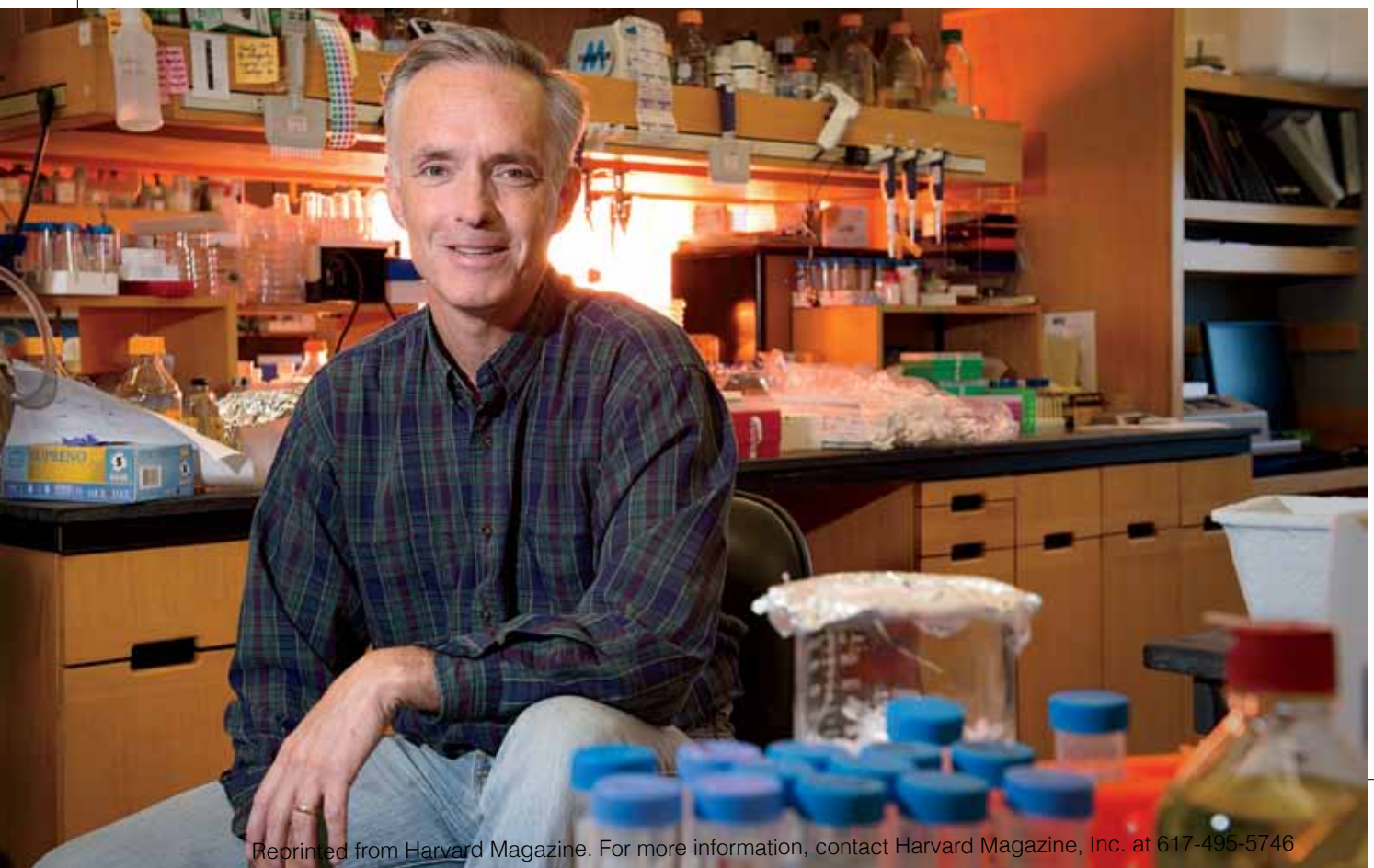
There have been calls of late for a second Asilomar to address synthetic biology's new possibilities, but to some observers, the frequently invoked conference falls short of current needs. In an essay in the forthcoming collection *Dreamscapes of Modernity: Sociotechnical Imaginaries and the Fabrication of Power*, which investigates how states variously conceptualize the roles of science and technology, Arizona State University assistant professor J. Benjamin Hurlbut, Ph.D. '10, examines the influence of what he terms "Asilomar-in-memory," documenting how the conference—controversial in its time—has come to be regarded as an exemplar of scientific responsibility and restraint. "Asilomar is remembered as a success because, in retrospect, important forms of scientific autonomy were maintained, and a powerful molecular biology and biotechnology emerged out of it, with some good social and economic consequences," he says. "But there were also social and political consequences that we've been playing catch-up on, because those questions were intentionally set aside at the time."

Asilomar's attendees were almost entirely molecular biologists, and as a result, the scope of the conference's debate was considerably narrowed, argues Pforzheimer professor of science and technology Sheila Jasanoff—Hurlbut's graduate adviser and editor of *Dreamscapes of Modernity*—in her 2005 book *Designs on Nature: Science and Democracy in Europe and the United States*. Asilomar purposefully bracketed questions of ethics and bioterrorism, she says. On legal issues, conference attendees focused primarily on product regulation and risk assessment, leaving aside more general questions around the processes by which the organisms were created.

More problematically, argues Hurlbut, Asilomar assumed and reinforced the mindset that scientists, by virtue of their specialist knowledge, were best positioned to define which issues arising from genetic engineering merited concern—a mindset that endures today. "At stake is how we ask questions about what ought to be done," he says. "What kinds of technological futures do we want? What kind of world do we want to live in, and how is it that projects in science and technology can and should contribute? That's a very difficult problem, but it's not a problem of who knows best in the purely *scientific* sense of who has the best knowledge. It's a question of who knows best in a *democratic* sense—of how we ask questions collectively about what's good for us."

Jasanoff cautions that, compared to earlier federally funded research initiatives like the Human Genome Project and the National Nanotechnology Initiative, Synberc has far fewer avenues of funding available for unaffiliated researchers to study synthetic biology's legal, social, and ethical implications. The consortium's primary principal investigators (13 currently, including Silver and Church) are chosen from the program's five university partners—the Universities of California at Berkeley and at San Francisco, as well as Stanford, Harvard, and MIT—and they nominate and vote to approve other affiliated researchers; Oye is the only primary researcher who is not an engineer.

"In this country, we seem to be structuring our oversight to be-



James J. Collins led a team that built a genetic toggle switch, a first step to constructing biological circuits and computers.

come more and more ingrown, built into the sciences and technologies that we're trying to oversee," says Jasanoff. "To some degree, the old model of self-regulation coming out of the Asilomar era in molecular biology is being re-imposed, with even less room for public oversight." At a 2009 symposium in Washington, D.C., titled "Opportunities and Challenges in the Emerging Field of Synthetic Biology," she posed several framing questions for the developing field. "How do we assign meaning to innovation? Who is responsible for both good and bad consequences," she asked. "Who gets to imagine the future?"

One pointed answer came from activist Vandana Shiva, as quoted in the declaration "Principles for the Oversight of Synthetic Biology," released by the environmental group Friends of the Earth. "Synthetic biology, the next wave of genetic engineering," she wrote, "allows seed, pesticide and oil companies to redesign life so that they can make more money from it." Indeed, on the point of ownership, synthetic biology evidences deep divides. Some strands of synthetic biology have aligned themselves closely with open-source ideals. The BioBricks Foundation has the mission of making its biological parts available for free, and it hosts OpenWetWare, the field's version of Wikipedia, complete with experimental protocols and lab notebooks, sometimes in exhaustive detail. By contrast, the Venter Institute has filed for a patent on the minimal "Mycoplasma laboratorium" genome, prompting legal challenges in response.

A second answer comes from some of the field's most unlikely adherents. The Do-It-Yourself Biology (DIYbio) or "biohacker" community, in a twist on the field's favored computer-industry metaphor, styles itself after the hacker subculture of programming, aiming to transform genetic engineering into an activity that amateurs can do in their homes or garages. On an open e-mail list with subject lines like "Inexpensive gel electrophoresis system?" and "Need a paper please," its practitioners swap genetic engineering tips and tricks. Communal hackerspaces hold workshops to teach basic lab techniques. While some biohackers are new to the lab, many have significant training and even advanced biology degrees. "In many ways, I think DIYbio is about where you do research, rather than who you are," says Roosth, who observed the movement's 2008 Cambridge beginnings. "By doing biological research at home, biohackers are critiquing the way biotechnology has been done in the last 30 years—the move toward big science, toward the patenting of biological parts."

Indeed, in an essay titled "A Biopunk Manifesto," biohacker Meredith Patterson argued for the necessity of citizen science (see "Popular Science," January-February 2014, page 54). "Biopunks deplore restrictions on independent research, for the right to arrive independently at an understanding of the world around oneself is a fundamental human right," she wrote. "Come, let us research together."

Synthetic Biology's Rorschach Test

From synthetic biology's beginnings, its practitioners have never been shy about sharing their lofty goals. Harnessing biology could mean new fuels, plastics, and foodstuffs; more diverse drug molecules and more quickly developed vaccines. More precise methods for genome editing mean that gene therapy, after early setbacks, is rapidly developing as an option to treat disease. It may become possible before long to reengineer species that have gone extinct. "Synthetic biology has made people feel like they can dream about things and take risks," says Silver. She cites one of the mottos of the field: "Engineering biology for the good of the world."

No surprise, then, that synthetic biology has exerted such an outsize influence on the public imagination. The National Science Foundation has sponsored an initiative called "Synthetic Aesthetics" that pairs research scientists with designers; its initial products were published this spring in a coffee-table book of the same name. The first synthetic biology film festival, in 2011, drew 130 entries, and a second will take place in Vienna this October. This year, iGEM drew 245 collegiate and 54 high-school teams; an estimated 15,000 students, instructors, and advisers have participated in the competition since its beginnings as a January course at MIT in 2003. Last year, in a crowd-funded campaign, a community lab in San Francisco called BioCurious raised nearly half a million dollars to build plants that glow; seeds are slated to reach the market this fall.

This fervor has prompted some critics to dismiss the field as no more than hype. "Similar to other new and trendy fields, synthetic biology has been defined so loosely that it can seem like all things to all people," noted a 2009 feature in *Nature News.* As MIT associate professor of chemical engineering Kristala Prather quipped in the article, "If you ask five people to define synthetic biology, you will get six answers."

Perhaps at its core, synthetic biology is a space upon which scientists and nonscientists alike project their own imaginings. For biologists, it means a rethinking of metaphors. If a cell is a computer and genes are circuits, then what will be the nature of the new menagerie? Elsewhere in the public consciousness, synthetic biology has found itself at the center of many social debates about the proper role of science and technology, highlighting and often undermining the established manner in which biology has been done, demanding an answer to the question of what is next.

Whatever synthetic biologists' original intent, the field has become a scientific Rorschach test, composed of equal parts scientific novelty and the sum of society's collective hopes and anxieties. As Hurlbut says, "Synthetic biology is less a field or a set of technologies, than a bunch of people with a vision."

It is perhaps fitting that synthetic biology has taken on a life of its own.

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