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Synthetic Biology

Should scientists try to create new life forms?

Using an advanced form of genetic engineering, scientists are manipulating the structure of cells to create new life forms designed to perform specific functions, such as detecting arsenic in drinking water or producing biofuels from algae. More than 500 companies, universities and other organizations worldwide are conducting research in the new field, known as synthetic biology, and developing products with the technology. Proponents say it will safely revolutionize everything from food and fuel production to medicine and manufacturing. But the field is largely self-regulated, leading critics to warn that synthetic biology — especially when used on an industrial scale — poses potential environmental and health risks that as yet are unexplored. Additionally, some ethicists question whether scientists should be creating new life forms. And others fear that the proliferation of do-it-yourself labs, where the public is free to experiment with synthetic biology, could enable terrorists to use the technology to create bioweapons.

Children are tested for malaria at a clinic in western Thailand. A synthetic version of the antimalarial drug artemisinin is expected to prevent hundreds of thousands of deaths from malaria each year, mostly of children in Africa and Asia, but could put local farmers who raise wormwood plants, from which the natural product is derived, out of business.

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Synthetic Biology

By Beth Baker

The Issues

In November, more than 200 teams of students from around the world competed in a science contest, devising novel ways to detect arsenic in drinking water, insert engineered micro-organisms into bees' digestive tracts to protect them from toxins and even engineer the common *E. coli* bacteria to cheaply and efficiently recycle gold from electronic waste.

Since it began a decade ago, the International Genetically Engineered Machine (iGEM) competition has involved 15,000 students, teachers and advisers who are experimenting with synthetic biology, a broad-based, emerging and largely self-regulated field considered by many as one of the most promising areas of science.

More than 500 companies, universities and other organizations worldwide are conducting research and developing products using synthetic biology. Some consider synthetic biology a natural evolution of genetic engineering, while others, such as synthetic biology pioneer J. Craig Venter, see it as the beginning of a revolutionary new era. Among the technology's "modest" goals, Venter said, are "replacing fossil fuel energy, ridding the world of most of what we know as agriculture [and] changing how we produce clean water and medicines." [1]

But some environmentalists say the health and environmental risks of the technology, especially its use for industrial purposes, are unknown. Critics warn that many experimenting with synthetic biology are computer scientists and engineers, not biologists or ecologists who would understand the effects of synthetic organisms on the environment. Others worry that no federal regulations specifically cover synthetic biology, and that amateur scientists can order synthetic genetic material over the Internet and experiment with it in do-it-yourself labs. Security officials are concerned that the technology could be used by terrorists. And some ethicists are uneasy about scientists creating life forms.

Getty Images/Bloomberg/Andrew Harrer

J. Craig Venter, a synthetic biology pioneer, says the technology could be instrumental in replacing fossil fuel energy and changing how clean water and medicines are produced. But environmentalists say not enough research has been done on the potential environmental impact of synthetic biology, and some warn about the danger of an accidental release of organisms produced by the technology.

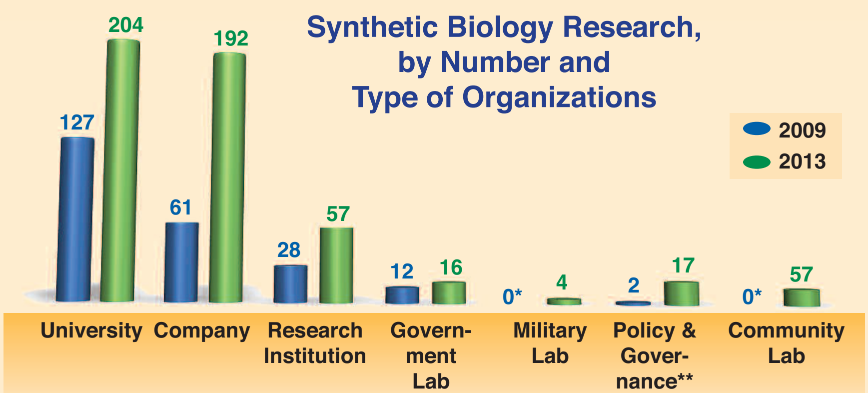
The technology is difficult to define. "If you were to ask five synthetic biologists to define their field, you'll get six different answers," one prominent research center has said. [2]

Synthetic biology builds on the science of genetic engineering, which inserts existing genes from one species into another. "Generally, there's no bright line between genetic engineering and synthetic biology," says Gregory E. Kaebnick, a research scholar at the Hastings Center, a Garrison, N.Y.-based bioethics research institute, and author of *Humans in Nature — The World As We Find It and the World As We Create It*. However, he adds, synthetic biology is sometimes described as "especially dramatic genetic engineering — or 'extreme genetic engineering,' as the critics sometimes say."

That's because synthetic biology takes genetic engineering one step further: Rather than inserting an existing gene from one organism into another, synthetic biology "represents the ability to synthesize — or create — genetic information outside of a standard cell," explains D. Keith Roper, program director of the National Science Foundation's (NSF) Division of Engineering Education and Centers, which funds many synthetic biology programs. Then researchers can "insert that genetic information into a cell, like reprogramming code in a computer," to get the cell to do different, potentially beneficial things. For example, scientists are trying to reprogram simple organisms such as bacteria, yeast and microscopic algae to ward off viruses or create renewable fuel.

More Groups Studying Synthetic Biology

The number of organizations conducting research on synthetic biology rose to more than 500 worldwide between 2009 and 2013. Nearly 200 companies were conducting such research in 2013, more than three times the 2009 total.



* *No data collected.*

** *Includes such organizations as the National Academy of Sciences and the Synthetic Biology Project at the Woodrow Wilson International Center for Scholars.*

Source: "Tracking the Growth of Synthetic Biology: Findings for 2013," Woodrow Wilson International Center for Scholars, http://tinyurl.com/pfuhrph

Synthetic biology has advanced rapidly. From 2009 to 2013 the number of companies worldwide conducting synthetic biology research tripled — from 61 to 192 — while the number of universities doing such research grew from 127 to 204. In the United States, 39 states and the District of Columbia have at least one facility working on synthetic biology. [3] (*See graph, above.*)

Experts project that the global synthetic biology market value will grow from its current $1.6 billion to $10.8 billion by 2016, with some companies already manufacturing products — such as pharmaceuticals, synthetic rubber, jet fuel and perfume fragrances — using parts and processes created through the technology. [4] (*See graph, p. 365.*) The United States has the most organizations working in the field, followed by the United Kingdom, Germany, Japan and China. [5] In January, Great Britain announced it was establishing three new synthetic biology research centers, calling the technology "one of the most promising areas of modern science." [6]

In the United States, Massachusetts and California have the greatest concentration of synthetic biology labs, partly because the NSF has spent $4 million a year since 2006 on synthetic biology research in those two states — part of a 10-year program. The NSF-funded Synthetic Biology Engineering Research Center (Synberc), a collaboration of the field's top scientists, operates from hubs at universities in the Boston and San Francisco areas. Other federal agencies have spent another $500 million to $1 billion since 2006 on synthetic biology research. [7]

There are two types of synthetic biology, both with "tremendous potential" in medicine, materials fabrication, agriculture and environmental protection, says Kenneth Oye, director of the Massachusetts Institute of Technology (MIT) Program on Emerging Technologies.

The first type "seeks to create 'artificial life,' " he says, "the development of novel organisms from scratch." In 2010, Venter made history by creating the first self-replicating synthetic life form after inserting an artificial genome inside a bacterium.

In the second type of synthetic biology, researchers are "moving away from customized design of each new organism to a modularized parts-oriented approach" that resembles conventional industrial processes, says Oye. By reducing the skill levels and dramatically cutting the costs associated with biological engineering, he says, scientists have been able to create "standardized inventories of parts" that can be repurposed for different uses, allowing the industrial-scale manufacturing of synthetic biology products.

"A lot of what my lab does is reduce the cost of things," says George Church, a professor of genetics at Harvard Medical School, and a leading synthetic biologist. A technology developed at his lab, called Multiplex Automated Genome Engineering (MAGE), has reduced "a millionfold" the cost of analyzing an organism's DNA sequence and synthesizing new genes, he says.

Using the MAGE technology, Church says, researchers can generate a few billion modified genomes per day, each one 4.7 million base pairs long. [8] This super-accelerated evolutionary process enables them to splice new genetic parts into cells, creating artificial mutations, then identify desirable molecules that allow the cell to live or die or out-compete other cells. "We're turning productivity into a Darwinian survival of the fittest," says Church.

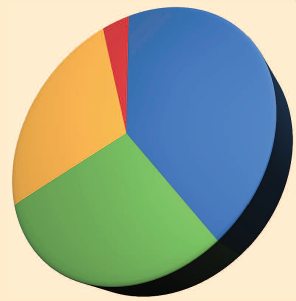
Another Synberc scientist, Stanford University assistant professor of bioengineering Drew Endy, and his colleagues created "BioBrick" parts — standardized microscopic parts often compared to toy Lego blocks, that contain pieces of DNA that can be connected to one another and inserted into a bacterium or yeast to perform a task, such as signaling the presence of a toxin by turning green. Different combinations of DNA ingredients can even be printed out as a sequence of genetic material on a 3-D printer. [9] A strong proponent of open access to synthetic biology, Endy helped create an online catalogue offering "off the shelf" synthetic genetic parts that can be ordered via the Internet and used to create new products.

But simplistic talk of 3-D printers and Legos may give the public the unrealistic idea that synthetic biology is simple, widening "the gap between the expectations of the scientist and expectations of the public," cautions Eleonore Pauwels, a public policy scholar at the Woodrow Wilson International Center for Scholars, a think tank in Washington. The public's expectations for dramatic scientific advances might be dashed, she says, because tinkering with living cells has many unknowns.

North America Dominates Synthetic Market

North America accounted for about 40 percent of the synthetic biology industry's global market value in 2011. Europe controlled 30 percent. Researchers project that the industry's market value will increase nearly sevenfold by 2016, from $1.6 billion in 2011 to $10.8 billion.

Synthetic Biology Market Value in 2011, by Region (in $ millions)



North America	($657.1)
Europe	($485)
Asia	($440.9)
Rest of World	($61.4)
Total:	**$1,644.4**

Source: "Sustainability Initiative Initial Findings & Recommendations," Synberc, Feb. 4, 2014, http://tinyurl.com/o5rzygy, using data from John Bergin, "Synthetic Biology: Emerging Global Markets," BCC Research, Wellesley, Mass., November 2011, http://tinyurl.com/p4sob2e

For instance, even the common *E. coli* bacteria — the most studied living organism (other than viruses) and considered the workhorse of genetic engineering due to its low cost and relative simplicity — is not well understood. "There may be 4,000 genes in *E. coli*, give or take," but no one knows what about a third of those genes do, says Leonard Katz, Synberc's research and industry relations director.

With so many unknowns, some environmentalists say not enough research has been done on the environmental impact of synthetic biology. "[T]here has been very limited consideration of the risks and benefits that synthetic organisms may pose to the biological world," said a report by the Bronx, N.Y.-based Wildlife Conservation Society. [10]

Ecologists worry about negative effects of an accidental release of synthetic organisms, and environmental justice advocates say some synthetic biology products, such as those used to create synthetic vanilla and the anti-malarial drug artemisinin, could ruin small farmers who grow the natural components of those products. (*See sidebar, p. 374.*)

International law enforcement agencies also fear that terrorists might use synthetic biology to create biological weapons. [11] "Synthetic biology presents capacities for destruction that are akin to those of breaking the atom," says ethicist Kaebnick. "But breaking the atom depended on huge governmental infrastructure. It was innately easier to monitor and control, but synthetic biology could be undertaken by small-scale labs."

In 2012, more than 110 environmental, consumer and religious groups called for a moratorium on commercial applications of synthetic biology until regulations specifically governing the new technology are developed. [12] (*See "At Issue," p. 377.*) Others warn about scientific hubris. When Venter announced the creation of the first self-replicating synthetic life form, religious organizations charged him with "playing God."

In response to Venter's creation, President Obama asked the Presidential Commission for the Study of Bioethical Issues to study the new technology. The panel proposed several ethical principles to guide public policy: public beneficence; responsible stewardship; intellectual freedom and responsibility; democratic deliberation, and justice and fairness. Along with "responsible stewardship," it also urged concern for the environment and future generations. However, the commission concluded in 2010 that the technology's risks, so far, were limited. [13]

Four years later, as new synthetic biology products hit the market, it remains unclear whether the public will embrace the technology. A 2013 public opinion poll found that 45 percent of respondents had heard "nothing at all" about the technology. In initial inquiries, the risks and benefits were seen as roughly equal by poll participants, but after hearing more details many raised concerns about bioterrorism, potential harm to humans and the moral implications of creating life. [14]

"It's the overall alteration of things to create new forms that is sometimes concerning," says ethicist Kaebnick.

Others say synthetic biology has a long way to go to meet its promises. The science "is really fascinating and promising and definitely worth pursuing," says law professor Jonathan Kahn of Hamline University in St. Paul, Minn., who specializes in the social justice implications of biotechnology. But, he adds, "I feel it's been way overhyped."

As synthetic biology continues to emerge, here are some of the key questions that scientists, environmentalists and ethicists are debating:

Getty Images/*The Washington Post*/Preston Gannaway

Glowing Plant, a synthetic biology company in San Francisco, has developed plants that emit light. But environmental groups began a letter-writing campaign last year urging the U.S. Department of Agriculture to halt the introduction of the plants until their production is regulated. Congress has yet to look into safety concerns raised about synthetic biology.

Is synthetic biology safe?

Proponents of synthetic biology say safeguards are in place to reduce potential risks to human health and the environment, but critics have raised concerns.

A 2012 article in the journal *Nature* said research is needed on how escaped microbes "might alter habitats, food webs or biodiversity" and on whether the organisms might quickly evolve or their genes might transfer into other natural organisms. "Once released, synthetic organisms cannot be retrieved," the authors warned. "It is imperative that funding and research communities take action to prevent future ecological disasters." [15]

The report called for dedicated, long-term government funding — a minimum of $20 million to $30 million over a decade — to assess environmental risks posed by synthetic organisms. The National Science Foundation (NSF) estimates that about 10 to 15 percent of its $4 million annual funding for Synberc — or about half a million dollars a year — is spent to study risk, containment, safety, security and related issues.

Jim Thomas, research program manager at the Ottawa-based ETC Group, a Canadian research and advocacy nonprofit that monitors the social and economic impact of technology, doesn't question the use of synthetic biology to better understand living systems and to increase knowledge of genetics. But given how much scientists don't know about how life works, he says, not enough research has been conducted on whether commercialized synthetic biology poses dangers to the environment or to workers who would be exposed to artificial organisms in the manufacturing process.

Synthetic biology is "a useful tool," he says, but "we draw a line at the lab door."

Roper of the NSF says researchers are being proactive about reducing the potential risks posed by organisms produced through synthetic biology. "The possibility of these reprogrammed cells finding an environmental niche where they could out-compete natural organisms presents a potential risk," he says. But, he adds, during decades of altering organisms' makeup through genetic engineering, safeguards have been put in place to minimize accidental releases. "After 50 years of dealing with this question for micro-organisms that have had their information content reprogrammed to some extent, we have yet to find an example that has had the ability to displace a natural organism."

Rina Singh, senior director, industrial and environmental, of the Washington-based Biotechnology Industry Organization (BIO), a trade association, says safety fears are overblown. "When you first hear you can engineer a microbe, you have fear in people," she says. "They start seeing visions of aliens we might be creating." Existing measures to control traditional genetically modified organisms can safely be applied to synthetic biology, she says.

Thomas is not reassured. "The biosafety concerns around genetically modified organisms are amplified many times [with synthetic biology]," he argues, citing the example of the corn borer and corn rootworm — pests that both developed resistance to a common insecticide after widespread use of genetically engineered corn designed to protect the corn crops. Just as with genetically modified corn, he says, there may be unintended consequences from synthetic biology. [16] With synthetic biology, Thomas says, "There will be larger numbers of organisms being modified, and the degree of modification novelty is much higher than in anything that's existed before." Synthetic organisms could spread and mutate in unexpected ways, ETC says.

Also of concern, Thomas says, is the harm to small farmers in developing countries whose crops and livelihoods are threatened by mass production of synthetic biology products.

Some applications are more worrisome than others, say critics of synthetic biology. Pharmaceuticals, they say, already go through a stringent regulatory process, but something like synthetic microscopic algae, seen by industry as a promising source of biofuel, has many unknowns.

"If you're engineering a yeast and keeping it in a tank where you can kill it if something goes wrong, that's less worrisome than having large ponds of cyanobacteria [blue-green algae] where ducks or winds can spread it around the world," says Jaydee Hanson, policy director of the nonprofit International Center for Technology Assessment, based in Washington, D.C., which analyzes the impact of technology on society.

"We know there are serious ecological effects as we change nature, so we need to do this carefully," Hanson continues. "We have plenty of mistakes we can look out on and say, 'gee, we probably shouldn't have let people import all those snakes [that are now] covering the Everglades.' Those are things we can see. With the algae they're engineering, we can't see them, but we can breathe [them] in."

Harvard's Church points out, "We breathe in algae every day. It's all over the place." Nevertheless, in their book *Regenesis — How Synthetic Biology Will Reinvent Nature and Ourselves*, Church and science journalist Ed Regis suggest requiring licenses for all aspects of synthetic biology, including small labs; designing cells that would self-destruct outside of the lab; and rigorous testing of synthetic organisms in contained ecosystems that simulate the natural world. [17]

As for algal biofuels, Singh says, "Some companies are exploring open pond systems, but they're a little further into the future because of the type of infrastructure we're talking about. A lot of the microalgaes [microscopic algae] are already known in nature, so you're not talking about something foreign — you've engineered it, so you have good control. It's not a new bug or anything like that."

Testifying before the Presidential Commission in 2010, synthetic biologist Venter said the unintentional spread of synthetic organisms might be prevented by implanting them with "suicide" genes that would trigger if the organisms escaped or by engineering the organism to depend on a sole source of food that does not exist in nature. [18] But whether manufacturers would be required to include these safety measures, and whether the government would monitor them, is unclear.

And biosafety expert Allison Snow, co-author of the 2012 *Nature* piece and professor of evolution, ecology and organismal biology at Ohio State University, says ecologists don't know whether suicide genes can spread to other organisms. "The consequences would depend on the type of suicide genes used," she said in an email. "For example, are the genes turned on by a specific chemical or temperature? For now, I think it is too early to know whether suicide genes raise environmental concerns because the specifics of how these genes would work are not available to my knowledge."

Val H. Smith, a professor of ecology and environmental biology at the University of Kansas and an expert on algal blooms, agrees, especially since many synthetic biology researchers are engineers or computer scientists — not ecologists or biologists.

So far, although algae has been screened, hybridized and redesigned, he notes, no unique new algal organism has been created from scratch. But once such organisms are developed, "My strongest concern is that if an accidental release occurs, then genes for enhanced productivity could potentially be transferred horizontally from genetically modified algae into normal 'wild-type' strains," he said in an email. The potential environmental effects are unknown.

The ETC Group, along with the environmental group Friends of the Earth and the International Center for Technology Assessment, supports "The Principles for the Oversight of Synthetic Biology," a document backed by 111 environmental, conservation, consumer and religious organizations around the world. [19] It calls for a moratorium on development of commercial applications of synthetic biology until regulations are developed specifically governing the new technology, based on the "precautionary principle." Widely used by European regulatory agencies, the precautionary principle requires companies to prove their products are safe for human health and the environment before they can be approved for widespread use. In the United States, the onus often is on the government to prove a product is dangerous before it can be regulated.

"While synthetic biology may be a useful tool in helping to better understand biological systems, it carries too many risks and unanswered questions to be allowed outside the lab at this time," Friends of the Earth said in announcing the principles in March 2012. [20]

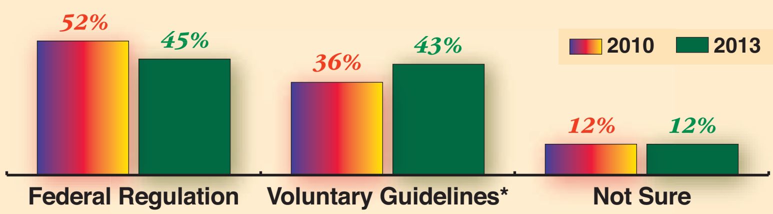
Does synthetic biology pose a national security risk?

Defense officials are among those who worry that synthetic organisms could fall into the wrong hands. Researchers, international consortia and

Support for Synthetic Biology Regulation Falls

The proportion of Americans favoring government regulation of synthetic biology research dropped 7 percentage points between 2010 and 2013, while the share of those supporting voluntary guidelines grew by the same amount. In 2013, Americans were almost evenly split on the issue.

Percentages Favoring Regulation or Voluntary Guidelines



* *Developed jointly by industry and government*

Source: "Awareness & Impressions of Synthetic Biology," Hart Research Associates, March 6, 2013, http://tinyurl.com/kx5mgfe

the FBI are working to control "dual-use" organisms — those developed for beneficial purposes but also having potential to do harm.

At the Geneva-based U.N. Biological Weapons Convention (BWC) Implementation Support Unit, Acting Director Piers Millet says efforts are under way to reduce the potential risk of synthetic biology.

"The possibility of a reliable, engineered, reproducible biotech platform that reduces the time to go from an idea to an application, cheaper, faster and by more people could change the world," he wrote in an email. "The same power . . . could also enable those with more malign motivations." He cites a 2012 BWC report that identified worrisome potential developments, such as the creation of novel means of delivering biological agents and toxins and new mechanisms that could disrupt the healthy functioning of humans, plants and animals. [21] Millet said he knew of no evidence that such actions have occurred.

Like Millet, Edward You, an FBI supervisory special agent, is actively involved in the world of synthetic biology, as part of the agency's directorate on weapons of mass destruction. "We haven't identified nefarious intent, but there's risk and vulnerability," he says. "As promising and powerful as synthetic biology is, the potential for misuse exists."

To reduce the risk, the bureau has 56 agents creating relationships with scientists, universities, companies and do-it-yourself (DIY) community labs around the country to instill sensitivity to security concerns. "How do we get as many 'white hats' as possible, so they'll come up with tools to address these concerns and identify the 'black hats' themselves?" asks You. "How do we skew it so legitimate research becomes overwhelmingly difficult for bad actors to use these capabilities? The best way . . . is making as salient a web of detection as possible. We're getting self-assessment from the scientific community themselves. Once they get our message, it expands their awareness, the tables are turned and they educate us."

The FBI has been a sponsor of the International Genetically Engineered Machine (iGEM) competition since 2009 and each year hosts a biosecurity workshop at the gathering. Students learn about international treaties such as the BWC and bioweapons criminal statutes. "It's not a sense of being burdensome and onerous but a sense of empowering them," says You. Drawing on a quote popularized in the "Spiderman" comic books, he says, "We tell them with great power comes great responsibility. They really glom onto that, and it heightens their sense of scientific citizenship."

Ultimately, though, You acknowledges, "We don't have the mandate, we don't have the authority and we sure don't have the resources to address this rapidly expanding field." Thus, he says, "Our whole approach is building relationships between the scientific and security communities."

MIT's Oye says the risk from "dual use" is "moderate" at this point because "there are many ways of doing harm to other people, and the methods of synthetic biology are rarely the most convenient or efficient approaches." However, over the longer term, he says, "The reductions in skill thresholds and wider access to power technologies do pose legitimate security issues."

Much of the concern has to do with the open-access attitude of many synthetic biologists and the spread of community do-it-yourself (DIY) synthetic biology labs such as the 40 small-scale labs that make up the so-called DIYbio network of community laboratories. (*See sidebar, p. 372.*) Tom Burkett, who co-founded one such lab, Baltimore Underground Science Space (BUGSS), says the lab has security measures in place.

"The DIYbio community has actually been extremely proactive about security, because it was a pretty early criticism," says Burkett. BUGSS controls all materials coming in and out, he says, and ensures the materials are on an approved safety list. "I've worked in academic and industrial labs, and I've worked in DIYbio, and I can say the procedures we do in a lot of ways are safer."

Both You and Millet say they have worked with the DIYbio movement, which Millet calls "a safe, community-driven space to explore modern biology."

Nonetheless, he continues, "They, and we, need to ensure that they are exploring [synthetic biology] safely and securely. These communities have made tremendous efforts to start off in the right direction. I think it is the responsibility of their governments to provide them with the resources they need to be able to ensure these spaces are no less safe or secure than an academic facility."

Katz, of Synberc, acknowledges that his organization's goal of making biology easier to engineer can be risky and that scientists are unlikely to come into contact with those who might be bent on doing harm. "How do we know somebody's not using this in some negative way?" he asks. "My belief is scientists are ethical and have good intentions and are trying to do something that's beneficial. We have safety issues that we deal with. We're not working on anything dangerous, and we have containment that we practice in the lab. But there are unintended consequences."

"The idea that scientists are good guys [so] we don't have to worry is preposterous," says the Hastings Center's Kaebnick. "But any system of monitoring synthetic biology and trying to protect society from bad uses is going to have to depend on good guys in science — and there are a lot of good guys. Somehow we have to come up with ways to empower [them] and it has to depend on some sort of professional self-monitoring. It's unrealistic to think the government should do this."

NSF's Roper says steps already are being taken to reduce the risks. The departments of Health and Human Services and Agriculture maintain lists of potentially dangerous micro-organisms and genetic materials, which only legitimate labs and institutions may use under very tight security. The Commerce Department tracks the movement of nucleic acids across state borders, and most manufacturers of DNA parts have voluntarily agreed to screen the orders they receive.

"[Government agencies] are looking for parts associated with pathogenicity and infectivity," says Oye. "They are also looking at the characteristics of customers and making judgments on the legitimacy and capabilities of customers. For example, a pharmaceutical company would be treated differently from a garage hobbyist."

On the international front, in addition to the BWC, the Australia Group is a voluntary network of nations dedicated to limiting the spread of chemical and biological weapons, including those potentially made in the future through synthetic biology. But only 42 countries — including the United States — have joined. China, a significant player in the synthetic biology realm, is not among the signatories.

Should the federal government regulate synthetic biology?

No federal regulations specifically cover synthetic biology. Generally, synthetic biology products and processes developed in the United States fall under the same set of voluntary guidelines, policies and rules that govern genetic engineering. These are implemented by the multi-agency Coordinated Framework for the Regulation of Biotechnology, under which federal agencies look at the safety of an end product, regardless of how it was developed.

The Coordinated Framework works well, says BIO's Singh. "It's not regulating the process, but the end use for the consumer," she says.

Crops, whether genetically engineered or created via synthetic biology, are regulated by the Department of Agriculture, while food products and cosmetics would fall under the rules of the Food and Drug Administration. The Occupational Safety and Health Administration (OSHA) takes care of workplace safety and the Department of Commerce keeps an eye on interstate shipment of infectious agents. For its part, the Environmental Protection Agency (EPA) oversees the introduction of "new" organisms under the Toxic Substance Control Act, although defining what is "new" is no simple matter. Complex criteria are used, depending on the extent of genetic manipulation and how different the result is from naturally occurring organisms. [22]

There also are federal regulations governing the growing of micro-organisms in uncontained areas, says the NSF's Roper. "Before any organization, institution or industry is allowed to expose or introduce any micro-organisms that could in any way alter the environment, they are required to outline their plans for use and provide containment and surveillance plans," he says. There are also various levels of government safety review boards in place, he adds.

The presidential commission on synthetic biology in 2010 decided self-regulation and a "culture of individual and corporate responsibility" was sufficient for the emerging field, and found "no reason to endorse additional federal regulations or a moratorium on work in this field at this time." [23] Instead, the panel endorsed a 2009 decision by the National Institutes of Health (NIH) to treat synthetic biology the same as traditional genetic engineering. [24]

The NIH process stemmed from a 1975 gathering of scientists at the Asilomar Conference Center in Pacific Grove, Calif., to hash out safety concerns about the emerging field of genetic engineering. The conference recommended a peer-review oversight group, the Recombinant DNA Advisory Committee, which continues to make nonbinding recommendations to the NIH director on related research, including synthetic biology.

But some experts say the Asilomar Conference's self-regulatory approach is no longer adequate if it ever was. Writing in the *Valparaiso University Law Review*, Hamline University law professor Kahn noted, "In the early 1970s, genetic research was largely conducted in the confines of universities, and there was no biotechnology industry of which to speak. Professors of molecular biology were primarily researchers, not patent holders or CEOs." [25] Today, top academic researchers spin off for-profit ventures or sell their patents to large corporations, whose financial goals may conflict with the public interest, he says. "My concern is that the research is moving towards [being just] commercially valuable rather than scientifically valuable. Sometimes these coincide, and sometimes they don't."

Hanson, of the International Center for Technology Assessment, says, "It's not a synthetic biology problem, it's a problem with weak regulation to begin with." He and other critics were already unhappy with regulation of genetic engineering even before synthetic biology emerged. Noting that food and cosmetics are prime candidates for synthetic biology, he says, "Cosmetics and dietary supplements are the weakest part of the FDA regulatory program. The next weakest is food safety. Since genetically modified organisms are mostly regulated through fiction, we'd like it stronger than that."

Moreover, unlike say, corn, a natural plant that has been genetically modified, new organisms created by synthetic biology may behave even more unpredictably, and their safety should be controlled through special regulations, say critics.

For example, say critics, a Kickstarter crowdsourcing campaign funded development of plants that glow, as "the first step toward sustainable lighting." Thousands of individuals have preordered seeds and starter kits to grow their own glowing plants, which will be shipped this summer. [26] "The industry argues that whatever regulations exist are perfectly adequate, and that you don't need anything more," says Thomas of the ETC Group. "The glowing-plants episode shows that's not true. There are no regulations relevant to this [plant]. This is crazy, frankly, and points to how far behind the regulatory side is."

Thomas prefers that the United States adopt the tougher regulatory approach used in Europe, where governments have adopted the precautionary principle. "If you have a new chemical and have no data [on its safety], you can't have market approval," he says.

As for small-scale DIYbio labs, Burkett says regulation of community labs like his in Baltimore is "inevitable."

"I would like to have a say in what that is," he says, not sounding very hopeful.

Meanwhile, public opinion is divided: 45 percent say synthetic biology should be regulated by the federal government and 43 percent say voluntary guidelines should be developed by government and industry. [27]

With the capabilities for synthesizing and sequencing genetic material spreading so rapidly, biosafety and biosecurity concerns will only get more worrisome. But, "given the paralysis and deadlock in Congress, it's necessary for lots of things to happen without changes in statute," MIT's Oye says. "You have to develop new regulations within existing statutory frameworks because of our paralysis." ■

BACKGROUND

Mendel's Peas

The age of modern biology began in the 19th century, with the painstaking experiments of the German monk Gregor Mendel. "Mendel is pivotal to genetics in the way that Charles Darwin is pivotal to biology as a whole," wrote Colin Tudge in *The Impact of the Gene — From Mendel's Peas to Designer Babies.* [28]

Beginning in 1854, Mendel spent eight years growing 34 varieties of peas, selecting them for particular characteristics such as the color of seed coat and the position of flowers. He hybridized 10,000 plants and demonstrated the proof of dominant and recessive "characters" that were passed on from parent to offspring. [29]

"He hypothesized that characters are conveyed from generation to generation by individual Mendelian factors (which we now call genes)," wrote Tudge. [30]

To Mendel's disappointment, his research was received with a yawn by contemporary biologists. Not until 1900 — 16 years after his death — was his paper rediscovered and its full significance understood.

In 1909 Danish botanist Wilhelm Johannsen suggested the term "gene" replace what had been called Mendelian factors. [31] Although scientists were by then observing thread-like chromosomes under a microscope, the makeup of the chromosome's genes remained a mystery. In 1943 Austrian physicist Erwin Schrödinger said in a famous series of lectures that became an influential book *What Is Life?* that "the gene was a message written in code." [32] The insight that genes carry information became a cornerstone of molecular biology.

In 1944 scientists discovered that genes were not proteins, as many had argued, but nucleic acids. Researchers Oswald Avery, Colin MacLeod and Maclyn McCarty of the Rockefeller Institute for Medical Research demonstrated that hereditary traits could be passed from one bacterial cell to another by the DNA (deoxyribonucleic acid) molecule. "With that finding, scientists knew for the first time the composition of the basic entities that controlled the heredity and development of

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Chronology

1900s-1950s

Chromosomes and genes are discovered.

1909
Danish botanist Wilhelm Johannsen coins the word "gene."

1911
American geneticist Alfred Sturtevant maps genes of fruit fly.

1912
French biologist Stéphane Leduc uses term "synthetic biology" to describe his cell experiments.

1943
Erwin Schrödinger, an Austrian particle physicist, hypothesizes that genes carry information.

1944
Researchers find that genes are made of nucleic acids.

1953
Biochemists James D. Watson and Francis Crick discover double helix structure of DNA.

1970s *Genetic engineering begins.*

1971
Paul Berg, a biochemistry researcher at Stanford University, splices DNA from one virus to another.

1972
Geneticist Stanley Cohen at Stanford and biochemist Herbert Boyer at the University of California, San Francisco, transfer DNA between species.

1975
Safety guidelines created for genetic engineering at Asilomar conference in California.

1977
British biochemist Frederick Sanger introduces way to sequence DNA.

1978
San Francisco-based Genentech genetically manipulates *E. coli* bacteria to produce insulin.

1980s-1990s

Genetic engineering is commercialized.

1980
Supreme Court allows first patent for a genetically modified organism, a bacterium for digesting crude oil in the event of oil spills.

1985
Kary Mullis, a biochemist at Cetus Corp. in Emeryville, Calif., develops polymerase chain reaction for mass replication of DNA.

2000s *Synthetic biology takes off.*

2000
Geneticist Francis Collins of the National Institutes of Health and synthetic biologist and entrepreneur J. Craig Venter announce sequencing of human genome.

2001
GreenFuel Technologies Corp. is founded in Cambridge, Mass., to make synthetic biofuel from algae; firm files for bankruptcy in 2009.

2003
Bioengineers at the Massachusetts Institute of Technology (MIT) develop *The Registry of Standard Biological Parts*, a list of synthetic DNA parts available off the shelf.

2004
MIT students initiate the International Genetically Engineered Machine competition.

2005
Synthetic biologist Jay Keasling's biotech firm, Amyris, in Emeryville, Calif., creates synthetic version of antimalarial drug artemisinin.

2006
For fun, five MIT undergrads use synthetic biology to reprogram *E. coli* to smell like bananas or wintergreen. . . . The National Science Foundation establishes the multi-university Synthetic Biology Engineering Research Center.

2008
Biologists Mackenzie Cowell and Jason Bobe, based in Boston, found DIYBio, a network of amateur synthetic biologists.

2010
Venter creates genome of first synthetic self-replicating life form. Report by Presidential Commission for the Study of Bioethical Issues concludes that no special regulations are needed, as yet, governing synthetic biology.

2012
A global group of 111 environmental, conservation, consumer and religious organizations endorse the "Principles for the Oversight of Synthetic Biology," which calls for a moratorium on the development of commercial applications of synthetic biology until regulations specifically governing the technology are developed.

2014
Researchers synthesize the first chromosome of a baker's yeast. . . . Evolva, a Swiss-based biotech firm, begins commercial production of synthetic vanillin.

BioHobbyists Embrace DIYbio

"These hackerspaces are going to be the life blood of innovation in the future."

In a former jar-lid factory known as King Cork & Seal on Baltimore's gritty east side is a small community lab known as BUGSS (Baltimore Underground Science Space). It's part of a growing do it yourself biology (DIYbio) network of 40 groups and community labs around the world.

The labs have garnered scary headlines suggesting that rogue amateur scientists creating mayhem by synthesizing and releasing new organisms. As a *Wall Street Journal* headline announced in 2009: "In Attics and Closets, 'Biohackers' Discover Their Inner Frankenstein." [1]

Indeed, the diffusion of synthetic biology poses some legitimate security concerns. People with nefarious intent could acquire genetic materials and lab equipment over the Internet and synthesize organisms for any number of bad purposes, such as poisoning water supplies. But experts say implementing such a plot is complicated and that potentially dangerous genetic materials are carefully screened and tracked by suppliers.

A 2013 study of DIYbio by the Woodrow Wilson International Center for Scholars, a Washington think tank, found that the public has "a miscomprehension about the community's ability to wield DNA and manipulate life." [2] DIYbio practitioners do not appear to be loners working secretly in their homes, the study found. "The capacity to inflict harm that most people are concerned about is way beyond anyone's capabilities to do alone in a basement at this point in time," says study coauthor Todd Kuiken, a senior research associate with the Wilson Center. "The DIY name is misleading. It's not do-it-yourself. It requires others to do it with you."

Still, the report noted, "As with any broad and decentralized movement, there is no way to know what every member is doing at any given time. This makes it difficult to assess safety and security risks and to rule them out with certainty."

The study included results of a 2013 survey of 359 participants in the loose-knit DIYbio community. It found that only 24 worked exclusively at home, nearly half worked at a community lab and 35 percent at hackerspaces (gathering spots for computer buffs).

At BUGSS, anyone can experiment and learn hands-on genetic engineering and synthetic biology skills, under the tutelage of Tom Burkett, a biology professor at the Community College of Baltimore County. DIY labs provide easy access to specialized equipment and expertise without enrolling in college courses. Membership in BUGSS is $850 for a year, with steep discounts for students and teachers.

The genetic materials used in the lab are carefully tracked and are all classified as Level 1, or no more dangerous than "things that can be worked with on your dining room table," Burkett says.

Burkett and Steve Stowell, who cofounded BUGSS in 2012, equipped the lab with second-hand items from eBay and from companies going out of business.

Burkett first got the idea for BUGSS after participating in the International Genetically Engineered Machine (iGEM) science competition in 2010, where he met Stowell, who works in "smart grid" technologies for the electric power industry. They both were part of Team Baltimore, consisting of people from local academic institutions and others interested in synthetic biology. "iGEM opened my eyes to the DIYbio community," Burkett says. This year for the first time, the iGEM competition is open to community labs, and BUGSS hopes to field a team.

On a recent Saturday, Burkett guided 10 workshop participants on how to clone a gene. The youngest, 13-year-old Marissa Sumathipala, who wore red shoes, a purple-checked shirt and braces on her teeth, says she wants to pursue a career in the life sciences. She already is making a mark in science competitions with such projects as "The epigenetic effects of a micro-

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life on earth," wrote journalist Ed Regis in *What is Life? Investigating the Nature of Life in the Age of Synthetic Biology*. [33]

Biochemists James D. Watson and Francis Crick won fame in 1953 by identifying the double-helix structure and reproductive function of DNA.

Genetic Engineering

The birth of genetic engineering and genomics in the 1970s was "potentially as revolutionary as the birth of agriculture in the Neolithic Era," according to synthetic biology pioneer Venter. [34] For the first time, scientists could cut genes from one species and splice them into another, a process called recombinant DNA.

With genomics — the study of the entire genetic structure or genome of organisms rather than individual genes — scientists could identify which sections of an organism's DNA correspond to particular genes, say, for disease resistance or other desirable traits. Before advances in genomics, "only in a few, rare cases did [scientists] know which genes — which particular stretches of DNA — they should be transferring into the organisms they wanted to transform," wrote Tudge. [35]

Biochemistry researchers Paul Berg of Stanford and Herbert Boyer of the University of California, San Francisco, and geneticist Stanley Cohen, also of Stanford, first used recombinant DNA, for which Berg won the Nobel Prize in 1980.

The first commercial application of genetic engineering involved transferring the human insulin gene into *E. coli* in 1978, allowing insulin to be mass produced. (Most *E. coli* strains gravity simulated environment on fruit flies." Her father, who drove her to BUGSS from their home an hour away in Virginia, says her research is way over his head.

The oldest participant is David Gray, a computer programmer who says he's too close to retirement for a career change but is intrigued with synthetic biology. "One thing that fascinates me is taking a naturally occurring phenomenon and repurposing it."

"This is a glimpse into the future," says Stowell. "It's a way to make all kinds of things — lights that blink, glues, a zillion and one applications. It's why I think ordinary citizens get involved with this. They can apply their creativity."

One BUGSS member is working on synthesizing pigments in hopes of developing a biological ink. Others, including a few artists, are hoping to develop a process to produce plant cells on a 3-D printer, and searching for a bacteria to degrade plastic debris in the ocean.

"We have a guy here who wants to produce beer that looks like a lava lamp," says Stowell.

Vince Glowacka, a workshop participant who has a degree in mechanical engineering, says, "These hackerspaces are going to be the life blood of innovation in the future."

The Wilson Center says DIYbio labs foster scientific education outside of traditional institutions. "Almost all of the well-known tropes about the dangers of DIYbio and citizen science are untrue," Daniel Grushkin, a fellow at the Wilson Center, said in releasing the report. "It's time for policymakers to consider how grassroots science movements like DIYbio can serve the greater good by fostering entrepreneurship and excitement about science literacy." [3]

Geneticist George Church of Harvard University says he has no problem with the learning side of the DIY movement. More worrisome, he says, is what he calls the movement's synthesis side. Just as computer hackers enjoy sending viruses and spam out over the Internet, a DIYbio malcontent could wreak havoc by releasing synthetic viruses or other organisms, he says, adding, "The synthetic side has to be very, very carefully monitored."

Courtesy Ross Wells

Vishal Nelson (left) and Evangelos Mantzavinos (center), students at Howard Community College in Columbia, Md., and 13-year-old Marissa Sumathipala learn how to conduct experiments in synthetic biology at the Baltimore Underground Science Space (BUGSS), part of a growing worldwide network of so-called do-it-yourself community labs.

— Beth Baker

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[1] Jeanne Whalen, "In Attics and Closets, 'Biohackers' Discover Their Inner Frankenstein: Using Mail-Order DNA and Iguana Heaters, Hobbyists Brew New Life Forms; Is It Risky?" *The Wall Street Journal*, May 12, 2009, http://tinyurl.com/lvqqrm9.

[2] David Grushkin, *et al.*, "Seven Myths & Realities about Do-It-Yourself Biology," Synthetic Biology Project, Woodrow Wilson International Center for Scholars, November 2013, p. 24, http://tinyurl.com/noszenq.

[3] "First-Ever Survey of Do-It-Yourself Biology Community Challenges Myths," Synthetic Biology Project, Woodrow Wilson International Center for Scholars, Nov. 18, 2013, http://tinyurl.com/kkl796f.

are harmless and do not cause food poisoning.) Until this breakthrough, insulin for treating diabetes was made from cows and pigs, sometimes causing adverse reactions. [36]

Since then, genetic engineering has enabled more rapid manufacture of vaccines and has been used to create a variety of new medicines and medical treatments, including new kinds of antibiotics and cancer treatments.

In 1985, chemist Kary B. Mullis developed a transformative tool called polymerase chain reaction (PCR), giving scientists the power to make billions of copies of a sample of DNA. The technique has been used in everything from detecting the AIDS virus in human cells to DNA analysis of crime scenes and analyzing trace amounts of DNA from fossils. [37]

"In the field of synthetic biology . . . most techniques are cutting-edge, far from the biological methods of the 1980s. But even for synthetic biologists, PCR is critical to getting science done," according to an article in the journal *BioTechniques*. [38]

Genetic engineering was soon applied to agriculture, as a way to reduce the use of toxic insecticides and increase crop yields. In 1992 the Food and Drug Administration determined that genetically modified crops were "substantially equivalent" to traditional crops, and in 1995 GMO foods were approved for human consumption in the United States. [39] In Europe and elsewhere, there has been considerably more public resistance to consuming food made from GMO crops, and they are required to be labeled.

In June 2000, Francis Collins, then head of the Human Genome Project and now director of the National In-

Synthetic Biology Can Have Unintended Consequences

Critics say the technology creates "a snarl of problems" and difficult tradeoffs.

Along with its promise, synthetic biology may have unintended effects on the environment and economic justice, say critics of the process.

Artemisinin, one of the world's most effective antimalarial drugs, is a case in point. A synthetic version of the drug was developed in 2005 by Amyris, a synthetic biology startup, with a multimillion-dollar grant from the Bill & Melinda Gates Foundation. Amyris was founded by Jay Keasling, a biochemical engineering professor at the University of California-Berkeley and director of the Synthetic Biology Engineering Research Center, a collaboration of synthetic biology scientists established by the National Science Foundation in 2006.

To make the drug, Amyris created a synthetic genome of artemisinic acid, a precursor of artemisinin, and inserted it into a common yeast. The French pharmaceutical firm Sanofi-Aventis now has a license to produce synthetic artemisinin, and large-scale production is underway.

However, while synthetic artemisinin is expected to prevent hundreds of thousands of deaths from malaria each year — mostly of children in Africa — it threatens the livelihood of thousands of small farmers in Asia, Africa and Brazil who grow sweet wormwood, the source of artemesia from which natural artemisinic acid is derived, say critics. [1]

"This is going to replace the artemisinin produced by 100,000 farmers," says Jim Thomas, a research program manager at the Ottawa-based ETC Group, a research and advocacy nonprofit that monitors the socioeconomic impact of technology. One-third of artemisinin already is being synthetically produced, he says, adding that pharmaceutical companies will likely prefer dealing with a large-scale manufacturer rather than small farmers in East Africa.

In addition, says Jaydee Hanson, policy director of the nonprofit International Center for Technology Assessment, based in Washington, D.C., which analyzes the impacts of technology on society, malaria already is developing resistance to natural artemisinin. "I wish Amyris had used their platform to make the next malaria drug," rather than to copy an existing drug that is becoming less useful, says Hanson. "They've got the ability to tweak the structures of these chemicals that they're producing. Why not look down the road, rather than copy one?"

Keasling has responded to such criticism by saying if it were American children dying each year, there would be little opposition. "It's not people in Africa who see malaria who say, 'Whoa, let's put the brakes on,' " he said in 2009. [2] Keasling did not respond to requests for an interview.

Gregory Kaebnick, a bioethicist with The Hastings Center, a bioethics research institute in Garrison, N.Y., says there are difficult tradeoffs. "It would be good to have enough artemisinin to treat malaria. We [in the United States] forget it's one of the worst infectious diseases in the world. Take that versus the livelihood for some wormwood growers. It's a snarl of problems."

Economic justice concerns and difficult tradeoffs also surround the production of synthetic vanillin and other products produced through synthetic biology. According to a report by the Montreal-based ETC Group, a research and advocacy organization that monitors the socioeconomic impact of technology, the incomes of some 80,000 farmers in Madagascar, the world's primary source of natural vanilla beans, are threatened by production of synthetic vanilla. [3]

But Neil Goldsmith, CEO of Evolva, a Swiss food and cosmetics company that is producing synthetic vanilla, says, "Vanilla orchid farming cannot readily expand beyond current levels

stitutes of Health, announced another milestone: the near-completion of the sequencing of the 3 million base pairs of the human genome. By his side was Venter, whose private lab had achieved this milestone nearly at the same time as the NIH. Researchers had hoped that the Human Genome Project would quickly lead to new therapies. But genetic medicine has not advanced as rapidly as initially hoped.

Synthetic biologists hope to accelerate that progress. "It's plain that excitement preceded success by many years," wrote bioethicist Kaebnick of the Hastings Center. "Anyone who has observed this history can be forgiven for adopting a wait-and-see attitude toward 'synthetic biology,' which, in the past few years, has been identified as the next big 'revolution' in biology." [40]

Synthetic Biology Emerges

The first DNA synthesizer went on the market in 1983. Rather than manipulating genes one at a time between organisms, scientists could use the synthesizer to rapidly churn out artificial genes.

In 2000 bioengineer James Collins of Boston University brought the perspective of an engineer to the field of genetics. "Many of us thought that working at the single-gene level was just a starting point, that we really needed to figure out how all these newly identified genes arising from the Human Genome Project fit into networks, pathways and circuits inside the cell," Collins said. [41]

Collins developed a circuit of genes for the first time, similar to an electronic transistor, that signaled two proteins in a bacterial genome to turn on and off. The technique demonstrated that engineering principles could be applied to biological parts.

In 2002, the first-ever micro-organism was constructed entirely from synthetic parts. Microbiologist Eckard without adversely impacting endangered species like the lemur and Sumatran tiger," which live in the same rainforest habitat as the vanilla plants. "These creatures also rely upon the rainforest."

Environmentalists and ecologists raise similar social justice concerns about the development of synthetic biofuels, even though they are billed as clean, renewable energy. Like corn-based ethanol, fuels produced through synthetic biology need raw materials, which themselves require large amounts of fuel to grow and harvest the sugar cane or other feedstocks that are then converted into energy. "You have to have a lot of sugar that you turn into a food for yeast that then gives you your biofuels," says Hanson.

In Brazil, the Amazon rainforest is threatened by industrial-scale sugar cane production for biofuels, including biofuels made through synthetic biology, says Thomas. Wherever synthetic biofuel is produced, "it will require a land grab for growing cellulose or sugars," he says.

In many places around the globe, foreign investors are purchasing vast tracts of arable land, some of it for biofuel production. "People are being pushed off their land," says Thomas, often because the indigenous owners and small-scale farmers do not have clear title to their property. [4]

Even algae, seen as a benign alternative to corn or sugar cane because it doesn't use valuable prime cropland, requires water to produce fuel — lots of water. A study requested by the Department of Energy (DOE) on the sustainability of algal biofuels, including those made through synthetic biology, was disappointing to the backers of the technology. [5]

"We were impressed how far the field has come," says microbiologist Jennie Hunter-Cevera, who headed up the DOE panel. She is founder and CEO of Hunter-Cevera and Associates, a consulting firm in Ellicott City, Md., that focuses on sustainability and integrated solutions to environmental problems.

"But what the DOE wanted to know was, can the technology be sustainable, especially in terms of water, land use and nutrients, and our conclusion was no. It was not," she says.

— Beth Baker

Sunil Elias

Vanilla beans dry in Madagascar, the world's primary source of natural vanilla. The production of synthetic vanilla threatens the livelihoods of thousands of vanilla farmers in the country, according to a report.

[1] "Extreme Genetic Engineering — An Introduction to Synthetic Biology," ETC Group, January 2007, p. 52, http://tinyurl.com/ok8jl6x.

[2] Michael Specter, "A Life of Its Own — Where Will Synthetic Biology Lead Us?" *The New Yorker*, Sept. 28, 2009, http://tinyurl.com/mcm8s3.

[3] "Case Study: Vanilla," ETC Group, October 2013, http://tinyurl.com/phrm2he.

[4] For background, see Jina Moore, "Resolving Land Disputes," *CQ Researcher*, Sept. 6, 2011, pp. 421-446.

[5] "Sustainable Development of Algal Biofuels in the United States," Committee on the Sustainable Development of Algal Biofuels, National Research Council, 2012, http://tinyurl.com/nuyalgt.

Wimmer of the State University of New York at Stony Brook and his team recreated the polio virus, based on Wimmer's own decoding of its genetic sequence two decades earlier. In 2003, Venter and some associates created a second virus from scratch, although neither was self-replicating.

In 2003 Jay Keasling, a professor of chemical engineering and bioengineering at UC Berkeley and director of Synberc, and colleagues founded Amyris, a company that aimed to create new products using synthetic biology. Its first success was a synthetic version of artemisinic acid, used to make an important antimalarial drug. (*See sidebar, p. 374.*) The Bill & Melinda Gates Foundation gave Amyris a multimillion-dollar grant to support its work on the drug, and by 2008 the company had licensed the technology on a royalty-free basis to the French pharmaceutical company Sanofi-Aventis. Large-scale production of the drug began in 2013.

Meanwhile, three bioengineers from MIT — Endy (who now is at Stanford), Tom Knight and Randy Rettberg — had established the Standard Registry of Biological Parts after realizing "that biological organisms were malleable enough and their molecular components interchangeable enough to be designed, engineered and put together from off-the-shelf 'factory' parts," known as BioBrick parts, wrote Regis. [42]

About that time, MIT students were being introduced to synthetic biology with a month-long course on designing biological systems. This grew into the iGEM competition, which by 2005 was attracting teams from around the globe and by last year had more than 200 teams competing. Among the hundreds of student-created projects in 2013 were a rainbow of pigmented bacteria, banana- and wintergreen-smelling bacteria and an arsenic biosensor. [43]

In 2006 the National Science Foundation announced it was making a 10-

Getty Images/*The Washington Post*/Peter DaSilva

New strains of yeast are tested at the Amyris laboratory in Emeryville, Calif., before going to a large drug-production facility in Brazil. As a start-up firm in 2005, Amyris developed a synthetic version of the widely used antimalarial drug artemisinin with a multimillion-dollar grant from the Bill & Melinda Gates Foundation. To make the drug, Amyris created a synthetic genome of artemisinic acid, a precursor of artemisinin, and inserted it into common yeast.

year investment in the field and established Synberc. Since then, Synberc researchers have spun off several biotech start-up companies.

In 2008 some iGEM alumni created DIYbio, a network of scientists and hobbyists pursuing synthetic biology in home and community labs. Worried that such unmonitored labs could be used to create bioweapons, the FBI in 2009 became an iGEM sponsor in order to nurture relationships with the synthetic biology community. (*See sidebar, p. 372.*)

In 2010 Venter announced his lab had created the first self-replicating synthetic life form, triggering media and religious outcry over scientists "playing God." The announcement prompted the Obama administration to ask the Presidential Commission for the Study of Bioethical Issues to explore synthetic biology's ethical implications. The panel agreed with a 2009 NIH decision to treat synthetic biology the same as genetic engineering — combining self-regulation with multi-agency oversight.

Meanwhile, Harvard's Church was developing his MAGE technology to rapidly sequence and modify genomes, dramatically reducing the time and the costs of developing synthetic biology products.

In March 2014, scientists, led by biologist Jef Boeke, director of the Institute for Systems Genetics at New York University's Langone Medical Center, announced they had successfully synthesized a baker's yeast chromosome. The effort was boosted by the labors of undergraduate students in a Build a Genome course at Johns Hopkins University. By synthesizing a genome for yeast, the researchers hope to have complete control of the organism, "whether to boost biofuel production or air pockets in bread." [44]

Endy called the project "a great example of 'do-it-together' biotechnology. [45]

As these developments were rapidly moving forward, environmental groups were trying to slow down the progress of synthetic biology. They raised concerns about accidental release of organisms into the environment, the potential ease of creating bioweapons and the effects of mass producing synthetic products on small farmers who grow the natural versions.

In 2012 the ETC Group, the International Center for Technology Assessment and Friends of the Earth issued "Principles for the Oversight of Synthetic Biology," calling for a commercial moratorium on the release and production of synthetic biology organisms until far more safety research has been conducted. More than 100 organizations around the world had signed on as of spring 2014. ■

CURRENT SITUATION

Synthetic Fuels

Research is moving forward in synthetic biology even as groups continue to raise concerns about safety and ethical issues. The U.S. Department of Energy is spending some $30 million annually on synthetic biology research and development, a significant part of the federal investment in the field, as part of its effort to develop clean, domestic, renewable energy sources. [46]

For example, the DOE-initiated Joint BioEnergy Institute (JBEI), led by Synberc director Keasling, is working on cutting-edge bioenergy projects, many of which use synthetic biology. "JBEI functions on a massive scale," says Katz of Synberc. "Synthetic biology is a huge component of it, because a lot of the pathways to make fuels are synthesized genes."

For instance, JBEI used synthetic biology to engineer a strain of the *E. coli* bacteria that could produce biodiesel directly from glucose. The institute then developed a technique to detect meta-

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At Issue:

Should there be a moratorium on synthetic biotechnology?

JAYDEE HANSON
SENIOR POLICY ANALYST, CENTER FOR FOOD SAFETY, AND POLICY DIRECTOR, INTERNATIONAL CENTER FOR TECHNOLOGY ASSESSMENT

WRITTEN FOR *CQ RESEARCHER*, APRIL 2014

Synthetic biology needs regulations tailored to this new science. Two years ago, 111 environmental, consumer and religious groups issued a document, "Principles for the Oversight of Synthetic Biology," calling for regulations that specifically govern synthetic biology before organisms created through this new technique are commercialized.

The first products of synthetic biology are leaving the laboratory, mostly made from new microorganisms approved by the Food and Drug Administration (FDA) under its Generally Regarded as Safe (GRAS) process, which allows the company — not the FDA — to assess product safety. GRAS should not be used for any food additives, much less additives produced using this extreme form of genetic engineering.

Synthetic biology products promised by U.S. and European companies include biosynthetized vanillin, saffron, cocoa butter, resveratrol, orange flavoring, grapefruit flavoring and oils for cosmetics and biofuels. These products of an extreme genetic engineering process with no regulatory history should not be approved through the GRAS process.

A few drugs, such as a synthetic version of the malaria drug artemisinin, also are being produced. But drugs go through stricter reviews requiring extensive testing. That testing should also be used for synthetic biology food and cosmetics products.

Plants engineered using synthetic biology, meanwhile, could slip through the U.S. Department of Agriculture's review process entirely. In 1986 the department's Animal and Plant Health Inspection Service (APHIS) avoided developing new regulations for genetically engineered crops by asserting that because such plants used plant pests (mostly viruses) to transfer DNA, existing regulations for plant pests would apply. Those "regulations" are a sad anachronism, because synthetic biology uses computers, not plant pests, to change the DNA of organisms. APHIS admits it does not have adequate regulations to review synthetic biology products.

Now is the time to develop regulations for synthetic biology, not after synthetic biologists release the next kudzu or gypsy moth. Those destructive organisms grew for decades before we realized that they should not have been introduced into the United States by scientists. Regulations are needed that anticipate possible damage to human health and the environment before the products are out of the lab, not after they have caused problems.

DR. RINA SINGH
SENIOR DIRECTOR, INDUSTRIAL AND ENVIRONMENTAL, BIOTECHNOLOGY INDUSTRY ORGANIZATION

WRITTEN FOR *CQ RESEARCHER*, APRIL 2014

While the term "synthetic biology" is relatively new, the science is not. Synthetic biology is an evolution of biotechnology, and it has been safely used in the development of products that provide societal benefits. A moratorium would harm patients waiting for cures and consumers seeking environmentally preferable alternatives to petrochemical-derived products.

While the first human genome was mapped a little more than a decade ago through a multiyear, multibillion-dollar effort, new genomes for plants and microbes are being mapped at a much faster rate and lower cost. Microbes that naturally perform a myriad of tasks, such as making bread and cheese, have been adapted to make vitamins, synthetic rubber, advanced biofuels and green plastics. With a new wealth of genomic data, scientists have increased the speed, precision and predictability of bio-based products. The biotechnology industry has had a decades-long record of safety under the current regulatory regime.

The term "synthetic biology" describes new biotech tools for harnessing nature's genomes. Applying new regulation simply because a new term has been coined is unwarranted and can actually chill much-needed scientific innovation.

A prominent example of the benefits of these new tools is the development of artemisinin, the most effective known treatment for malaria. The drug, which derives from the wormwood tree, cannot be grown in sufficient supplies to treat the rapidly rising worldwide incidence of malaria. Employing synthetic biology to produce this drug promises a more readily available, lower-cost supply.

Another example is the development of 1,4-butanediol. The chemical's name may be unfamiliar, but it can be polymerized into synthetic rubber, usable in running shoes, spandex clothes, tires and car parts. The synthetic biology application earned a Presidential Green Chemistry Award in 2011 because it enables the production of this useful chemical in shorter pathways, with fewer environmental waste products and from sugars instead of more costly, polluting oil.

The U.S. economy, our environment and human health all benefit from biotech and synthetic biology innovation, and we expect even more significant advances in the future. The U.S. biotechnology industry has evolved over the past four and a half decades under an effective, science-based regulatory system. A moratorium on scientific progress turns this system on its head.

Continued from p. 376

bolic changes in microbes during the fuels production, enabling it to stabilize the *E. coli* strain and thus triple fuel production. [47]

Other DOE funding comes through the Advanced Research Projects Agency-Energy (ARPA-E), including 10 projects that make up its Plants Engineered to Replace Oil (PETRO) program. Scientists also are experimenting with efficient ways to produce fuel for cars from tobacco, pine trees, sorghum and sugarcane plants by bypassing photosynthesis and extracting energy directly from the plants.

"Current biofuels production is limited by both the inefficient capture of solar energy by plants and the inefficient processes [used] to convert CO_2 [carbon dioxide] from the atmosphere into fuels," according to ARPA-E. "PETRO projects are experimenting with various plants . . . to create molecules already found in petroleum-based fuels that can be dropped directly into the tanks of existing vehicles." [48]

Getty Images/Bloomberg/Aaron M. Sprecher

A Boeing 737 at George Bush Intercontinental Airport in Houston is filled with fuel made from algae by Solazyme Inc. Synthetic microscopic algae is seen by industry as a promising source of biofuel, but environmentalists say there are many worrisome unknowns, including the possible harm caused when winds or waterfowl spread the algae growing in open-air ponds. A recent study for the Department of Energy found that algal biofuels technology is not sustainable, especially regarding water and land use.

Another ARPA-E program uses synthetic biology to try to make electrofuels — liquid fuels that are 10 times more energy efficient than existing biofuels, such as ethanol. Unlike biofuels, which typically require lots of water, fertilizer and agricultural land, electrofuels use engineered organisms to create the fuel. For example, an ARPA-E-funded start-up called Ginkgo BioWorks, based in Boston, used synthetic biology to engineer *E. coli* to allow the bacteria to metabolize carbon dioxide, methane and other compounds — a process that does not occur in nature. The compounds are then converted into fuel.

Similar technology is being tested for commercial use at Joule Unlimited, a Boston-based company with production facilities in Texas and New Mexico. The company is producing fuel from blue-green algae, says cofounder Church, from Harvard, who serves as a technical adviser to Joule. "The process is more efficient in terms of converting photons to carbon resources like fuels," he says.

However, some early attempts at synthetic biofuels have proved too expensive to compete with fossil fuels. A company cofounded by Church called LS9 spent nine years and $81 million trying to produce high volumes of diesel from sugar and in 2010 received the EPA's Presidential Green Chemistry Award. [49] But the cost was too high, and in January LS9 was sold to another company that plans to use the process to develop specialty chemicals. [50]

Biomanufacturing

The DOE's investment in biofuels is part of the government's "National Bioeconomy Blueprint," which argues that investment in biotechnology research and manufacturing is a fundamental component of keeping the U.S. economy growing. Synthetic biology is seen as key to the next generation of biomanufacturing.

"Much work lies ahead, including identifying and standardizing biological and molecular components, but this powerful new area of technology has immense potential," said the report. "Strategic investments in synthetic biology have the potential to move the bioeconomy forward in all sectors." [51]

For example, using DNA synthesis and sequencing, researchers at DuPont and Goodyear Tire and Rubber Co. have created synthetic BioIsoprene, a trademarked molecule that plays the same role as the rubber plant enzyme. So, rather than tapping rubber trees to make natural rubber or creating artificial rubber from petrochemicals, synthetic rubber is now being made using engineered microorganisms. BioIsoprene potentially could be used in a variety of products, from surgical gloves to jet fuel. [52]

Synthetic biology may create alternatives to many other oil-based products, not only fuels. Bioacrylic acids, created through synthetic biology, are being used to improve adhesives, paints and diapers. The "Bioeconomy Blueprint" suggests that bioacrylics could capture some of the $8 billion global market in petroleum-based acrylic. [53]

Even imitation vanilla, which is made from petrochemicals, can now be made from an engineered yeast using synthetic biology. This year the Swiss firm Evolva will begin marketing synthetic vanillin (for vanilla) to manufacturers. "This platform gives us an alternative route for producing natural ingredients for consumer products — all in a more sustainable, affordable, high quality way," said CEO Neil Goldsmith in an email. "You can think of us as a 21st-century specialist brewer. Instead of brewing beer, of course, we can 'brew' things like saffron, resveratrol, stevia and vanillin." (Resveratrol, found in red wine, reportedly has medicinal qualities. Stevia, a natural sweetener that does not raise blood sugar levels, is considered a healthy alternative to sugar.)

In 2013 New York-based manufacturer International Flavors and Fragrances announced partnerships with both Evolva and Berkeley-based Amyris, the synthetic biology company founded by Keating, to make products using synthetic biology. [54]

Among other synthetic biology products in use are a customized gene that enables faster manufacture of new flu vaccines; a cheaper version of succinic acid, used to regulate acidity in manufacturing food, drugs and cosmetics; medicines to treat cholera, diabetes, cancer and hypertension; and a host of chemicals, plastics and polymers used in manufacturing. [55]

Safety Concerns

Product safety is considered under the Coordinated Framework, but in many cases there are no regulations that would trigger agency review of these new products, says Todd Kuiken, a senior research associate with the Wilson Center and a co-author of the center's study on synthetic biology.

Environmentalists' call for a moratorium on commercial applications until synthetic biology-specific regulations are developed has gained little momentum so far. At the international level, environmental organizations are trying to raise their concerns about synthetic biology at gatherings such as the Convention on Biological Diversity, which meets in June in Montreal.

Environmental groups say they hope to spark consumer backlash to synthetic organisms similar to the public reaction against genetically modified food and crops. In November, the ETC Group and Friends of the Earth launched a satirical "branding" competition, calling on people to rename synthetic vanilla ("Vat-nilla" and "Frankenilla" were suggested by the groups). The ETC Group also initiated a letter-writing campaign in 2013 asking the USDA's Animal and Plant Health Inspection Service, which regulates genetically modified plants, to halt the introduction of glowing plants.

At the least, these critics want products made through synthetic biology to be labeled as such. Similar efforts by environmental and consumer groups have failed to get genetically modified foods labeled in the United States, even though countries in Europe require GMO foods to be labeled.

So far, Congress has not looked into safety concerns about synthetic biology. Eventually, Kuiken says, "A product will come out and test the system enough that either Congress gets involved or someone in the FDA or other agency says we have to re-evaluate how we're looking at this." ■

OUTLOOK

Fits and Starts?

Although synthetic biology is here to stay, it's too early to know if it will be the scientific revolution of the 21st century, as many proponents believe, or will have a more limited impact. It is also hard to predict whether environmentalists will succeed in creating a public backlash to products created through synthetic biology, as occurred with genetically modified crops.

The field is going to grow bigger, predicts Singh of BIO. "We've invested a lot, and we have actual products to show for it."

The research is "going much faster now," says Harvard's Church, who predicts that before long his lab's work on making every gene in a cell multivirus-resistant will bear fruit — perhaps even in humans.

In the very near term, Hanson, of the International Center for Technology Assessment, predicts that cosmetics applications, such as synthetic fragrances for perfumes, will be a growth area. "Cosmetics are poorly regulated," he says. "They would be the kind of markets I'd expect companies would look at."

ETC's Thomas says the best outcome may be for synthetic biology to actually be "a bubble that bursts." That would avoid the environmental and social justice concerns that environmental organizations such as his have raised, he says. Even if that were to happen, he says, "In the process there will probably be releases of all kinds of novel organisms that might have risks. There could be impacts on farmers. If you have a vat of organisms producing vanillin, that can push down product prices."

He also predicts a battle over whether synthetic biology ingredients in food can be labeled "natural," such as the synthetic version of the sweetener stevia, which Evolva will soon have on the market. "There will be many people opposed to food from synthetically modified organisms passed off as natural, and that will give rise to consumer concern," Thomas says. "Many of the same concerns people have with genetically modified food will be amplified with having synthetic biology products in their Coke and ice cream."

In the late 1990s, a biotech industry effort to get genetically modified foods certified as "organic" triggered a massive public backlash, and the proposal was rejected. [56]

Hamline University's Kahn predicts synthetic biology will grow in fits and starts — and stalls. "Some applications will prove very fruitful and a lot won't, and I'll be very surprised if any live up to the hype," he says. "It's very hard to know in advance what will be a revolutionary change, technologically speaking. In the abstract, a lot sounds so great. In application, life is a lot messier."

Many scientists agree. In the area of medicine, for instance, the National Science Foundation's Roper and others stress that it's important to manage expectations, especially when people's lives are at stake.

"Our basic understanding of biology is still very limited," he says. "All of the expectations about synthetic biology have frankly not been able to be met in the time frame that investors would have liked. Our basic understanding of even a single cell to grow and propagate is in its infancy. We are trying in a very short amount of time to overcome 2 billion years of programming by nature."

Synberc's Katz agrees. "There's a lot of unexplained biology still going on," he says. "Whether we'll ever be able to control it to the extent that engineers want to do is questionable, but we're working towards that." ■

About the Author

Beth Baker is a freelance journalist in Takoma Park, Md., who writes on health care and whose articles have appeared in numerous publications, including *The Washington Post*, *AARP Bulletin*, *Ms.* and *BioScience*, where she is features editor. She has received two National Mature Media Awards for her reporting on aging and media fellowships to study aging and cancer issues from, respectively, Case Western Reserve University and the National Press Foundation. Her books include the newly released *With a Little Help from Our Friends – Creating Community as We Grow Older* (Vanderbilt University Press, 2014).

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DIYBio, http://diybio.org/ Email: contact@diybio.org. A virtual organization promoting do-it-yourself synthetic biology community labs; provides free online ask-a-biosafety-expert service, a lively blog and a global discussion forum.

ETC Group, 180 Metcalfe St., Suite 206, Ottawa, ON K2P 1P5; 1-613-241-2267; www.etcgroup.org. Monitors the effects of technology on humans and the environment; is among more than 100 environmental, consumer and religious groups that support "The Principles for the Oversight of Synthetic Biology," which calls for caution in the development of synthetic biology.

Friends of the Earth, 1100 15th St., N.W., 11th Floor, Washington, DC 20005; 202-783-7400 and 2150 Allston Way, Suite 240, Berkeley, CA 94704; 510-900-3150; www.foe.org/projects/food-and-technology/synthetic-biology. National environmental group that has free, downloadable resources documenting ecological and justice concerns related to synthetic biology, including biofuels production and effects on biodiversity.

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