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Biology's Brave New World

The Promise and Perils of the Synbio Revolution

Laurie Garrett

In May 2010, the richest, most powerful man in biotechnology made a new creature. J. Craig Venter and his private-company team started with DNA and constructed a novel genetic sequence of more than one million coded bits of information known as nucleotides. Seven years earlier, Venter had been the first person in history to make a functioning creature from information. Looking at the strings of letters representing the DNA sequence for a virus called phi X174, which infects bacteria, he thought to himself, "I can assemble real DNA based on that computer information." And so he did, creating a virus based on the phi X174 genomic code. He followed the same recipe later on to generate the DNA for his larger and more sophisticated creature. Venter and his team figured out how to make an artificial bacterial cell, inserted their man-made DNA genome inside, and watched as the organic life form they had synthesized moved, ate, breathed, and replicated itself.

As he was doing this, Venter tried to warn a largely oblivious humanity about what was coming. He cautioned in a 2009 interview, for example, that "we think once we do activate a genome that yes, it probably will impact people's thinking about life." Venter defined his new technology as "synthetic genomics," which would "start in the computer in the digital world from digitized biology and make new DNA constructs for very specific purposes. . . . It can mean that as we learn the rules of life we will be able to develop robotics and computational systems that are self-learning systems." "It's the beginning of the new era of very rapid learning,"

LAURIE GARRETT is Senior Fellow for Global Health at the Council on Foreign Relations.

he continued. "There's not a single aspect of human life that doesn't have the potential to be totally transformed by these technologies in the future."

Today, some call work such as Venter's novel bacterial creation an example of "4-D printing." 2-D printing is what we do everyday by hitting "print" on our keyboards, causing a hard copy of an article or the like to spew from our old-fashioned ink-printing devices. Manufacturers, architects, artists, and others are now doing 3-D printing, using computer-generated designs to command devices loaded with plastics, carbon, graphite, and even food materials to construct three-dimensional products. With 4-D printing, manufacturers take the next crucial step: self-assembly or self-replication. What begins as a human idea, hammered out intellectually on a computer, is then sent to a 3-D printer, resulting in a creation capable of making copies of and transforming itself. In solid materials, Skylar Tibbits of the Massachusetts Institute of Technology creates complex physical substances that he calls "programmable materials that build themselves." Venter and hundreds of synthetic biologists argue that 4-D printing is best accomplished by making life using life's own building blocks, DNA.

When Venter's team first created the phi X174 viral genome, Venter commissioned a large analysis of the implications of synthetic genomics for national security and public health. The resulting report warned that two issues were impeding appropriate governance of the new science. The first problem was that work on synthetic biology, or synbio, had become so cheap and easy that its practitioners were no longer classically trained biologists. This meant that there were no shared assumptions regarding the new field's ethics, professional standards, or safety. The second problem was that existing standards, in some cases regulated by government agencies in the United States and other developed countries, were a generation old, therefore outdated, and also largely unknown to many younger practitioners.

Venter's team predicted that as the cost of synthetic biology continued to drop, interest in the field would increase, and the ethical and practical concerns it raised would come increasingly to the fore. They were even more prescient than they guessed. Combined with breakthroughs in another area of biology, "gain-of-function" (GOF) research, the synthetic genomics field has spawned a dizzying array of new possibilities, challenges, and national security threats. As the scientific community

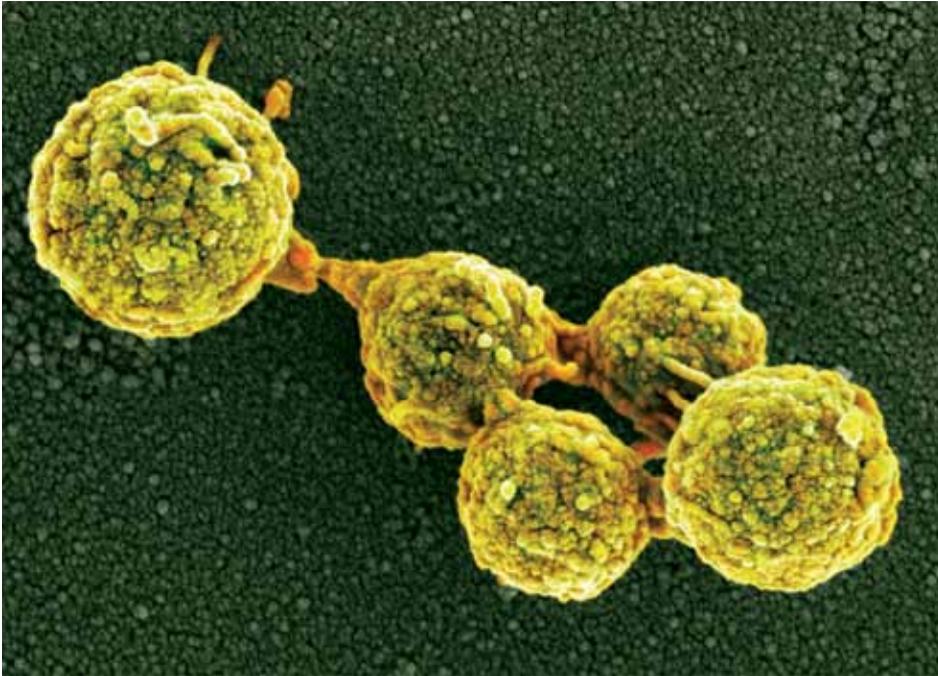
has started debating “human-directed evolution” and the merits of experiments that give relatively benign germs dangerous capacities for disease, the global bioterrorism and biosecurity establishment remains well behind the curve, mired in antiquated notions about what threats are important and how best to counter them.

In the United States, Congress and the executive branch have tried to prepare by creating finite lists of known pathogens and toxins and developing measures to surveil, police, and counter them; foreign governments and multilateral institutions, such as the UN and the Biological Weapons Convention, have been even less ambitious. Governance, in short, is focused on the old world of biology, in which scientists observed life from the outside, puzzling over its details and behavior by tinkering with its environment and then watching what happened. But in the new biology world, scientists can now create life themselves and learn about it from the inside. As Venter put it back in 2009, “What we have done so far is going to blow your freakin’ mind.”

CODING LIFE

Shortly after Venter’s game-changing experiment was announced, the National Academy of Sciences’ Institute of Medicine convened a special panel aimed at examining the brave new biology world’s ethical, scientific, and national security dimensions. Andrew Ellington and Jared Ellefson of the University of Texas at Austin argued that a new breed of biologists was taking over the frontiers of science—a breed that views life forms and DNA much the way the technology wizards who spawned IBM, Cisco, and Apple once looked at basic electronics, transistors, and circuits. These two fields, each with spectacular private-sector and academic engagement, are colliding, merging, and transforming one another, as computer scientists speak of “DNA-based computation” and synthetic biologists talk of “life circuit boards.” The biologist has become an engineer, coding new life forms as desired.

Gerald Joyce of the Scripps Research Institute in La Jolla, California, frets that as the boundaries blur, biologists are now going to be directing evolution and that we are witnessing “the end of Darwinism.” “Life on Earth,” Joyce has noted, “has demonstrated extraordinary resiliency and inventiveness in adapting to highly disparate niches. Perhaps the most significant invention of life is a genetic system that has an extensible capacity for inventiveness, something that likely will not be achieved soon for synthetic biological systems. However, once informational



Germ 2.0: the first self-replicating bacteria made in a lab, May 2010

macromolecules are given the opportunity to inherit profitable variation through self-sustained Darwinian evolution, they just may take on a life of their own.”

This is not hyperbole. All the key barriers to the artificial synthesis of viruses and bacteria have been overcome, at least on a proof-of-principle basis. In 2002, researchers at SUNY Stony Brook made a living polio virus, constructed from its genetic code. Three years later, scientists worried about pandemic influenza decided to re-create the devastating 1918 Spanish flu virus for research purposes, identifying key elements of the viral genes that gave that virus the ability to kill at least 50 million people in less than two years. What all this means is that the dual-use dilemma that first hit chemistry a century ago, and then hit physics a generation later, is now emerging with special force in contemporary biology.

Between 1894 and 1911, the German chemist Fritz Haber figured out how to mass-produce ammonia. This work revolutionized agriculture by generating the modern fertilizer industry. But the same research helped create chemical weapons for German use during World War I—and Haber was crucial to both the positive and the negative efforts. Three years after Haber won the Nobel Prize in Chemistry, his compatriot Albert Einstein won a Nobel Prize for his contributions to

physics. Einstein's revolutionary theories of relativity, gravity, mass, and energy helped unravel the secrets of the cosmos and paved the way for the harnessing of nuclear energy. They also led to the atom bomb.

The problem of "dual-use research of concern" (DURC)—work that could have both beneficial and dangerous consequences—was thus identified long ago for chemistry and physics, and it led to international

As the scientific community has started debating "human-directed evolution," the biosecurity establishment remains behind the curve.

treaties aimed at limiting the most worrisome applications of problematic work in each field. But in this respect, at least, biology lagged far behind, as the United States, the Soviet Union, and many other countries continued to pursue the development of biological weapons with relatively few restrictions. These efforts have not yielded much of military

consequence, because those who aspire to use bioweapons have not found ways to transmit and disperse germs rapidly or to limit their effects to the intended targets alone. That could now be changing.

Dual-use concerns in biology have gained widespread publicity in the last couple of years thanks to GOF research, which attempts to start combating potential horrors by first creating them artificially in the lab. On September 12, 2011, Ron Fouchier of the Erasmus Medical Center, in Rotterdam, took the stage at a meeting in Malta of the European Scientific Working Group on Influenza. He announced that he had found a way to turn H5N1, a virus that almost exclusively infected birds, into a possible human-to-human flu. At that time, only 565 people were known to have contracted H5N1 flu, presumably from contact with birds, of which 331, or 59 percent, had died. The 1918 influenza pandemic had a lethality rate of only 2.5 percent yet led to more than 50 million deaths, so H5N1 seemed potentially catastrophic. Its saving grace was that it had not yet evolved into a strain that could readily spread directly from one human to another. Fouchier told the scientists in Malta that his Dutch group, funded by the U.S. National Institutes of Health, had "mutated the hell out of H5N1," turning the bird flu into something that could infect ferrets (laboratory stand-ins for human beings). And then, Fouchier continued, he had done "something really, really stupid," swabbing the noses of the infected ferrets and using the gathered viruses to infect another round of animals, repeating the process until he had a form of H5N1 that could spread through the air from one mammal to another.

“This is a very dangerous virus,” Fouchier told *Scientific American*. Then he asked, rhetorically, “Should these experiments be done?” His answer was yes, because the experiments might help identify the most dangerous strains of flu in nature, create targets for vaccine development, and alert the world to the possibility that H5N1 could become airborne. Shortly after Fouchier’s bombshell announcement, Yoshihiro Kawaoka, a University of Wisconsin virologist, who also received funding from the National Institutes of Health, revealed that he had performed similar experiments, also producing forms of the bird flu H5N1 that could spread through the air between ferrets. Kawaoka had taken the precaution of altering his experimental H5N1 strain to make it less dangerous to human beings, and both researchers executed their experiments in very high-security facilities, designated Biosafety Level (BSL) 3+, just below the top of the scale.

Despite their precautions, Fouchier and Kawaoka drew the wrath of many national security and public health experts, who demanded to know how the deliberate creation of potential pandemic flu strains could possibly be justified. A virtually unknown advisory committee to the National Institutes of Health, the National Science Advisory Board for Biosecurity, was activated, and it convened a series of contentious meetings in 2011–12. The advisory board first sought to mitigate the fallout from the H5N1 experiments by ordering, in December 2011, that the methods used to create these new mammalian forms of H5N1 never be published. *Science* and *Nature* were asked to redact the how-to sections of Fouchier’s and Kawaoka’s papers, out of a stated concern on the part of some advisory board members that the information constituted a cookbook for terrorists.

Michael Osterholm, a public health expert at the University of Minnesota and a member of the advisory board, was particularly concerned. He felt that a tipping point had been reached and that scientists ought to pause and develop appropriate strategies to ensure that future work of this sort was safely executed by people with beneficial intentions. “This is an issue that really needs to be considered at the international level by many parties,” Osterholm told journalists. “Influenza is virtually in a class by itself. Many other agents worked on within BSL-4 labs don’t have that transmissibility that we see with influenza. There are many agents worked on in BSL-4 that we wouldn’t want to escape. But I can’t think of any that have the potential to be transmitted around the world as with influenza.”

Paul Keim, a microbiologist at Northern Arizona University who was chair of the National Science Advisory Board for Biosecurity, had played a pivotal role in the FBI's pursuit of the culprit behind the 2001 anthrax mailings, developing novel genetic fingerprinting techniques to trace the origins of the spores that were inserted into envelopes and mailed to news organizations and political leaders. Keim shared many of Osterholm's concerns about public safety, and his anthrax experience gave him special anxiety about terrorism. "It's not clear that these particular [experiments] have created something that would destroy the world; maybe it'll be the next set of experiments that will be critical," Keim told reporters. "And that's what the world discussion needs to be about."

In the end, however, the December 2011 do-not-publish decision settled nothing and was reversed by the advisory board four months later. It was successfully challenged by Fouchier and Kawaoka, both papers were published in their entirety by *Science* and *Nature* in 2012, and a temporary moratorium on dual-use research on influenza viruses was eventually lifted. In early 2013, the National Institutes of Health issued a series of biosafety and clearance guidelines for GOF research on flu viruses, but the restrictions applied only to work on influenza. And Osterholm, Keim, and most of the vocal opponents of the work retreated, allowing the advisory board to step back into obscurity.

A GLOBAL REMEDY?

In the last two years, the World Health Organization has held two summits in the hopes of finding a global solution to the Pandora's box opened by the H5N1 experiments. The WHO's initial concern was that flu scientists not violate the delicately maintained agreements among nations regarding disease surveillance and the sharing of outbreak information—a very real concern, given that the 2005 International Health Regulations, which assign the WHO authority in the event of an epidemic and compel all nations to monitor infectious diseases and report any outbreaks, had taken 14 years to negotiate and had been challenged by some developing countries, such as Indonesia, from the day of their ratification.

Jakarta resisted sharing viral samples on the grounds that Western pharmaceutical companies would seek to patent products derived from them and ultimately reap large profits by selling vaccines and drugs back to poor countries at high prices. So Indonesia refused to share samples of the H5N1 flu virus that was spreading inside its borders; made

wild accusations about the global health community in general, and the United States in particular; and even expelled the U.S. negotiator working on the issue. Eventually, a special pandemic-prevention agreement was hammered out and approved by the World Health Assembly (the decision-making body of the WHO) in 2011, serving as a companion to the International Health Regulations. But by 2012, fewer than 35 countries had managed to comply with the safety, surveillance, and research requirements of the regulations, and many samples of H5N1 and other pathogens of concern had yet to be shared with global authorities and databases. Public health experts worried that a pandemic might unfold before authorities knew what they were up against.

All the key barriers to the artificial synthesis of viruses and bacteria have been overcome.

The WHO knew that Egypt's primary public health laboratory in Cairo had been raided during the riots that ultimately toppled the Mubarak regime in early 2011 and that vials of germs had gone missing—including samples of the H5N1 virus. Egypt has a robust H5N1 problem, with the second-largest number of human cases of the disease (behind, you guessed it, Indonesia). Although it was assumed that the rioters had no idea what was in the test tubes and were merely interested in looting the lab's electronics and refrigeration equipment, nobody can say with certainty whether the flu vials were destroyed or taken.

From the WHO's perspective, the Egyptian episode demonstrated that the extensive security precautions taken by the Dutch to ensure the security of Fouchier's work and the ones that the Americans had adhered to regarding Kawaoka's were not going to be followed in biology labs in many other countries. Margaret Chan, the WHO's director general, and Keiji Fukuda, an assistant director general, remembered the SARS epidemic of 2003, during which Chinese leaders dissembled and dragged their feet for months, allowing the disease to spread to 29 countries. They knew that even in countries that claimed to have met all the standards of the International Health Regulations, there were no consistent dual-use safety regulations. Across most of Asia, the very concept of biosafety was a new one, and a source of confusion. Even in Europe, there were no consistent guidelines or definitions for any aspects of dual-use research, biosafety, or biosecurity. European countries were far more concerned about genetically modified food products than about pathogens and

microbes; they were preoccupied with enforcing the 2000 Cartagena Protocol on Biosafety, which despite its name has nothing to do with terrorism, national security, or the sorts of issues raised by dual-use research; its focus is genetically modified organisms.

The WHO's first dual-use summit, in February 2012, pushed Fouchier and Kawaoka to reveal the details of their experimental procedures and outcomes to their scientific colleagues. Fouchier's boasting about mutations seemed less worrying when the scientist indicated that he had not used synthetic biological techniques and that although his virus had spread between caged ferrets, it had not killed any of them. The technical consultation on H5N1, which was dominated by flu virologists, led the scientists to decide that the work was less dangerous than previously thought and that the moratorium on it could soon be lifted.

An exasperated Osterholm told the New York Academy of Sciences that the United States and the WHO had no clear protocols for DURC, no standards for determining safety, and no plans for a coordinated global response. But many other scientists engaged in the debate were less concerned, and they complained that the potential public health benefits of GOF research might be held back by excessive worries about its potential risks. In meeting after meeting, they claimed, the FBI, the CIA, and other intelligence agencies had proved unable to characterize or quantify the risk of bioweapons terrorism, GOF work, or synthetic biological research.

I BELIEVE THE CHILDREN ARE OUR FUTURE

Advocates for open, fast-paced synthetic biological research, such as Drew Endy of Stanford University and Todd Kuiken of the Wilson Center, the latter one of the leaders of a growing do-it-yourself international biology movement, insist that attention should be paid not just to the dangers of synthetic biology but also to its promise. Endy reckons that two percent of the U.S. economy is already derived from genetic engineering and synthetic biology and that the sector is growing by 12 percent annually. His bioengineering department at Stanford operates on a budget of half a billion dollars a year, and Endy predicts that synthetic biology will in the near future lead to an economic and technological boom like that of Internet and social media technologies during the earlier part of this century.

Many biology students these days see the genetic engineering of existing life forms and the creation of new ones as the cutting edge of

the field. Whether they are competing in science fairs or carrying out experiments, they have little time for debates surrounding dual-use research; they are simply plowing ahead. The International Genetically Engineered Machine contest, in which teams of college students compete to build new life forms, began at MIT in 2004; it was recently opened to high school teams as well. Last year's contest drew more than 190 entries by youngsters from 34 countries. What sounds like science fiction to one generation is already the norm for another.

In just a few years, synthetic biological research has become relatively cheap and easy. In 2003, the Human Genome Project completed the first full sequencing of human DNA. It cost several billion dollars, involved thousands of scientists and technicians toiling in more than 160 labs, and took more than ten years. A decade later, it was possible to buy a sequencing device for several thousand dollars and sequence one's entire genome at home in less than 24 hours. For even less, a private company will sequence your

Einstein's revolutionary theories helped unravel the secrets of the cosmos. They also led to the atom bomb.

genome for you, and prices are still dropping. Sequencing costs have plummeted so far that the industry is no longer profitable in the developed world and has largely been outsourced to China. In vast lab warehouses outside Beijing, Shanghai, and Shenzhen, automated sequencers now decipher, and massive computers store, more genetic information every month than the sum total of the information amassed from James Watson and Francis Crick's 1953 discovery of DNA to Venter's 2003 synthesis of the phi X174 genome.

To understand how the field of synthetic biology works now, it helps to use a practical example. Imagine a legitimate public health problem—say, how to detect arsenic in drinking water in areas where ground-water supplies have been contaminated. Now imagine that a solution might be to create harmless bacteria that could be deposited in a water sample and would start to glow brightly in the presence of arsenic. No such creature exists in nature, but there are indeed creatures that glow (fireflies and some fish). In some cases, these creatures glow only when they are mating or feel threatened, so there are biological on-off switches. There are other microorganisms that can sense the presence of arsenic. And there are countless types of bacteria that are harmless to humans and easy to work with in the lab.

To combine these elements in your lab, you need to install an appropriate software program on your laptop and search the databases of relevant companies to locate and purchase the proper DNA units that code for luminescence, on-off switches, and arsenic sensing. Then, you need to purchase a supply of some sort of harmless bacteria. At that point, you just have to put the DNA components in a sensible sequence, insert the resulting DNA code into the bacterial DNA, and test to see if the bacteria are healthy and capable of replicating themselves. To test the results, all you have to do is drop some arsenic in a bottle of water, add some of your man-made bacteria, and shake: if the water starts to glow, bingo. (This slightly oversimplified scenario is based on one that was actually carried out by a team from the University of Edinburgh in the International Genetically Engineered Machine contest in 2006.)

The most difficult part of the process now is putting the DNA components in a sensible sequence, but that is unlikely to be true for long. The world of biosynthesis is hooking up with 3-D printing, so scientists can now load nucleotides into a 3-D “bioprinter” that generates genomes. And they can collaborate across the globe, with scientists in one city designing a genetic sequence on a computer and sending the code to a printer somewhere else—anywhere else connected to the Internet. The code might be for the creation of a life-saving medicine or vaccine. Or it might be information that turns the tiny phi X174 virus that Venter worked on a decade ago into something that kills human cells, or makes nasty bacteria resistant to antibiotics, or creates some entirely new viral strain.

INFORMATION, PLEASE

What stymies the very few national security and law enforcement experts closely following this biological revolution is the realization that the key component is simply information. While virtually all current laws in this field, both local and global, restrict and track organisms of concern (such as, say, the Ebola virus), tracking information is all but impossible. Code can be buried anywhere—al Qaeda operatives have hidden attack instructions inside porn videos, and a seemingly innocent tweet could direct readers to an obscure Internet location containing genomic code ready to be downloaded to a 3-D printer. Suddenly, what started as a biology problem has become a matter of information security.

When the WHO convened its second dual-use summit, therefore, in February 2013, about a third of the scientists and government officials in attendance were from the United States, representing at least 15 different agencies as diverse as the FBI, the Centers for Disease Control and Prevention, the Department of Defense, and the Office of the U.S. Trade Representative. Although other countries brought strong contingents, the message from the Obama administration was clear: we are worried.

Each country party to the Biological Weapons Convention is required to designate one agency to be responsible for guaranteeing compliance with the treaty's provisions. For the United States, that agency is the FBI. So now, a tiny office of the FBI, made even smaller through recent congressional budget cuts and sequestration, engages the scientific community and tries to spot DURC. But the FBI has nothing like the scientific expertise that the biologists themselves have, and so in practice, it must rely on the researchers to police themselves—an obviously problematic situation.

Other countries have tried to grapple with the dual-use problem in other ways. Denmark, for example, has a licensing procedure for both public- and private-sector research. It requires researchers to register their intentions before executing experiments. The labs and personnel are screened for possible security concerns and issued licenses that state the terms of their allowable work. Some of the applications and licenses are classified, guaranteeing the private sector trade secrecy. Such an effort is possible there, however, only because the scale of biological research in the country is so small: fewer than 100 licenses are currently being monitored.

The Dutch government sought to control Fouchier's publication of how he modified the H5N1 virus through the implementation of its export-control laws, with the information in question being the commodity deemed too sensitive to export. Although the government lifted the ban after the first WHO summit, a district court later ruled that Fouchier's publication violated EU law. Fouchier is appealing the decision, which could have profound implications across Europe for the exchange of similar research. Among the lessons of the recent U.S. intelligence leaks, however, is that it may well be impossible to have airtight controls over the transmission of digital information if the parties involved are sufficiently determined and creative.

In line with their emerging engineering perspective, many biologists now refer to their genomics work as “bar-coding.” Just as manufacturers put bar codes on products in the supermarket to reveal the product's identity and price when scanned, so biologists are racing to genetically

sequence plants, animals, fish, birds, and microorganisms all over the world and taxonomically tag them with a DNA sequence that is unique to the species—its “bar code.” It is possible to insert bar-code identifiers into synthesized or GOF-modified organisms, allowing law enforcement and public health officials to track and trace any use or accidental release of man-made or altered life forms. Such an approach has been used for genetically modified seeds and agricultural products, and there is no good reason not to mandate such labeling for potentially worrisome dual-use work. But bar-coding has to be incorporated by the original researchers, and it is not going to be implemented by those with malicious intentions. So there are no quick or easy technological fixes for the problem.

FROM WHO TO HAJ

The 2013 WHO summit failed to reach meaningful solutions to dual-use research problems. The financially strapped WHO couldn't find the resources to follow up on any of the recommendations produced by the summit. Worse, the attendees could not even manage to come up with a common framework for discussion of the issue. Poor nations felt it was an extremely low priority, with African representatives complaining that their countries didn't have the resources to implement biosafety guidelines. As one representative put it, speaking on the condition of anonymity, “We are the ones that actually suffer from all of these diseases. We are the ones that need this research. But we cannot do it. We do not have the facilities. We do not have the resources. And now, with all these DURC worries, our people cannot get into your laboratories to work by your side [in the United States or Europe] for security reasons. This whole DURC issue is simply holding us back, whether that is the intention or not.”

Noticeably quiet at the three-day conference were the representatives from large developing countries such as Brazil, China, India, and South Africa. And when any of them did speak up, it was to emphasize their concerns about who would hold the patents on products made with dual-use research, to insist on the need for technology transfer, or to mouth platitudes about how their countries' researchers already operated under strict scrutiny. The Chinese delegates, in particular, were adamant: all necessary provisions to ensure biological safety, they assured the gathering, are in place in their country. Two months after the meeting, a team of scientists at China's National Avian Influenza Reference Laboratory at the Harbin Veterinary Research

Institute used GOF techniques to manufacture 127 forms of the influenza virus, all based on H5N1, combined with genetic attributes found in dozens of other types of flu. The Chinese team had taken the work of Fouchier and Kawaoka and built on it many times over, adding some synthetic biological spins to the work. And five of their man-made superflu strains proved capable of spreading through the air between guinea pigs, killing them.

Less than a decade ago, the international virology community went into an uproar when U.S. scientists contemplated inserting a gene into stockpiled smallpox viruses that would have made solutions containing the virus turn green, for rapid identification purposes. What the U.S. researchers thought would be a smart way to track the deadly virus was deemed a “crime against humanity.”

Earlier this year, in contrast, when a new type of bird flu called H7N9 emerged in China, virologists called for GOF research as a matter of public health urgency. When the virus was subjected to genetic scrutiny, both Fouchier and Kawaoka declared it dangerous, noting that the very genetic changes they had made to H5N1 were already present in the H7N9 strain. In August, Fouchier’s group published the results of experiments that showed that the H7N9 virus could infect ferrets and spread through the air from one animal to another. And Fouchier, Kawaoka, and 20 other virologists called for an extensive series of GOF experiments on the H7N9 virus, allowing genetic modifications sufficient to turn the bird flu into a clear human-to-human transmissible pathogen so as to better prepare for countering it.

As health research authorities in the relevant countries mull the scientists’ request to manipulate the H7N9 virus, other microbes offer up mysteries that might be resolved using GOF techniques. The Middle East respiratory syndrome, or MERS, appeared seemingly out of nowhere in June 2012 in Saudi Arabia, and by September 2013, it had infected 132 people, killing almost half of them. Although the virus is similar to SARS, much about the disease and its origins is unknown. There were numerous cases of apparent human-to-human transmission of MERS, especially within hospitals, and Saudi health officials worried about the possible spread of MERS throughout the Islamic world. There is no vaccine or cure for MERS. If work to determine the transmissibility of H7N9 is to be permitted, shouldn’t researchers do something similar to see what it would take to transform MERS into a casually transmitted form, likely to spread, for example, among haj pilgrims?

When HIV emerged in the early 1980s, nobody was sure just how the virus was transmitted, and many health-care workers feared that they could contract the then 99 percent lethal disease through contact with their patients. Schools all over the United States banned HIV-positive children, and most sports leagues forbade infected athletes from playing (until the NBA star Magic Johnson bravely revealed that he was infected, turning the tide against such bans). Had it been technically possible to do so, would it have been wise to deliberately alter the virus then, giving it the capacity to spread through the air or through casual contact?

WHAT NOW?

Scientists and security experts will never come to a consensus about the risks of dual-use research in synthetic biology. After all, almost 35 years after smallpox was eradicated, debates still rage over whether to destroy the last remaining samples of the virus. The benefits of synthetic biological research are difficult to assess. Its proponents believe it will transform the world as much as the ongoing revolution in information technology has, but some others are skeptical. Moving aggressively to contain the possible downsides of dual-use research could hamper scientific development. If it were to get truly seized by the issue, the U.S. government, for example, could start to weave a vast bureaucratic web of regulation and surveillance far exceeding that established elsewhere, succeeding only in setting its own national scientific efforts back while driving cutting-edge research to move abroad. Unilateral action by any government is destined to fail.

What this means is that political leaders should not wait for clarity and perfect information, nor rush to develop restrictive controls, nor rely on scientific self-regulation. Instead, they should accept that the synthetic biology revolution is here to stay, monitor it closely, and try to take appropriate actions to contain some of its most obvious risks, such as the accidental leaking or deliberate release of dangerous organisms.

The first step in this regard should be to strengthen national and global capacities for epidemiological surveillance. In the United States, such surveillance has been weakened by budget cuts and bureaucratic overstretch at the federal, state, and local levels. The Centers for Disease Control and the U.S. Department of Agriculture represent the United States' first line of defense against microbial threats to human health, plants, and livestock, but both agencies have been cut to the bone. The Centers for Disease Control's budget has been cut by 25 percent since

2010, and it recently dropped by a further five percent thanks to sequestration, with the cuts including funding that supported 50,000 state, territorial, city, and county public health officers. It should be a no-brainer for Congress to restore that funding and other support for the nation's public health army.

At the same time, the Centers for Disease Control and the Department of Agriculture must become better at what they do. In the coming age of novel microbes, focusing attention on a small list of special pathogens and toxins, such as the Ebola virus, anthrax, and botulinum, offers a false sense of security. Even the recent suggestion that H5N1 be added to the National Select Agent Registry, which keeps track of potentially dangerous biological agents and toxins, seems beside the point: a simple, ubiquitous microbe such as *E. coli*, a bacterium that resides in the guts of every human being, can now be transformed into a killer germ capable of wreaking far more havoc than anything on that registry.

Solving the puzzle of just what to watch for now and how to spot it will require cooperative thinking across national and professional boundaries. Within the United States, leaders of organizations such as the Centers for Disease Control, the FBI, the Department of Health and Human Services, the Department of Defense, and the intelligence agencies will need to collaborate and pool their information and expertise. And internationally, multilateral groups such as the WHO and its food and agriculture counterparts will need to work with agencies and institutions such as Interpol, the Association of Southeast Asian Nations, the Pan American Health Organization, and the African Union.

The Biological Weapons Convention process can serve as a multilateral basis for DURC-related dialogue. It offers a neutral platform accessible to nearly every government in the world. But that process is weak at present, unable to provide verification akin to that ensured by its nuclear and chemical weapons counterparts. Given their own problems, in fact, international institutions are currently ill equipped to handle the dual-use research issue. Grappling with severe budget constraints for the third year in a row, the WHO, for example, has shrunk in size and influence, and its epidemiological identification-and-response capacity has been particularly devastated.

It is in the United States' own interests, as well as those of other countries, to have a thriving global epidemiological response capability housed within the WHO, acting under the provisions of the International Health Regulations. U.S. disease sleuths may not be welcome

everywhere in the world, but WHO representatives, at least in principle, are allowed inside nearly every country. Congress should therefore appropriate \$100 million a year for five years for direct support of the WHO's epidemiological surveillance-and-response system. To make sure U.S. underwriting doesn't become a meaningless crutch, Washington could make it clear to the WHO's World Health Assembly that some of that American support should be directed toward building indigenous epidemiological surveillance capabilities in developing countries, in order to bring them into compliance with the International Health Regulations. If U.S. legislators feared that such support for the WHO would morph into a multiyear entitlement program, they could have Washington's financing commitment start in 2014 and gradually decrease to zero by 2019, as other donor countries added their own assistance and recipient countries reached sustainable self-reliance. Congress should also continue the U.S. Agency for International Development's PREDICT Project, which is tasked with identifying new disease threats and to date has trained 1,500 people worldwide and discovered 200 previously unknown viruses.

Any global surveillance effort will require harmonized standards. At present, however, there are no agreed-on biosafety laboratory standards or definitions of various aspects of biosecurity, GOF research, or even DURC. So key U.S. agencies need to work closely with their foreign counterparts to hash out such standards and definitions and promulgate them. A model for emulation here might be the Codex Alimentarius, established by the UN Food and Agriculture Organization and the WHO in 1963 to standardize all food-safety guidelines worldwide.

In an era when e-mailed gene sequences have rendered test-tube transport obsolete, the proper boundaries of export and its control are increasingly difficult to define. At the core of the dual-use research problem is information, rather than microbes, and overregulating the flow of information risks stifling science and crippling international collaborative research. To deal with this problem, the U.S. Department of Commerce, the U.S. Department of Agriculture's Animal and Plant Health Inspection Service, and the Office of the U.S. Trade Representative must create a regulatory framework appropriate to dual-use research. Here, a model for regulation might draw from the experiences of the International Plant Protection Convention and the Animal and Plant Health Inspection Service's engagement through the U.S. Trade Representative's Office of Services and Investment. For

Internet traffic in genomes, many nucleotide distribution centers already monitor “sequences of concern,” demanding special information on individuals seeking pathogen-related genetic details. This approach should be embraced by governments.

So what should governments and institutions be on the lookout for? Evidence of the covert deliberate alteration of a life form that turns a creature into a more dangerous entity. If governments permitted or supported such research, they would be accused of violating the Biological Weapons Convention. The United States is by far the largest funder of basic science and the world's powerhouse of biological research, and so it would be at the greatest risk of being the target of such accusations. But sunlight is a good disinfectant, and it is legitimate to ask for any such research to be explained and defended openly. The State Department, in concert with the Department of Health and Human Services' Office of Global Affairs, should develop briefing materials for diplomatic personnel, explaining synthetic biology, GOF work, and DURC and thus balancing the United States' image as the foremost center of biomedical research against concerns about the creation of man-made pathogens. The State Department should promote cooperation on detecting and controlling DURC and on managing the shared global risk of the inappropriate release of synthetic pathogens; it should also support assistance programs aimed at hardening the safety of labs and monitoring them worldwide.

The tracking of novel DNA and life forms should be implemented on a voluntary or mandatory basis immediately. Private biotechnology companies and distributors of DNA components should assign biosecurity tags to all their man-made products. The trade in genomic sequences should be transparent and traceable, featuring nucleotide tags that can be monitored. The genomic industry should self-finance the necessary monitoring and enforcement of standards of practice and permit unrestricted government inspections in the event of breakdowns in biosafety or lab security.

Last year, Friends of the Earth, the International Center for Technology Assessment, and the ETC Group jointly issued a report called *The Principles for the Oversight of Synthetic Biology*, which called for the

Scientists and security experts will never come to a consensus about the risks of dual-use research in synthetic biology.

insertion of suicide genes in man-made and GOF-altered organisms—sequences that can be activated through simple changes in the organisms' environs, terminating their function. Although such suicide signals may be technically difficult to implement at this time, dual-use research should strive to include this feature. The three organizations have also called on industry to carry damage and liability insurance covering all synthetic biological research and products, a seemingly obvious and wise precaution. The BioBricks Foundation, meanwhile, is the loudest proponent of synthetic biology today, proclaiming its mission as being “to ensure that the engineering of biology is conducted in an open and ethical manner to benefit all people and the planet. . . . We envision synthetic biology as a force for good in the world.” Such ethics-based scientific organizations can drive awareness of the field and its problems and increase sensitivity among researchers to legitimate public concerns, and so their activities should be encouraged and expanded.

The controversies and concerns surrounding dual-use research in synthetic biology have arisen in less than four years, starting from the moment in 2010 when Venter announced his team's creation of a new life form described as “the first self-replicating species on the planet whose parent is a computer.” Before Venter's group raced down such a godlike path, it went to the Obama White House, briefing officials on a range of policy and ethical issues the project raised. For a while, the administration considered classifying the effort, worrying that it might spawn grave dangers. Instead, much to Venter's delight, the White House opted for full transparency and publication. “Perhaps it's a giant philosophical change in how we view life,” Venter said with a shrug at a Washington press conference. He wasn't sure. But he did feel confident that what he called “a very powerful set of tools” would lead to flu vaccines manufactured overnight, possibly a vaccine for the AIDS virus, and maybe microbes that consume carbon dioxide and emit a safe energy alternative to fossil fuels. Now that synthetic biology is here to stay, the challenge is how to ensure that future generations see its emergence as more boon than bane. 🌍