BIG IDEA

SAFEGUARDING BIOLOGY

By George Church

THE PRECAUTIONARY PRINCIPLE TRADITIONALLY SUMMARIZED AS "FIRST, DO NO HARM" SHOULD NOT BE REDUCED TO "FIRST, DO NOTHING," ESPECIALLY REGARDING TECHNOLOGICAL FIXES FOR OUR DETERIORATING BIOSPHERE AND ECONOMY.

If the cause of the bio-decay is population growth, which, in turn, is due to technology, then the idea of fixing it with technology merits a heavy dose of humility and reflection. Many technological developments "seemed like a good idea at the time" but had huge unintended consequences: Irrigating crops led to malaria; riverside settlements led to cholera; insect management led to a birdless silent spring; fertilizer led to microbial blooms and fish-kills; and so on.

Despite such risks, technological paralysis is not an option if our civilization is to endure and flourish. We must face the challenges posed by melting ice caps, massive famines, entrenched pandemics, emerging diseases, and a host of other threats. Of the many proposed technological solutions for these ills, each bears its own potential for inadvertent disaster—and a requisite, complicating need for safeguards that can be prohibitively expensive. But what if a technology's safeguards could directly enhance its capabilities to address our global problems? Ironically, this may be the case for one of the most feared and misunderstood advancements in recent years: biotechnology.

Life itself is the most powerful technology of all, a technology developed and honed not through orderly procedures in a laboratory but through billions of years of trial and error by natural selection. To date, the revolution in biotechnology has allowed us to harness the power of living things in ways never before possible, but the precautionary principle has precluded its use in many instances. Now, we stand on the brink of developing transformative methods that could make biotechnology not only safer but more useful against some of the world's most pressing problems.

Consider the problem of global warming, caused by rising levels of atmospheric carbon dioxide (CO_2). Even if we achieve huge successes with energy conservation and alternative energies like wind, nuclear, and solar, this won't lower existing CO_2 levels. To do that, we need to capture CO_2 from the atmosphere and sequester it. We could spend money (and energy) pumping CO_2 to some inaccessible site like the ocean floor, but the political determination to do so may be hard to muster. On the other hand, we could co-opt biological processes to sequester the CO_2, potentially even folding it into useful products like plastics, roads, and buildings. Nature sequesters massive amounts of CO_2 all the time: About 15 percent of the total 2 x 10^{12} tons of atmospheric CO_2 is removed each year by processes like photosynthesis. But most of that CO_2 returns to the atmosphere at the same rate, liberated from the decomposing bodies of the "bio-builders" (animals, plants, etc.) by the "bio-destroyers" (mostly parasitic viruses and microbes). This evolutionary arms race between growth and decay has raged since the dawn of life; if we could find a way to give the builders even a slight edge, sequestering a lot more CO_2 would be just one of many potential applications.

Let's start with the viruses. Viruses seem biologically unbeatable because they can tolerate much higher mutation rates and can reproduce much faster than their host organisms. So every evolutionary strategy that the host may try is immediately countered by many viral changes. To circumvent this, we'd have to place the host in isolation and protectively alter it in a way that no amount of viral mutation could overcome. But what Achilles heel could all viruses share? They show enormous diversity—indeed, no gene is universal to all viruses, whereas all cells share hundreds of genes. Every virus does, however, expect its host to allow it to reproduce.

One crucial step in the reproduction of all viruses (and provided only by the cell) is protein synthesis, the assemblage of proteins from a set of 20 different amino acids. Protein synthesis proceeds according to the universal DNA translational code, which allows a cell to read the nucleotide bases (A, C, G, T) on a strand of DNA three at a time to determine which amino acid goes where within a protein. These DNA triplets are called "codons." A little arithmetic reveals that the translational code is redundant: The number of possible triplet combinations of the four DNA bases is 64, so there can be one, two, four, or even six codons per amino acid (there are also three codons set aside for telling the cellular machinery to stop making a specific protein).

Given this knowledge, the modern tools of biotechnology allow us to do something amazing: We can alter the translational code within an organism by modifying the DNA bases of its genome, making the organism effectively *immune* to viral infection. My colleagues and I are exploring this within *E. coli*, the microbial powerhouse of the biotech world. By simply changing a certain 314 of the 5 million bases in the *E. coli* genome, we can change one of its 64 codons. In 2009 this massive (albeit nanoscale) construction project is nearing completion via breakthroughs in our ability to "write" genomes. This process is increasingly automated and inexpensive—soon it will be relatively easy to change multiple codons. Viral genomes range from 5,000 to a million bases in length, and each of the 64 codons is present, on average, 20 times. This means that to survive the change of a single codon in its host, a virus would require 20 simultaneous, specific, spontaneous changes to its genome. Even in viruses with very high mutation rates, for example HIV, the chance of getting a mutant virus with the correct 20 changes and zero lethal mutations is infinitesimally small.

Can biotechnology safely reverse the course of our deteriorating biosphere?

Altering the translational codes of genetically engineered organisms (GEOs) could have an important additional benefit. GEOs are very unpopular in some communities (e.g., Europe) in part because of concerns that engineered genes might become ecologically invasive, a sort of molecular kudzu. This is a legitimate concern, but we must also acknowledge that it's insufficient to simply always choose "natural" over "unnatural." Utilizing new translational codes in GEOs might provide the isolation from functional gene exchange that we've been looking for.

If we engineer organisms to be resistant to all viruses, we must anticipate that without viruses to hold them in check, these GEOs could take over ecosystems. This might be handled by making engineered cells dependent on nutritional components absent from natural environments. For example, we can delete the genes required to make diaminopimelate, an organic compound that is essential for bacterial cell walls (and hence bacterial survival) yet very rare in humans and our environment. The geneticist Roy Curtiss and his colleagues have already pioneered this protective measure. Or perhaps we can make our favorite GEO strain addicted to a totally unnatural amino acid like fluorotryptophan, as conceived by Andrew Ellington and his coworkers. Even if such GEOs escaped the laboratory, they would not find fluorotryptophan or diaminopimelate and would quickly die—and they couldn't be rescued by exchanging DNA with other microbes.

But actions speak louder than words. These safety features will be accepted and used only if they undergo rigorous testing in physical isolation and review by a diversity of critics. The battery of necessary tests is formidable, and includes ensuring that GEOs are not toxic to immunocompromised lab animals, as well as lab examinations of ecological challenges like unwanted gene transfer and harmful mutations.

If we can construct safety measures that pass all these tests, the door will be opened to potentially allow more sophisticated biotechnological interventions in areas like human health.

We already have a mandate in the form of the emergence of the HIV pandemic; those infected currently require a lifetime of expensive drugs to stay symptom free. A once-in-a-lifetime injection of bioengineered stem cells capable of making HIV-resistant blood T-cells might seem more cost effective—and might be closer at hand than the elusive HIV vaccine. We routinely transplant blood stem cells based on pioneering work from Don Thomas in the 1950s. Current limitations like taking cells from bone and irradiating the recipient are inefficient and dangerous; these obstacles could be overcome with bioengineering. In that context, the removal of viral receptors or addition of antiviral gene networks to those stem cells could become very attractive strategies. Further, the problems of cancer and aging lie in the fundamental "design" of our genomes. It would be surprising if we could fix such planned obsolescence with pharmaceuticals consisting of a few atoms (or "bits" of target-binding information)—but with proper bioengineering, we could change the gigabits of faulty software in our cells.

Still, all discussions of accelerating technology, unintended consequences, and safeguards could eclipse a larger concern: Are we simply going too fast? How do we decide on an optimal pace for our technological progression? We have become accustomed to twofold improvement every two years in the costs of computing and digital telecommunications—from French semaphore lines in 1792 to multiplexed optical fibers today. The pace of cost improvement in "reading" DNA followed a similar curve from 1968 until recently, but in 2004 it suddenly jumped to tenfold per year, a pace that continues today. Similar exponential advances in "writing" DNA have been evident since the 1970s. These three exponential technologies might become increasingly synergetic, with potentially profound effects.

My hope for the future is that our accelerating technologies will bring improvements in standards of living, accompanied by shifts to sustainable population sizes and increased health care and education for everyone. At the other extreme, physical or social limitations could cause technology to level off and stagnate exactly at a time that we desperately need to make rapid progress. Ultimately, our future will be what we make of it. Let us choose wisely, with carefully engineered safety and broad community engagement.

—George Church is director of the Center for Computational Genetics at Harvard Medical School. *(For full bio, see page 8)*

Q&A Craig Venter

BIOLOGICAL SELF-REGULATION

The biologist, entrepreneur, and genomics research pioneer, on whether the biology community needs to convene an Asilomar 2.0 for synthetic genomics

IN 1975 SCIENTISTS CONVENED IN ASILOMAR, CALIFORNIA, TO SELF-IMPOSE RULES FORBIOTECHNOLOGY RESEARCH. DO WE NEED A NEW CONFERENCE?

I don't think so. Asilomar came at a crisis point in molecular biology; there was a lot of fear out there. We have not waited for a crisis—there has been a steady dialogue. For example, my group undertook bioethical reviews with bioethicists from the University of Pennsylvania before our first experiments began.

WHAT OTHER EXPERIENCE HAVE YOU HAD WITH REGULATION?

My group has created a bacteriophage virus. Because that work was sponsored by the US Department of Energy, it prompted an extensive review within the government, including the White House, to consider whether to classify it or to allow open publication. One of the few good things to come out of the Bush administration was that they allowed open publication. We were asked to work with a new community—the National Science Advisory Board for Biosecurity—that has representatives from all parts of the executive branch. The first thing I'm aware of that the NSABB did was to review and approve the work on the 1918 flu virus, which was really quite extraordinary.

My own rules were that no human pathogen be made, but the 1918 flu virus reconstruction was in retrospect very justified, because the work allowed them to see for the first time why it was so lethal.

HOW DOES THE REGULATORY DISCUSSION CONTINUE TODAY?

I got a grant from the Sloan Foundation along with researchers from MIT to look at the risks and the benefits associated with synthetic genomics. We published the report in October 2007. Everything I do is done very openly. The bioengineering scare in Europe has kept discussion active. So, there, we've chosen to talk about the environmental crisis—including climate change. Whichever countries apply biotechnology successfully to climate change will create tens of millions of new jobs. This is the only thing I can see eliminating the burning of oil.

HOW DO WE DEAL PROPERLY WITH THE RISKS, WASTES, AND IMPACTS OF LARGE-SCALE CULTIVATION OF SYNTHETIC ORGANISMS?

There is need for broader discussion on a regulatory level on how to deal with the outputs of the bioreactors these organisms are raised in. If we are going to cover a million hectares with solar-conversion biocells, obviously, we are going to need to deal with excess biomass and environmental threats. Look at the shipping industry and ballast water. A supertanker's water ballast moves huge numbers of bacteria and viruses from port to port. We've been moving trillions of organisms around; what's amazing is that colonization hasn't happened more often. Whether we need laws for it, they would need to be thoughtful laws. The US has had it backward the past eight years with science literacy. Hopefully that is going to change next year, but we need a broader dialogue before there is any attempt to regulate what only might happen.

—Interviewed by TJ Kelleher