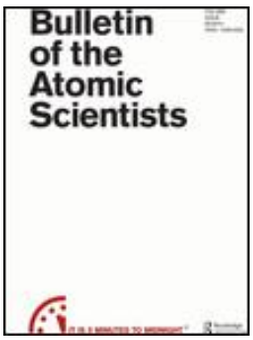

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Interview: George Church

The fields of genetic sequencing and synthetic biology have a tried-and-true supporter in Harvard geneticist George Church. While recognizing the potential for misuse in any discipline, from biology to calculus, it is clear to him that the benefits outweigh the risks.

On any given day, George Church can be found in his lab examining the genetic makeup of people from across the country. A professor of genetics at Harvard Medical School, Church began his research into DNA in 1974. Thirty-five years later, he is leading groundbreaking research in gene sequencing and synthetic biology. His Personal Genome Project (PGP), launched in 2005, sequences the DNA of thousands of volunteers and makes their medical information and genetic data available to anyone, anywhere in the world, interested in researching the human genome. From evaluating vaccine reactions to discovering a person's predisposition toward cancer, PGP-associated research has the potential to make individual health care more effective. In addition, at the Wyss Institute in Boston, Church is synthesizing and modeling biomedical and ecological systems.

Church's work is not without its detractors, especially when it comes to issues of privacy, regulation, and the potential for biological misuse. But he is not afraid to engage these skeptics. While he warns about enabling do-it-yourself biologists to create dangerous, unregulated organisms, he is quick to point out that, outside of academic or industry research, few people have the tools to use genetic data for malign purposes—such as synthesizing a deadly pathogen. And, he argues, voluntary standards put in place by the biotech industry are effective in controlling who can obtain potentially dangerous biological materials. Is Church an enabler, then, for better or worse? It seems it's a label he's comfortable with.

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BAS: Where did synthetic biology come from, and where is it now?
CHURCH: Some people correctly think synthetic biology emerged out of advances in genetic engineering and recombinant DNA in the 1970s, which itself emerged out of scientists' increased ability to synthesize DNA chemically and to engineer DNA with molecular biology, restriction enzymes, ligase, and so forth. Basically, it's a convergence of living systems with biochemical and chemical systems.

What is new about synthetic biology is that it has become more of an engineering discipline where you can select interoperable parts and specified parameters under specified conditions. Your expectation is that when you put together new sets of these parts, they work in the same way. It's like putting together standardized electrical or mechanical parts. All of this is accompanied by computerized design tools and whole disciplines of synthesis similar to large-scale integrated circuits in electronics.
BAS: What types of backgrounds do people who enter the field have?
CHURCH: In the early days, it was microbiologists. But there has been a steady flow of physicists, chemists, and, more recently, engineers. The engineers have created synthetic biology in their own image by taking into account what they've learned as civil, mechanical, electrical, or computer science engineers.

These days, the people I recruit to my lab tend to be cross-trained in multiple fields. They come out of an undergraduate education with double majors in electrical engineering and biology, physics and biology, or biophysics and computer science.
BAS: Considering the diverse backgrounds of synthetic biology researchers, how are people trained to understand dual-use risk?
CHURCH: Altogether too infrequently, in science at least, the big questions—such as security concerns or the economics of unintended consequences—are rarely taught. A student will receive safety instructions—for example, on how not to spill acid on his shoes. He also might get instructions on how to conduct himself as a scientist ethically. But this is usually restricted to avoiding scientific misconduct—that is, plagiarism and fraud. Training rarely covers the topic of global, existential risk.
BAS: When should such risk assessment be taught?
CHURCH: It should be taught in every single course, even abstract courses. A teacher can dial down the amount of time spent on risks, but there at least should be a small amount of time dedicated to them. Even calculus classes should discuss potential dangers, because such math is used to launch ballistic missiles. Risk analysis also applies to how nuclear, chemical, and biological materials could be deployed. Personally, I inject it into every course I teach—no matter the topic. Even one discussion of how technologies can go wrong helps students think more proactively and outside the box.

BAS: How did the Personal Genome Project start? And how has it evolved?

CHURCH: The PGP started from the realization that genome synthesis technology was coming. It is aimed at public health and at discovering the interactions between human genes and the environment in order to produce traits. The process is this: First, each participant has to get 100 percent on an entrance exam, which ensures they understand what will be done with the genetic, medical, and behavioral information we collect and the project's risks and benefits. It is an unusual protocol, but thousands of people are getting 100 percent. That's their way of proving to us that they and their families are fully informed and enthusiastic. Second, our team of scientists collects personal and medical data on the volunteers—such as medicines taken, where their grandparents are from, and whether they are near-sighted or far-sighted. Then the researchers take samples of skin and saliva for DNA and RNA examination. The data is then made available to the public. The project has about 15,000 volunteers, and the PGP has been approved to expand to 100,000 people. We hope that it will go even larger than that. Remarkably enough, it's still the only project in the world that has approval to put genes, traits, and environmental data from humans in an open-access database where there is no restriction on who can look at it and come up with innovative ways of analyzing it.

"We think that PGP is a great opportunity to find a relationship between what you inherit and your response to the environment. In other words, who is going to be susceptible to a particular infectious agent? Who is going to respond well to a vaccine? Who is going to have an autoimmune response to an infectious agent?"

BAS: Specifically, what are some of the ways the PGP may be able to aid the public?

CHURCH: Well, there are inherited diseases and environmental interaction. We think that the PGP is a great opportunity to find a relationship between what you inherit and your response to the environment. In other words, who is going to be susceptible to a particular infectious agent? Who is going to respond well to a vaccine? Who is going to have an autoimmune response to an infectious agent?

We currently have many pilot projects within the Personal Genome Project. We aren't sure that all of them will scale up to hundreds of thousands of individuals, but we hope they will. The first project, of course, is sequencing the whole genome; we're dedicated to that. We're also sequencing the immune systems of PGP volunteers as they get a series of vaccines to see how they respond to an initial new flu vaccine, then the next seasonal flu vaccine, and so on. Subsequent vaccines may have an overlap effect that boosts a response. We've followed this through about 18 months so far and

have looked at the response. The process could be beneficial for monitoring what's going through the population, how people are responding to it, and the length of their immune memory.

BAS: Do you follow the project's volunteers throughout their lives, or is this a genetic snapshot in time?

CHURCH: We're trying to do both retrospective and prospective data collection. We want to do retrospective, of course, because we can do that right away. We gather as much data as we can from their medical records and their memory. Then we follow them prospectively as far as possible. The retrospective gives us more data sooner, while the prospective will likely be more accurate. We don't feel that we have to wait for 20 years to write their story. There's a huge amount we can do with either their current data or whatever they can recall of their past.

BAS: Is the process of genome sequencing expensive?

CHURCH: The cost of sequencing has come down about a millionfold in the last five or six years. It cost $3 billion to sequence the first genome, and now we've got dozens of genomes getting down to a price somewhere in the $2,000 range. So it's affordable. Think of it this way: You could save $2,000 in health care costs over the course of an 80-year lifetime by catching problems earlier or choosing medicines wisely. Like insurance, everyone should get it even though only a few will be unlucky. And the price is still dropping.

BAS: Do you know how many scientists are contributing to the project, either crunching the data or working on sequencing the genes?

CHURCH: Our closest set of collaborators may be about 100 people worldwide. But we don't regulate who uses the project data. It's like Wikipedia, except that it's harder to manage because on Wikipedia everyone is putting their comments on one page. Many scientists download our data and go off and work on it elsewhere. The consequence of not regulating the data is that we have no idea who is using it. We monitor who is logging in. But that's just the tip of the iceberg because they can download the data and then send it to whomever they want. There are literally no restrictions.

The same thing goes for the cell lines that we collect from volunteers. We store and freeze these replicating cells to enable experimental follow-up from the computational genome analyses. Most cell line repositories have all kinds of restrictions: commercial restrictions, privacy restrictions, and so forth. Ours have no strings attached. You can obtain our cell lines, make as many copies as you want, and send them all over the world—all without keeping track of them. We want people with different backgrounds to get engaged in the project. Again, it's the same as Wikipedia in some sense. A lot of the best Wikipedia pages aren't written by the world's foremost expert on a particular subject.

BAS: What are the responsibilities of the scientists doing this work or of other actors when a genome characteristic is discovered that may demonstrate a person's predisposition toward a certain disease, for example?

CHURCH: When we started the Personal Genome Project there wasn't a national law that protected individuals from genetic discrimination by insurers or employers. But after 12 years of discussion, the Genetic Information Nondiscrimination Act was passed in 2008. It makes it illegal for insurance companies and employers to use genetic information to discriminate against an individual. It was something that many geneticists were working toward, and it changes things. It's still possible for someone to discriminate in the same sense that it's possible to rob a bank, but it's clearly a bad idea from a business sense because it's illegal and now everyone is watching.

"It's not sufficient for the professionals to have a code of conduct; we need to be watching out for amateurs, people who are up to no good, and people who are likely to cause accidents. All synthetic biologists should be under surveillance to catch bio-error and bioterror."

BAS: There are some people who feel government regulation of the biotech industry is unnecessary or superfluous. When the law was working its way through the government process, were there any groups that thought it was a bad idea?

CHURCH: There was some concern that the law might have short-term economic consequences for employers or insurers. For example, people might be tempted to falsely claim that they had experienced discrimination. But in the end, Congress decided that the benefits outweighed the risks to society. An important caveat: Congress limited the law to employment and health care insurance. So life insurance, for example, is exempt. You could imagine how a person could play the system by discovering that he has a predisposition toward a disease and then stocking up on life insurance.

BAS: What are your thoughts on do-it-yourself, or basement, biotech?

CHURCH: A lot of the do-it-yourself biology movement started from people that are involved in the Personal Genome Project. So I have to accept some responsibility.

I am concerned about people doing things in ignorance. But the main antidote to ignorance is education and providing people with compelling extracurricular activities within schools that get them turned on to science. In addition, we need better surveillance. I've been an advocate for surveillance for a long time. It's not sufficient for the professionals to have a code of conduct; we need to be watching out for amateurs, people who are up to no good, and people who are likely to cause accidents. All synthetic biologists should be under surveillance to catch bio-error and bioterror. That means

we need a computational infrastructure that tracks who is ordering what and checks it against lists of suspicious reagents and equipment. But the checking must be done by the industry. So I've been involved in starting industry associations that bring together competitive interests and get them to work together so that they share their knowledge of regulations, knowledge of select agents, and knowledge of computational algorithms, software, legal costs, and computer programming. Then surveillance happens behind a united front. The process is working quite well so far.

BAS: How does surveillance affect people who aren't academically trained or professionally a member of the biotech industry?

CHURCH: Even if you're part of the academic community, it's very hard to build your own machines, purify your own chemicals, synthesize your own DNA, put the DNA into cells, and do it in a safe manner so you don't kill yourself. If you're outside of academia, it can be even harder. You have to order at least some of the necessary items, and if you don't have approval, then red flags are raised—the goal of the surveillance movement.

BAS: Do you foresee a situation in which profit might get in the way of voluntary safety regulations?

CHURCH: There are many ways that the social fabric can reinforce positive behavior. People serving on boards of biotech firms, such as myself, could say, "Do the right thing." There also could be a boycott. That hasn't happened yet, but if there were one or two companies that aren't following best practices, a big scientific society could say they aren't going to buy DNA from them. After all of this, the government can come in and add its weight to the "best practices" by creating an international agreement to minimize "escapees."

BAS: So government regulation is last?

CHURCH: That's often the way it works. I would say we end up regulating the right way: Start out with an academic idea, allow it to move into industry, then into customer-based activism that reinforces the need for companies to do things the right way. After this community-level regulation is in place, then the national governments and United Nations can take action at a state or global level. I've spoken with both Secretaries-General Kofi Annan and Ban Ki-moon on this subject. The United Nations is ready to encourage biotech globally and to do so responsibly.

BAS: When do you expect international action to be put in place?

CHURCH: It really could be done at any time, because there are international industry associations. But it will probably be another couple of years. Once it becomes evident that a huge fraction of our manufacturing, agriculture, medicine, and so forth is based on genetics, then there will be activity at the United Nations.

BAS: Is the future of biotech really unlimited?

CHURCH: Everything has some limits, but there's certainly reason to believe that there's going to be a lot of growth. Biology is one of the few technologies that is capable of making huge atomically precise objects. It's also capable of incredible efficiencies and complexities because we've inherited billions of years of catalysts, evolved widgets that do photosynthesis very well, for example, and ways to manipulate polymers. There's going to be a lot of growth in the energy field; chemicals are going to be produced biochemically. We'll be making electronic parts from biology. This is a little forward looking, but I think it's pretty amazingly unlimited.

BAS: Looking forward, is there a specific disease or trait that you're interested in pursuing after PGP?

CHURCH: In a way, I'm interested in all diseases and traits, not one exclusively. My group tries to develop basic technology that a scientist can use for almost anything—not even limited to biology, much less to one disease. These are basics like being able to read and write the DNA. We've been working on bringing down the cost of these processes and, therefore, the cost of reading and writing cells and organisms—all to make a variety of applications more efficient for scientists and manufacturers around the world. My group tries to be an enabler, opening doors for people to do specific work in the field. ■

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