Dr. George Church, a molecular geneticist at Harvard Medical School with joint appointments at Harvard and MIT, is an internationally recognized leader in the field of DNA research. He helped develop the first direct genomic sequencing method and the Human Genome Project in 1984.

Dr. Christine Marshall-Walker is an instructor in biology at Phillips Academy. She holds a PhD in neurobiology and behavior from Columbia University and joined the PA faculty in 2008 after a post-doctoral research fellowship at Harvard Medical School. She teaches an independent research course in molecular genetics.

George Church '72 Is Making the Future

Q&A with Christine Marshall-Walker

Christine Marshall-Walker: George, you've approached some of the most daunting biological challenges out there: solving nucleic acid structures, automating DNA sequencing, engineering DNA microarrays. Each of these achievements, in its own right, has revolutionized our ability to navigate the natural world.

George Church: Mm-hmm.

CMW: And now you're focusing a lot of effort on synthetic biology. It's work that is getting out there in the press. At the same time, most people don't understand what synthetic biology is. It's still a relatively new concept. Could you explain what we mean by "synthetic biology" and how it might be used?

GC: A lot of what my group does is technology development. And some of what we do is work to bring down the price.

CMW: You're talking about the $1,000 genome sequence?

GC: Yes. I think average people know that the price for electronics, for example, has come down significantly during their lifetime, even if they're young. And that's about a factor of 1.5 per year, multiplicative. So the result is this exponentially decreasing cost.

I've been involved in applying computers to automating biology, both reading and writing DNA. You can think of synthetic biology as writing biology. We've got enough confidence in our ability to read it that we can start writing it more and more. And we've brought down both costs even faster than 1.5-fold per year. More like 10-fold per year—a million-fold in six or seven years, which is really, really fast. If I brought down the cost of your cell phone by, say, a million-fold, you probably wouldn't buy a million cell phones. I would hope not, anyway! What's interesting is that we've brought down the price of reading genomes by a million-fold, and the main complaint we hear is, "We want more." It seems to be, so far, a truly inexhaustible demand, an insatiable appetite for this sort of thing. To answer your second question, what can't we do with biology, really?

CMW: You've harnessed the power of bacteria to produce compounds in high volumes very cheaply. Do you see this as revolutionizing the pharmaceutical industry?

GC: I've started two companies that make commodity chemicals; fuels, detergents, that sort of thing. They have attracted customers like Proctor and Gamble, and Chevron, and so forth. And those are entirely biological processes. Basically, we take photons and carbon dioxide, which most people consider a waste product in the atmosphere, and turn them into gasoline, diesel, and detergents. Hopefully, that will result in more efficient farms, and being able to produce things on land that's currently not suitable for farming. Desert land and marginal, uneven land could be used in these photosynthetic processes.

CMW: Is there a timeline for that?

GC: We've been working on these since about 2007. And they now have reached the pilot plant phase, which means they're producing thousands of liters a day. And then the next phase is just to scale up, until they're making billions of liters.

CMW: The words, "synthetic biology" or "genetically modified organism" can induce anxiety in many. There is a fair amount of generalized fear and mistrust of those biotechnologies, as well as the people who are pushing them forward. And the popular media does little to quell those fears. What would you say to someone who has reservations about your work? How might *you* explain the overall benefits relative to the inevitable associated risks?

GC: Well, there are three kinds of scientists. The first are those who simply don't worry. They say, "I'm just doing my job. I'm not going to worry about this stuff." There's another set that says, "There are no risks." And then there's my category, which tries to alert people to risks in advance. I try to not underplay it too much. I don't want people to be anxious, but I *do* want them to be concerned. We've published some papers on what some of the concerns are, having to do with pollution, gene transfer into the environment, and bioterrorism. But with each of those, we've also considered potential solutions.

In terms of foods, most countries of the world can't afford the luxury of worrying about whether it's genetic-modified or not. A lot of the people who won't

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eat it in modified food will, however, inject it into their body. We also use genetic-modified organisms to make drugs like insulin. I don't think that's a contradiction. They're worried about escape into the environment. But the processes by which you make drugs for injection tend to be much more constrained physically. So they have some good points there. And part of our research is actually aimed at making safer genetically modified organisms. It's to decrease the likelihood that things could escape.

CMW: Like replication incompetence?

GC: Exactly. Some of the things we're working on couldn't have been done when Monsanto came out with its first big thing. We've evolved much more sophisticated technology. We want to improve the nutritional properties, and the tastiness of foods, which was not part of the original Monsanto goal. It was mostly about herbicides. And, you know, that's just an environmental red flag. How do you know the herbicide resistance isn't going to escape? How do you know the kind of factory farming that comes along with herbicides is really the best strategy?

I'm much more interested in nuanced approaches, like using perennials to fight erosion, reducing fertilization, and ultimately reducing herbicide use. I think the second round of genetically modified organisms will, hopefully, be a lot more thoughtful, and attractive to everybody. Time will tell.

CMW: Hmm… I wonder if we could switch gears and talk a bit about Andover. What type of kid were you when you started at PA?

GC: I could go on for hours about PA. It was a formative time. It was just like the scene in *The Wizard of Oz* where it changed from black and white to color. I mean, literally I was starved, in so many ways—socially, athletically, academically, in almost every way imaginable. And then I went to Andover, and it just totally changed overnight. I was very cerebral before I went to Andover, and extraordinarily shy.

CMW: How did your perception of yourself change?

GC: I did three different sports and was on two varsity teams. I went nuts on extracurriculars, like photography, cycling, and greenhouse. I just realized there are no limits to what you can do.

CMW: Can you tell us the story about the computer in the basement?

GC: As a very young kid I got fascinated by bugs, biology, and computers. I was exposed to computers at the World's Fair in New York in 1965. Even before that, it was just irresistible attraction. I tried to build some of my own, and they were pathetic. You know, I built a little analog computer, a little mechanical computer. And so when I came to Andover I said, "Oh, Andover must have a computer somewhere, right?" Finally somebody said, "Yeah, I think there's one in the basement of Morse Hall." It was a scary basement, you know? There wasn't good lighting, no furniture. There was one Teletype in there, like the ones that they used in newsrooms. And so I kneeled in front of the Teletype. And I just started typing stuff into it. I typed, "How do I work this thing?" And it came back with the answer, "What?" I said, "Wow. Artificial intelligence!" Actually, it was a pretty advanced system, because most of the other people in the world were doing punch cards. So this was actually kind of communicating in my language. But after ten more questions I realized its only answer was, "What?" [Laughs]

We were hooked up to a GE 635 at Dartmouth, where they had a project to try to test the idea of time-sharing, where they would connect a computer to a Teletype at quite a distance, via a telephone line. It was the beginning of a network. This was before the Internet, before even Arpanet. These guys at Dartmouth were just visionary.

Another big impact was my ninth grade math professor, Creighton Bedford. I was placed into "baby math," which bugged me. I was doing my best to be a good student, but the teacher recog-

Opposite page: Church shows Marshall-Walker models of tRNA and ribosomes that he made in his lab using 3D printing. He solved the structure for tRNA in the 1970s.

Left: Graduate student technicians in Church's Harvard Medical School lab check sizes of some DNA fragments.

nized [my boredom]. So about halfway through the year he said, "I think you should just take off and do whatever you want." [Laughs] "You don't have to show up for the rest of the year." But he gave me one of his books, and he said, "Here's a book that I did my Master's on." It was a very advanced book. "Just see what you can do with it." And that was it. He didn't lead me through. It turns out it was on linear algebra. But I didn't know that I wasn't supposed to be able to handle it. So I did it. I programmed it into the computer. I translated the math into the computer, and I wrote a linear algebra program that later I would use with similar concepts. I still use it in my lab today.

I had him again as a professor in eleventh grade, and the same thing happened. He just said, "Why don't you take some time off?" So I spent that year doing calculus. And, again, I'd program it into the computer. This time I was aping some seniors at MIT who had programmed a computer to do calculus, formal calculus. So if I said, "What's the derivative of X squared?" it would come out 2X as the answer. It's all symbolic. So it actually had to really understand what I was saying in symbols. And I thought that was kind of cool. I actually pulled that off in the time my math professor freed up for me. This was like cutting edge research at MIT at the time.

CMW: You were given an unbelievable amount of flexibility, at a pretty critical time in your academic development.

GC: It was amazing, but I don't think this was a school policy.

CMW: Would you say that's something that you still love about your research? The academic freedom?

GC: I try to pass this on to the next generation. If you're not making mistakes, you're not trying. If you're getting straight As, you're not trying. You should follow your dreams. They're not such bad things. They're not something to be scared of. And if you dream big dreams, you're probably going to get some distance into your dreams, whatever they are. And if they're little bitty dreams, that's where you're going to end up. But you need the right environment, where everybody around you is taking risks—a fair number are failing and a fair number are succeeding wildly. And both of those are acceptable outcomes.

CMW: That's such a great message for our students. As you look at your work, as a body of work, what gives you the most satisfaction so far?

GC: Well, there are a bunch of things. I've trained a lot of wonderful people. A lot of satisfaction comes from that. We've created technologies that are in use in the real world. I'd always dreamed that that would be the case. What I really want to do is walk into the grocery store and see something I made. I haven't quite gotten to that point yet. [Laughs] Or a filling station. We'll get there, you know. Hopefully, something from LS9 and Proctor and Gamble will be at the grocery store and the gas station.

CMW: Something that will make our lives better?

GC: Maybe get us out of this economic depression that we're in, or at a minimum, allow us to survive as a species. If you have the perception that we've discovered everything we're going to discover, that we've invented everything we're going to invent, or that we've exhausted all of the natural resources we have, then basically, you feel like a retiree and we should start digging our graves.

From my perspective everything that surrounds me is exponential growth curves. The computer industry's still getting better—at 1.5 fold per year. DNA is getting better at a faster clip—somewhere between 1.5 and 10—and that results in radical change, year after year. And for some reason or other, you get just a few layers out from where my lab is, and you don't see this anymore.