

Profile of George M. Church

George Church wants to rewrite the genetic code. A virtual manual of protein synthesis, the code reflects how organisms interpret strings of letters in the genome into strings of amino acids in proteins. Exploiting the code's redundancy, Church, a recently elected member of the National Academy of Sciences and a professor of genetics at Harvard Medical School, hopes to alter the genetic code of bacteria to enable the production of proteins with unnatural amino acids, a step toward radical genome tailoring that could someday lead to a range of applications in medicine and microbiology. To that end, Church's graduate student, Marc Lajoie, peers into a laboratory plate containing bacterial cells, illuminated by a light box in the glass-walled genetics department. As the cells glow lime-green, Lajoie smiles, pleased that his attempt to rid the code of a redundant instruction is well under way. By deleting the instruction, a triplet of nucleotide bases that normally serves as a stop sign for protein synthesis, from the bacterial genome, Church and his team can repurpose the so-called "stop codon." They can reinsert the codon into bacteria as an instruction to incorporate a synthetic amino acid into proteins, thus helping engineer superorganisms. Such organisms could help produce improved drugs for diseases and fend off viruses that plague vaccine manufacturing plants. With his talent for decoding and reconstituting genomes—the genetics equivalent of deconstruction—Church has helped redefine the field of recombinant DNA technology.

Born on MacDill Air Force Base near Tampa, Florida, Church spent a childhood marked by interests in mathematics, mineralogy, and entomology. "When I was 8, I was curious about insect metamorphosis and would rush to the library to learn about metamorphic processes I had observed," he recalls. Before long, his scientific curiosity extended to computers, years before personal computers became a prized novelty.

Church's well-recognized gift for invention owes a debt to his childhood obsession with computers; frustrated by his inability to acquire a personal computer, he fashioned simple yet functional homebrew computers at the age of 10. But it was not until he left home three years later to attend Philips Academy, a preparatory school in Andover, Massachusetts, that he found an outlet for the technical wizardry that has come to define his career in genetics. At Philips Academy, Church spent hours in a basement computer laboratory mastering then-novel programming lan-



Image courtesy of Shawn Douglas.

George M. Church.

guages, such as Basic, Lisp, and Fortran. When it came time to enroll in college, Church left Andover for the warmth of North Carolina and the academic reputation of Duke University, where he blazed through a bachelor's program in zoology and chemistry in 2 years.

Church's entry into the world of laboratory science began at Duke, where he worked as a research assistant in X-ray crystallography, a field that combined his interests in computers and biology. "It was one of the few fields in biology with any automation that had a solid physical theory behind it and used computers extensively," Church recalls. Working on a mainframe computer shared by many universities, Church and his coworkers used crystallography to unravel structural details of the interaction between DNA and proteins, later compiling their findings into his first peer-reviewed publication, a 1977 article in PNAS (1). Soon, Church left Duke to pursue a doctoral degree at Harvard University.

Tinker, Tailor, Polymath

If there is a single theme that unites Church's work in genetics over his four-decade career, it is the pursuit of technologies that have pushed the frontiers of biology ever farther. During graduate work at Duke on the link between the sequence of nucleotide bases in RNA molecules and their 3D structure, Church realized that advances in molecular biology depend, in large measure, on the ability to sequence DNA rapidly and in-

expensively, a goal that remained distant during the late 1970s. Toward that goal, Church began doctoral work with Harvard University molecular biologist Walter Gilbert, who went on to win the 1980 Nobel Prize in chemistry for his invention of nucleic acid sequencing techniques.

One part of Church's graduate work helped establish the regulatory function of introns—DNA sequences interspersed between protein-coding genes that were once believed to lack function—in the genomes of mitochondria, the energy factories of cells. Another project led to a 1984 PNAS article on a method to determine unique DNA sequences from mouse genomes (2). The method circumvented the status quo, which involved cloning genes piecemeal into bacterial cells to sequence them. Instead, Church demonstrated how nucleic acid probes could be used to decode genomes immobilized on solid supports, paving the way for next-generation sequencing. After obtaining his doctoral degree in 1984, Church continued to explore ways of speeding up DNA sequencing.

One outcome of those efforts was "multiplex" DNA sequencing, a term of art borrowed from the electronics industry, where engineers had devised ways to make multiple signals flow through a wire at the same time. By analogy, Church's technique allowed biologists to simultaneously sequence mixtures of DNA strands tagged with different chemicals, jump-starting the genomics era.

A triumph of technology, multiplex DNA sequencing contributed to the Human Genome Project, the outcome of a little-known gathering in Alta, Utah, of a dozen scientists convened by the US Department of Energy in the winter of 1984. "The meeting's original goal was to estimate mutation rates in populations exposed to radiation," Church recalls. But the group soon realized that the goal was too ambitious for the technology of the time. "We instead suggested sequencing the genome of one individual as a step toward estimating mutation rates. By the end of the meeting, we had a coherent enough case that the head of the DOE division started writing checks to a handful of labs for genome sequencing," he adds. Thanks to this serendipitous meeting, the DOE emerged as a frontrunner in genome sequencing, and when the National Institutes of Health eventually

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launched the project in 1990, Church became one of its architects, helping establish the first of its genome sequencing centers. Nearly a decade later, Church further refined his sequencing technique, cloning and amplifying a set of single DNA molecules on a glass slide (3).

Following a six-month stint in 1984 at the Massachusetts-based biotechnology firm Biogen Research Corporation, where Gilbert had moved most of his laboratory, Church set out with his girlfriend to California, where the two settled into different laboratories for postdoctoral research. Church pursued genomics research in the laboratory of University of California, San Francisco stem cell biologist Gail Martin, a pioneer in embryonic stem cell technology.

Dial-a-Genome

It is a testament to Church's technical acumen that despite a short-lived postdoctoral sojourn with a slim publication record, he was offered an assistant professorship in genetics at Harvard University in 1986. At Harvard, he continued to work on DNA sequencing, his efforts culminating in a 1999 report in *Nucleic Acids Research* on the refinement of multiplex sequencing (3). Measured on its own merit, the report was a minor advance, but 6 years later, it led to a breakthrough published in *Science* that foreshadowed the advent of next-generation DNA sequencing (4). In that paper, Church described how a common, inexpensive fluorescence microscope could be outfitted to double as an automated sequencer that could decode the genome of an *Escherichia coli* bacterium, a genetic engineering workhorse, with less than one error per million reads of nucleotide bases (4). What is more, the paper demonstrated that millions of sequences could be read in a single run; the repurposed Nikon microscope soon became the forerunner of Church's second-generation sequencer, the Polonator G.007, developed in partnership with scientific equipment manufacturers Danaher and ABI. Until then, research teams racing toward the goals of the Human Genome Project had largely relied on instruments based on a technique called capillary sequencing. Church's findings meant that genome sequencing could be vastly sped up and its cost greatly reduced. In the wake of the publication of the 2005 *Science* article (4), the cost of sequencing began to plummet. "The price started coming down at a rate that was fast even by Silicon Valley standards; instead of 1.5-fold per year, the price dropped 10-fold per year," Church says.

What began as an effort to automate a method in molecular biology soon grew into a project of titanic scale, one that has

begun to transform medicine. In early 2006, Church launched the Personal Genome Project, aimed at first at sequencing the genomes of 10 volunteers, including himself and Harvard University psychologist Steven Pinker, in hopes of correlating the information mined from DNA with actual human traits, ranging from eye color to proneness to cancer. By bridging genotypes with phenotypes for tens of thousands of individuals, Church hopes to build a public database from which meaningful links might be drawn between genetic scripts and the fates they encode.

With his trademark knack for streamlining unwieldy projects, Church laid out a plan to achieve his goal: Recruit volunteers with a demonstrable understanding of basic genetics, obtain their informed consent, sequence their genomes, record a range of their health-related traits, crunch the numbers to wrest meaningful links, and share the data openly. By then, Church had refined his sequencing technology to the point where speed soared and cost dropped exponentially. Today, the cost of sequencing a human genome hovers tantalizingly close to the long-sought goal of \$1,000. "By my reckoning, for most people in industrialized nations with relatively good-quality medical care, whole-genome sequence information could already be a part of the standard medical record," Church says. "The medical community has been slow to incorporate many components of the digital revolution, and this is one of them," he adds.

Church's pioneering efforts in genome sequencing led to the mushrooming of private enterprises, including California-based 23andMe and Navigenics, Boston-based Knome, and Iceland-based deCode Genetics, that provide people with information regarding potential risks for certain medical conditions based on their genome sequences, vaulting genomics into the public domain. But those strides in personal genomics have understandably been met with guarded optimism. Because some genetic associations do not directly translate into clinically meaningful measures of disease risk thanks to the often-multifactorial nature of disease and complex environmental influences, personal genomic data is not always actionable even though it represents a wealth of information that might help basic researchers gain insights into human diseases. Other questions, related to privacy and genetic discrimination, have led personal genomics into murky terrain.

Faced with these valid concerns, Church takes the long view: "The standard practice in biomedical research is to obtain informed consent from patients and

promise to de-identify their private information. That promise is not always easy to keep." Thus, he opted to recruit people who were willing to have their information in the public domain, initially predicting he would have few, if any, volunteers. Today, the project boasts more than 16,000 participants, emboldened partly by the passage of the 2008 federal Genetic Information Non-discrimination Act, which prohibits US employers and insurance firms from discrimination based on genetic information. The same year, *Time* magazine epitomized personal genetic testing as the "invention of the year," lending the project the luster of public support. In October 2011, *Nature* published the results of a survey of more than 1,500 readers, most of whom responded that they would have "their genome sequenced or analyzed if the opportunity arose," a sign that the effort continues to gain favor (5). As for the clinical utility of personal genomics, Church maintains that its participatory nature holds promise for individual clinical decisions and for scientific advancements. "The multifactorial nature of diseases has been addressed for decades by focusing on the most predictable and actionable traits. Today, this approach extends to 2,400 genetic diseases. What we need are better software and educational tools to teach people to identify information that is predictive and actionable," he says.

The Code Fixer

Just as he helped turn the marginal into the mainstream with his technology to read DNA sequences rapidly, Church has brought his expertise to bear on writing novel DNA sequences. Church and others are now attempting to synthesize DNA scripts that could someday be used to engineer bacteria with useful abilities, reprogram cellular development, create tissues in the laboratory, and produce vaccines and drugs for diseases, to name a few applications of synthetic biology, a moniker for a rarefied form of recombinant DNA technology in which genetic modules from disparate sources are cemented together like bricks in a building to endow organisms with desirable traits. To that end, Church has championed a group of Boston-based do-it-yourself amateur biologists, who have performed feats of genetic engineering using tools available to garage scientists. Supported by a group of researchers from Harvard and elsewhere, participants in the DIYbio movement launched community workspaces in Cambridge, Massachusetts and Brooklyn, New York, where citizen scientists practice crowd-sourced genetic engineering.

Synthetic biology gained ground in 2009 when Church developed multiplex automated genome engineering, a method to mint a billion genomes a day. Before long, molecular biologist Craig Venter stitched together a synthetic version of a bacterial genome and inserted it into a cell whose genome had been removed, an achievement hailed as a fine approximation of the creation of life in the laboratory.

Two years later, Church gave the field a further boost by demonstrating that the genetic code of *E. coli* bacteria can be manipulated with unprecedented precision. Together with then-postdoctoral fellow Farren Isaacs, Church removed the amber stop codon, a triplet of nucleotide bases that normally serves as a termination signal for bacterial protein synthesis, from each of the 314 sites in which it occurs in the bacterial genome (6). Known as a massively parallel intervention, the wholesale deletion of the stop codons means that they can be returned later to the bacterial genome and

repurposed to encode novel entities, such as amino acids not naturally found in bacterial proteins. Such an orchestrated modification of extant genomic templates, Church's favored route in synthetic biology, can help create organisms with novel functions relatively quickly. "Our goal in this case was to change the genetic code to make a bacterial cell resistant to multiple viruses for use in industrial microbiology; changing the genome radically gets you to a range of practical products," Church says.

Those products are already underway. In June 2010, the California-based biotechnology firm LS9, founded by Church, won a Presidential Green Chemistry Award for engineering bacteria to convert sugar into a diesel-like mix of hydrocarbons, paving the way for the large-scale production of alternative fuel. In October 2011, the Massachusetts-based biotechnology firm Joule, another of Church's endeavors, won the *Wall Street Journal* Technology Innovation

Award for engineering photosynthetic ability into bacteria, enabling them to convert sunlight, carbon dioxide, and nonpotable water into renewable fuel. "Both companies are now producing alkanes in pilot plants in Texas, New Mexico, and Florida. Alkanes, unlike ethanol, are compatible with automobile engines and meet the industry standards for diesel for cars, jet fuel, etcetera," he says.

With efforts that have spanned many intellectual latitudes, Church continues to push the boundaries of biology with the force of technology. To the inevitable question, "How will advances in genomics transform clinical practice in the next 5 years?" he responds: "The exponential advances in technology mean 5 years is actually quite a long time. At the very least, I think we will have much more do-it-yourself biology, similar to the homebrew electronics that Steven Jobs and Steve Wozniak made famous."

Prashant Nair, *Science Writer*

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