

Meet Exhibit I

George Church has made a name for himself as an 'information exhibitionist'. **Erika Check Hayden** explores how the technological sage is turning his gaze to the next horizon — you.



One day in the 1980s, while a graduate student at Harvard University, George Church decided to change the way he saw the world. He started with simple tools — scissors, cardboard, and sticky tape — and he ended up working at his bench with a pair of homemade blinkers affixed to his temples. Asked about the nearly forgotten episode, an older, wiser, now-tenured Church chuckles at his younger self, but he still defends the stunt's essential point. "I was making a statement," he says, taking a break from running one of the largest, most eclectic biology labs in the United States. "Sometimes scientists put on blinders and don't see the big picture."

Performance art's loss was science's gain, but Church has never lost sight of the point he was trying to make that day — indeed, he has spent his career scanning the horizon for the new, the different and the maybe-just-possible. As biology has become ever more specialized, Church has continued to widen the scope of his work. Yet he brings to each new project a depth and intensity of vision that suggests he knows when to put the blinkers on as well as when to take them off.

Church spends most of his time dreaming up far-fetched ideas and doggedly pursuing them. His thoughts on DNA sequencing, first formulated decades ago, led to some of the high-output sequencing techniques now revolutionizing biology. His inquiries have led him to jointly found Codon Devices in Cambridge, Massachusetts, one of the first synthetic-biology firms. He has also founded two other companies, LS9 near San Francisco,

California, which makes biofuels, and Knome in Cambridge, Massachusetts, which sells personal-genome sequencing services.

Some of Church's ideas don't work out. But many do. And it's his willingness to take risks that colleagues say is his biggest contribution to science. "He has a certain breadth to his knowledge," says Robert Weiss, a genomics scientist at the University of Utah in Salt Lake City, who has known Church since the 1980s. "He can cross disciplines successfully and integrate ideas to move a field forward, and he has done that repeatedly."

Open access

A tall and soft-spoken vegan whose salt-and-pepper beard lends him the aura of a mountain sage, Church's placid manner conceals a tendency to go to extremes to defend his convictions. Last year, when former Massachusetts Institute of Technology (MIT) biologist James Sherley felt that he was denied tenure due to racial discrimination, Church was among a handful of scientists who protested outside the MIT president's office in Cambridge. And Church has posted his birth date, mother's maiden name and signature on his web page to make the point that information wants to — and should be — free. His wife convinced him to remove his social security number, but other information, such as a map of the route he walks each morning to work, stayed up. Fritz Roth, a former student who now runs his own lab at Harvard Medical School in Boston, Massachusetts, calls

him "the information exhibitionist".

The title certainly seems apt for a current venture: the Personal Genome Project. Church has already begun sequencing portions of the genomes of ten volunteers: himself, Sherley, entrepreneur and futurist Esther Dyson and seven other individuals, six of whom have also revealed their identities. But unlike other large individual sequencing projects under way, such as the Chinese Yanhuang Project and the International 1,000 Genomes Project, Church will also collect information about his study subjects' 'phenotypes' — traits such as eye colour, height and medical conditions — and study how genes contribute to these phenotypes. Then he will publicly release the data in stages and study how this affects the participants, the practice of

medicine, and society at large.

Along the way, Church plans to continue refining DNA sequencing and analysis in the hope of attracting more volunteers — perhaps thousands or millions. The project is a culmination of everything that preoccupies Church: technology development, large-scale biology, data transparency and the public interpretation of science. Society at large, he says, doesn't really know how to handle most genetic information. "I'm trying to make sure that there's enough information at a low enough risk so that all of the stakeholders in this technology, now or in the near future, will have a test set to work with," Church says.

Church's project has roots going back decades.

**"Sometimes scientists put on blinders and don't see the big picture."
— George Church**

S. OGDEN

Church had had an aptitude for engineering even as a child. Yet he was inspired to apply that talent to biology by his second stepfather, a doctor Church refers to as his “third father”. “I figured that everything in his black bag, such as antibiotics, and in his office, such as ultrasound, was invented by someone — maybe like me,” he says. In his twenties, Church typed all the known nucleic acid sequences into a computer in one afternoon to make predictions about how corresponding RNA sequences might fold — an exercise that made him wish it were possible to know the DNA sequence of every person on Earth.

In 1976, he was kicked out of the biochemistry department of Duke University in Durham, North Carolina — he thought his time in graduate school was better spent publishing papers on RNA folding than on attending class — and found his feet at Harvard University in 1977. There, he sought out a like-minded mentor in Walter Gilbert, a biochemist who had developed one of the two standard methods for sequencing DNA. “There just weren’t a lot of engineers in biology back then, and his lab seemed like an oasis where you could do technology and get away with it,” Church says.

In 1980, Gilbert’s sequencing work earned him the Nobel Prize in Chemistry, which he shared with Paul Berg and Frederick Sanger.

Sanger had developed the other foundational DNA sequencing strategy, which was — and still is — the basis for most sequencing projects. Not long afterwards, Church and Gilbert joined a series of discussions on the possibility of a Human Genome Project, an audacious plan at the time, considering not even a simple micro-organism had been sequenced.

You get what you pay for

Sequencing was a labour-intensive, error-prone process that cost US\$10 per base — which meant that sequencing the whole human genome would cost \$30 billion. The process needed to become a lot cheaper and faster, and the question was how — and if — that could happen. Church thought that the project should aim big. He advocated a strategy called ‘multiplex’ DNA analysis, one that he had developed and refined, partly with Gilbert’s help. The strategy involved anchoring pooled DNA to a solid base, then exposing the DNA to a series of reagents to produce image readouts, all on the same machine — an approach that Church thought should save

time, reagents, human effort, and money.

Setting up his first lab in 1986, Church worked to develop his concept. He was up against tight competition. Other labs were working on multiplexing, and the company PerkinElmer, now based in Waltham, Massachusetts, was investing industrial dollars on a sequencing machine developed by Applied Biosystems in Foster City, California. The machine improved and automated the traditional Sanger sequencing method.

In the mid-1990s, the US Department of Energy ran a comparison between the Applied Biosystems machines and other sequencing

notes, pointing out that another Harvard lab is still working on the method.

As the lab grew, Church gained a reputation for his cutting-edge ideas and eccentric personality. There was a rumour circulating around his department that for a few years as a graduate student, Church had eaten nothing except a nutrient broth he ordered from a laboratory reagent supplier. He confirmed it with a post on his web page. He got the idea after participating in an experiment on leucine deficiency for which he was forced to subsist on a “semi-synthetic diet” of “cookie-like and jello-like ‘foods’”. “He smelled like yeast extract the whole time,” remembers one scientist who knew him then.

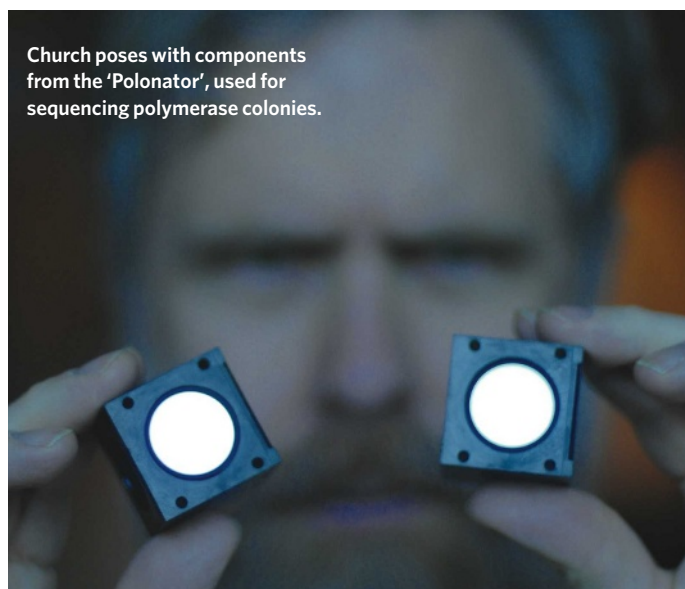
People magnet

Church’s reputation became a magnet for equally unorthodox students. Robi Mitra, an electrical engineer looking to join the lab in 1997, recalls what Church told him: “He said, ‘I like to believe that we get up every day and believe what we do is the most important thing we can be doing, and I’m looking for other people who believe that too.’” The pep talk worked: Mitra signed up, and began working on what is Church’s current concept for multiplex sequencing, dubbed ‘polony’ sequencing. In the polony technique, DNA molecules tethered to beads are amplified and processed in discrete units, or ‘polymer-

ase colonies’ — hence the nickname polony. Separating the DNA into individual colonies makes it much easier to analyse the results of the sequencing reactions.

In 1999, Mitra and Church published the proof of concept that the polony technology worked (R. Mitra & G. M. Church. *Nucleic Acids Res.* 27, e34, 1–6; 1999). Parts of the technology were licensed to the biotechnology company Agencourt in Beverly, Massachusetts. In 2006, Applied Biosystems — the very company that had beat Church’s bid to power the human genome project — acquired part of Agencourt, and took out a licence on Church’s polony technology. Last year, Applied Biosystems began selling the ‘SOLiD’ system — a machine that uses some of the same concepts as Church’s sequencing technology. It can sequence the amount of DNA contained in the human genome in less than a month.

The SOLiD is only one of the ‘next-generation’ sequencers now available, other are made by 454 Life Sciences in Branford, Connecticut, and Illumina in San Diego, California, which have also licensed inventions from Church’s

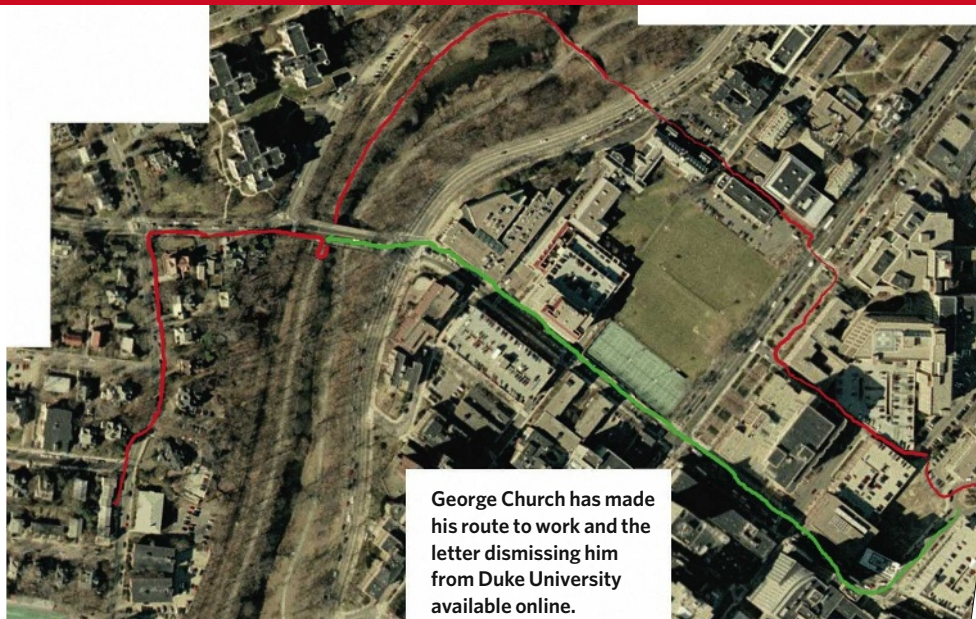


Church poses with components from the ‘Polonator’, used for sequencing polymerase colonies.

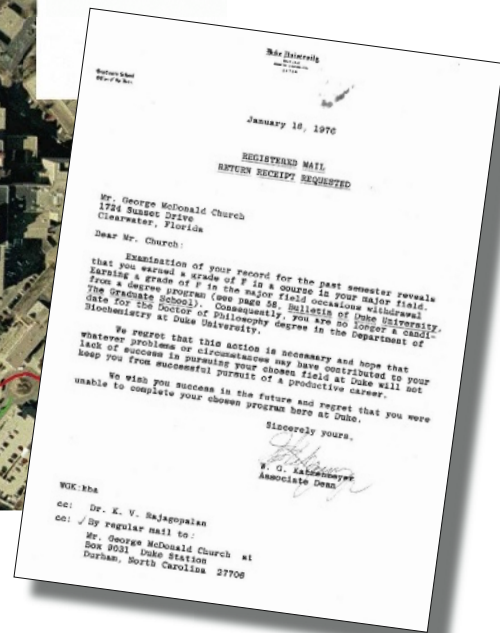
techniques, including Church’s. Applied Biosystems won. Its sequencers were able to deliver finished genomes faster than multiplexing, and the company’s machines became the workhorse of the Human Genome Project for the next decade.

Church was disappointed but he didn’t give up, predicting that Applied Biosystems’ sequencer would never be cheap enough for mass use. “You tend to get what you ask for, and if you ask for a genome for \$3 billion it will be very hard to do a thousand genomes with the technology that can do that,” Church says.

Plugging away throughout the 1990s, Church deployed some outlandish ideas. One project, for example, aimed to sequence DNA by passing it through a membrane protein channel while measuring changes in the flow of ions caused by differences in the size and charge of individual DNA bases. “Where many people would say this is practically not feasible, he would say, ‘If you can’t tell me what law of thermodynamics it violates, I don’t see why we can’t do it,’” says Roth, who took on the project as a student. “I wouldn’t say it failed utterly,” he



George Church has made his route to work and the letter dismissing him from Duke University available online.



G. CHURCH

lab in the past. So it seems that Church was eventually proven right: a single human genome is old news, and the scientific world is abuzz with projects to sequence more.

In Church's Personal Genome Project, which began last year, his lab will sequence 1% of each participant's genome, mostly protein-coding regions. Church has also sent blood cells from each participant to a New Jersey company that will 'immortalize' the cells, turning them into stable lines for further study. The participants agreed to give extensive information related to appearance and mental and physical health. Last year, they met to discuss questions such as what to tell their families or the press — something that will become an issue when Church begins releasing this information to the world.

Information release

The decision to release data — to participants and the public — is the most controversial aspect. The community norm for genetics studies, and the policy set by funding agencies such as the National Institutes of Health, is that study participants' identities must be kept private. Genetic information may be distributed to researchers, but it must first be 'delinked' from information that could identify its source.

Church calls this a futile and counterproductive policy. As the amount of publicly available information about us increases, so does the likelihood that our identities can be linked to that information — whether or not we want it to be. Meanwhile, scientists can't predict what genetic information will be linked to any trait, so it makes more sense to provide a completely unbiased set of information. "When you walk into a doctor's office you don't have a chador covering your face or a voice-masking device. You walk in freely exposing yourself so that every aspect of your being can be inspected, and that helps physicians make a diagnosis," Church

"If you can't tell me what law of thermodynamics it violates, I don't see why we can't do it."
— George Church

argues. "De-identification creates a research tool that is impoverished relative to what a physician would see."

The difference, however, is that once a doctor makes a diagnosis, the patient controls it, deciding who to tell and what to say. If a person's genetic predisposition to, say, Alzheimer's disease is available to anyone, he or she could face serious consequences — the loss of a job or health insurance, or distressing reactions from friends and family.

Church says that he has already solicited a lot of advice about his project. And he argues that as genomic information becomes more available — as is already happening with the debut of personal genomics services offered by companies such as deCODE Genetics in Reykjavik, Iceland; 23andme (which Church advises) in Mountain View, California; and Navigenics in Redwood Shores, California — people may become less fearful of sharing genetic information with others. If everyone finds that he or she carries some genetic risk, as is likely to be the case, people may not think others' risks are such a big deal.

Scientists can do a lot to minimize the blowback from genetic disclosure. For an example,

Church points to the insurance industry. "They're trying to reduce costs, and sometimes they can reduce costs in a way that benefits both the patient and them," Church says. "It's up to researchers and insurance companies and, to some extent, patient advocacy groups, to be creative and figure out where those win-win situations are."

Church thinks carefully about the societal implications of his work and believes that openness can head off disaster. In 2004, for instance, he helped set up an international effort to head off malevolent uses of synthetic biology. But Church says that there should be restrictions on, or at least monitoring of, technologies that allow individual scientists to

synthesize DNA, to minimize the threat that someone could cook up their own deadly microbes.

In fact, Church's willingness to engage those outside the scientific community is rare among scientists. It is tempting to speculate that his willingness to deal with outsiders stems from his experience of going against the scientific grain. Although a number of luminaries in the field acknowledge his intelligence and abundance of ideas, several, who did not wish to be quoted for this story, say that they have been annoyed by his stubbornness — his refusal to go along with the 'community consensus', his unwillingness to be swayed from his convictions by other scientists' arguments, and his insistence on pursuing ideas that seem unworkable or impractical. Yet it is also true that courtesy is one of his defining traits. Because he doesn't engage in the sort of public sniping that has marked high-profile endeavours such as the Human Genome Project, many who disagree with Church still have tremendous respect for him.

And Church's critics have to admit, he is remarkably persistent. Few would have pursued a project such as multiplexing for decades after such a discouraging start. Now, Church's determination has spawned a project that is moving genomics out of labs and into regular people's lives.

Church's singular focus is remarkable for someone who has such a broad vision, as he himself admits. Thinking back on his graduate school stunt with homemade blinkers, Church jokes that he has always had a touch of the scientific attention deficit disorder (ADD). "Even back then, I was entirely too broad for my own good," Church says. "But it seems as if society likes my flavour of ADD."

Erika Check Hayden writes for Nature from San Francisco. See Editorial, page 745.

G. CHURCH