CREDIT: MARIE WU

NEWS

The Life Hacker

He is a pioneer of genome sequencing, but Harvard University's George Church wants to do more than read DNA. He is changing the genetic code itself

BOSTON—"We're going into the inner sanctum," says George Church, gliding through a series of doors and passages, waving his key card to get in. At the center of this labyrinth in Harvard University's Wyss Institute for Biologically Inspired Engineering is a tiny locked room that Church opens with an old-fashioned metal key. Inside is a device that the 57-year-old biologist invented and built with the help of a local robotics company. He calls it MAGE, and it does look slightly magical, as if the contents of a molecular biology laboratory have flown off the benches and arranged themselves into a box. The effect is enhanced as Church—nearly 2 meters tall with an impressive wizard's beard—looms over the desk-sized contraption. But the real magic comes with what MAGE does: Millions of normal *Escherichia coli* bacteria go in one end; a vast menagerie of microbes with new genomes comes out the other end. "I'm hoping this thing will be worth $200 billion," he says.

A statement like that isn't unusual for Church. It sounds brash at first, but laboratories around the world are trying to genetically alter bacteria and other kinds of cells to make industrial chemicals from biomass efficiently, and the potential payoff is huge. Church argues that MAGE, which stands for multiplex automated genome engineering, will be an indispensable tool for doing that.

In a debut of the technology several years ago, Church produced billions of different versions of the *E. coli* genome, identifying one that is five times more efficient at producing the antioxidant lycopene (*Science*, 21 August 2009, p. 928). "That was just a proof of concept," he says. Now he's setting his sights on more lucrative chemicals, such as dyes, and also on enabling MAGE to refashion nonbacterial genomes.

Synthetic biology, with its goal of reengineering cells as industrial machines, is the epitome of ambition. But even in a field of risk-takers, Church stands out. "He always talks about such wild experiments," says J. Christopher Anderson, a synthetic biologist at the University of California, Berkeley, and one of Church's collaborators. "And then he rolls them out. He actually makes some of them work."

Church's scientific risk-taking has paid off. Earlier this year, Church was elected to the U.S. National Academy of Sciences. He is one of four scientists sharing a $20 million grant from the U.S. National Institutes of Health to develop efficient ways to change the genetic makeup of stem cells as a way of treating disease. Church has also helped to create or guide more than two dozen start-up companies and generated 34 biotechnology patents himself—not to mention leading the charge in personal medicine with his Personal Genome Project, in which he and others voluntarily bared their genomes (*Science*, 21 December 2007, p. 1843).

"There are people who are good at identifying the problems for the field, and there are others who are good at doing the experiments," says Jason Chin, a molecular biologist at the University of Cambridge, U.K. Church is rare in that "he does both."

But whether Church can pull off his most ambitious experiment—reinventing the genetic code—is another question. If he succeeds, biotechnology will have a new workhorse cell. And the planet will have a novel life form.

Flunking and thriving

The faint twang in Church's accent betrays his roots in Florida, where he grew up with a series of father figures before heading off to boarding school at 13. He showed a precocious talent for hacking complex systems—not just figuring out how the systems work but subverting them to his will. At the age of 10, he built an analog calculator from spare radio parts. By 16, he was writing his own computer programs—he tried everything from ecological modeling to algorithmic poetry.

By the time he became a graduate student in the 1970s, Church was already an accomplished scientist, with a high-profile paper modeling how proteins bind to DNA. He also wrote the software that helped solve the structure of transfer RNA (tRNA), a molecule that helps make proteins and would later become central to his grand quest.

Yet in 1976, 2 years into his Ph.D. studies at Duke University, Church ran into trouble. He had skipped so many classes to spend more time in the lab that he was about to flunk out. Fortunately, Harvard accepted the distracted student, who buckled down

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and took the required classes. "I'm glad they took a chance on me," says Church, now a Harvard professor.

When Church finished his Ph.D. in 1984, it seemed impossible to read the sequence of a cell's genome, let alone tinker with its content. Church and his Harvard Ph.D. adviser, Walter Gilbert, invented one of the first automatic DNA sequencing methods, widely popular at first but then overtaken by another technology. Just a few years later, Church invented multiplex DNA sequencing, in which many DNA strands can be deciphered in parallel (*Science*, 8 April 1988, p. 185), a method that has inspired countless applications, such as computer chip–like microarrays that track the activity of thousands of genes.

Church took a cue from telecommunications. Thousands of simultaneous telephone conversations can share the same wire because the data streams are uniquely tagged and then combined—"multiplexed"—so they can be teased apart at the other end. Similarly, with fluorescently glowing molecules as tags, and the help of computers to make sense of the data, Church showed that the chemistry of millions of separate molecules, such as strands of DNA, could be tracked and analyzed.

Church's latest ambition is not just to sequence genomes but to completely redesign them. The M in MAGE, the contraption locked away in his lab, is what makes this possible. By multiplexing many simultaneous changes to DNA within a single population of cells, rather than the traditional method of sequentially introducing changes in one generation of cells at a time, Church can edit genomes on the fly, creating a vast diversity of bacteria to evaluate for their commercial utility.

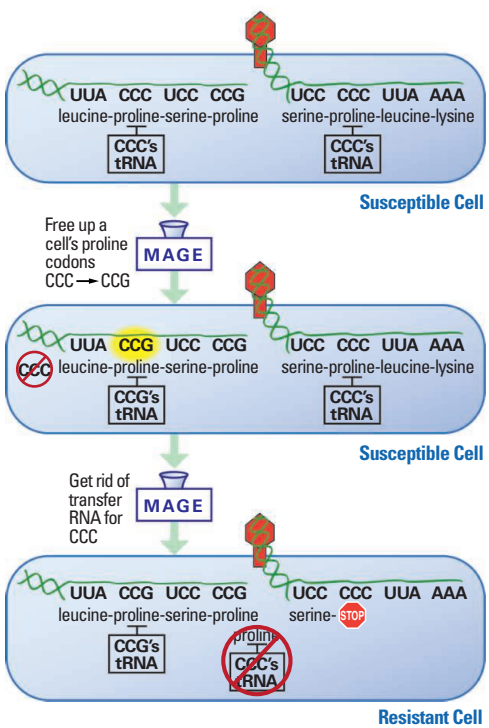
The ultimate hack

Church has even more ambitious plans for MAGE. He wants to hack into a cell's genetic code to make the cell impervious to viruses. That could be a boon to industries that use giant batches of bacteria and other cells to churn out enzymes and other valuable chemicals, Church notes. He points out that in 2009 a virus contaminated drug-producing hamster cells at the nearby biotech company Genzyme. The virus shut down a whole plant, leaving patients stranded.

The complicated, multistep hack that Church believes can make cells virus-proof revolves around the way genes encode their protein-making instructions. Genes are inscribed as a series of DNA base-pair triplets, called codons. The triplet combinations of DNA's four-letter alphabet give rise to 64 possible codons, more than enough for the cell's 20 amino acids, as well as stop signals to mark the ends of genes. To make a protein, specific tRNA molecules read these codons and, until a stop codon is reached, attach the right amino acid to a growing chain.

Viruses take advantage of this system by using the very same codon code in their genes and thus fooling the cell's tRNAs into helping to churn out viruses. But what if Church changed the cell's genetic code and the way tRNA handled that code? With the cell thus rewired, any infecting virus trying to replicate would only make gobbledygook proteins.

The crucial first step is to "free up" a codon in a cell's genome. Because there are multiple codons that specify the same amino acids, one type of codon can be swapped for another that does the same job. If one did this across the entire genome, making a synonymous swap for every single instance of a codon, then the cell no longer needs that codon's tRNA. So there would be no harm done by deleting it. But viruses still depend on the codon, and when they infect this modified cell, that lack of that tRNA would cause viral protein production to hit a premature dead end (see diagram).



Virus immunity. After one of the transfer RNAs is edited out from a cell's genetic code, invading viruses (red) should get nowhere.

All that swapping and deleting is easier said than done, however. "We thought about doing this back in 2003," Anderson says. "But we realized that with traditional methods, it would take forever" because thousands of changes to the genome were required. In addition, such wholesale genome editing might cripple the cell.

In July, a team led by Church showed that cells can handle at least some genome editing. The researchers freed up one of the three stop codons in *E. coli* (*Science*, 15 July, p. 348). In each of the 314 places in the *E. coli* genome where the "amber" stop codon marks the end of a gene, they used MAGE to replace it with an "ochre" codon, which does the same job. And in unpublished follow-up work, they deleted the gene for the protein that reads the amber codon. These strange new bacteria are alive and well, Church says.

Getting from here to virus resistance will require much more work. Instead of eliminating a stop codon in cells, Church's team has to make at least 3000 replacements to get rid of an amino acid codon, not to mention deleting the gene for the corresponding tRNA.

Whether a cell can survive this massive rewiring remains to be seen. But if the virus-resistance hack works, it may be possible to further modify the cell's code such that its genes cannot be read correctly by other cells should the genes escape into the environment, making Church's new life forms environmentally friendly.

There are other efforts under way to hack the genetic code and teach cells new tricks. Like the DNA sequencing method he helped create 20 years ago, Church's rewired cells may turn out to be an also-ran. "Synthetic biology is such a young field," Chin says. "It's not clear what research will stand the test of time."

Church isn't worried. He continues to tinker with MAGE, trying to make a version that will allow him to edit the genomes of stem cells to treat cancer and other diseases. But his dreams don't stop there.

"I wouldn't mind being virus-free," he says with equal parts mirth and earnestness. It may be too late to reengineer all of his own cells to prevent viral infections, but Church doesn't rule out the possibility of rewiring the genome of a human embryo to be virus-proof. That would be the ultimate life hack.

–JOHN BOHANNON

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