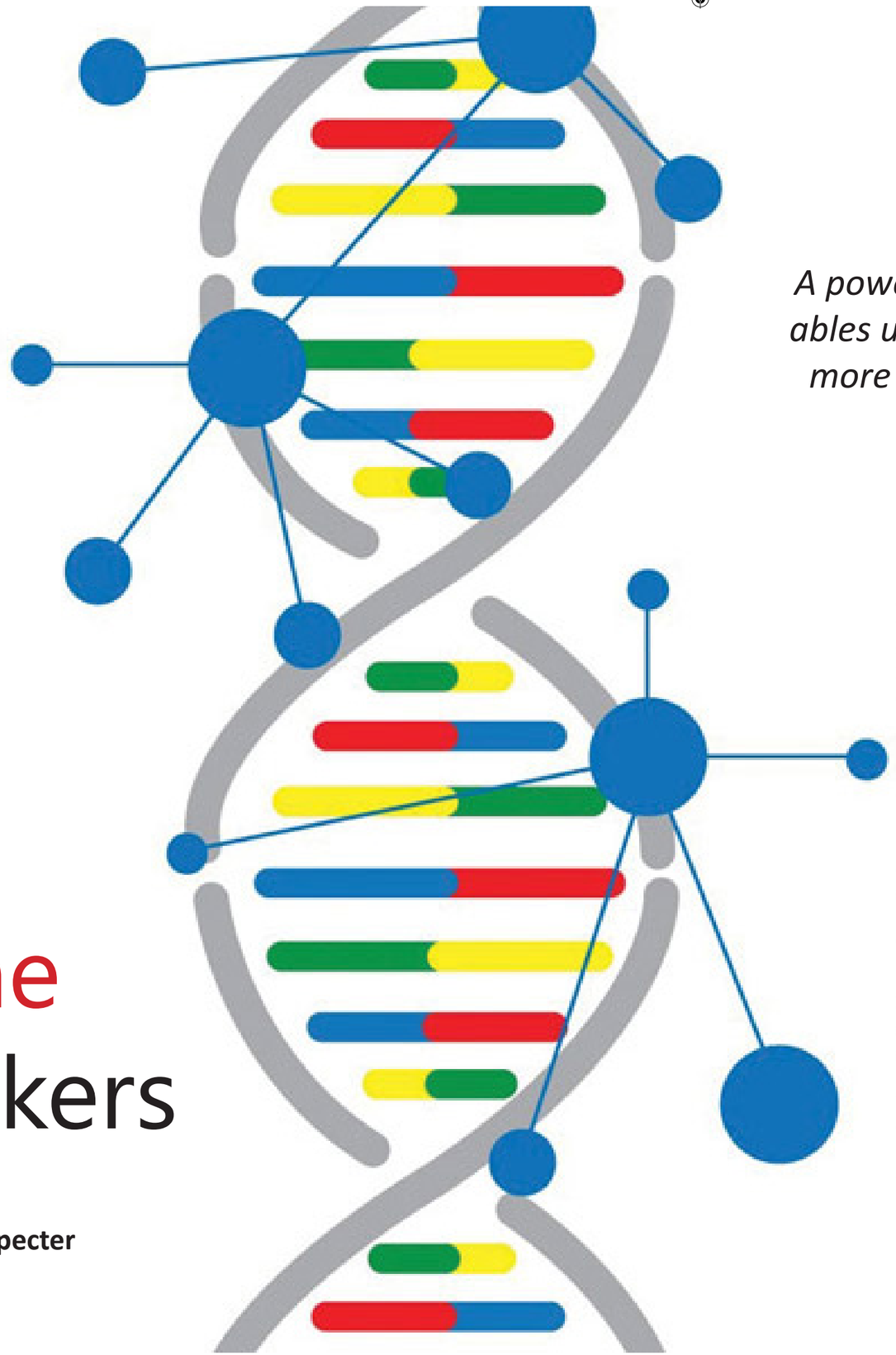

The Gene Hackers

By Michael Specter

A powerful new technology enables us to manipulate our DNA more easily than ever before.

At thirty-four, Feng Zhang is the youngest member of the core faculty at the Broad Institute of Harvard and M.I.T. He is also among the most accomplished. In 1999, while still a high-school student, in Des Moines, Zhang found a structural protein capable of preventing retroviruses like H.I.V. from infecting human cells. The project earned him third place in the Intel Science Talent Search, and he applied the fifty thousand dollars in prize money toward tuition at Harvard, where he studied chemistry and physics. By the time he received his doctorate, from Stanford, in 2009, he had shifted gears, helping to create optogenetics, a powerful new discipline that enables scientists to use light to study the behavior of individual neurons.

Zhang decided to become a biological engineer, forging tools to repair the broken genes that are responsible for many of humanity's most intractable afflictions. The following year, he returned to Harvard, as a member of the Society of Fellows, and became the first scientist to use a modular set of proteins, called TALEs, to control the genes of a mammal. "Imagine being able to manipulate a specific region of DNA . . . almost as easily as correcting a typo," one molecular biologist wrote, referring to TALEs, which stands for transcription activator-like effectors. He concluded that although such an advance "will probably never happen," the new technology was as close as scientists might get.

Having already helped assemble two critical constituents of the genetic toolbox used in thousands of labs throughout the world, Zhang was invited, at the age of twenty-nine, to create his own research team at the Broad. One day soon after his arrival, he attended a meeting during which one of his colleagues mentioned that he had encountered a curious region of DNA in some bacteria he had been studying. He referred to it as a CRISPR sequence.

"I had never heard that word," Zhang told me recently as we sat in his office, which looks out across the Charles River and Beacon Hill. Zhang has a perfectly round face, its shape accentuated by rectangular wire-rimmed glasses and a bowl cut. "So I went to Google just to see what was there," he said. Zhang read every paper he could; five years later, he still seemed surprised by what he found. CRISPR, he learned, was a strange cluster of DNA sequences that could recognize invading viruses, deploy a special enzyme to chop them into pieces, and use the viral shards that remained to form a rudimentary immune system. The sequences, identical strings of nucleotides that could be read the same way backward and forward, looked like Morse code, a series of dashes punctuated by an occasional dot. The system had an awkward name—

clustered regularly interspaced short palindromic repeats—but a memorable acronym.

CRISPR has two components. The first is essentially a cellular scalpel that cuts DNA. The other consists of RNA, the molecule most often used to transmit biological information throughout the genome. It serves as a guide, leading the scalpel on a search past thousands of genes until it finds and fixes itself to the precise string of nucleotides it needs to cut. It has been clear at least since Louis Pasteur did some of his earliest experiments into the germ theory of disease, in the nineteenth century, that the immune systems of humans and other vertebrates are capable of adapting to new threats. But few scientists had considered the possibility that single bacterial cells could defend themselves in the same way. The day after Zhang heard about CRISPR, he flew to Florida for a genetics conference. Rather than attend the meetings, however, he stayed in his hotel room and kept Googling. "I just sat there reading every paper on CRISPR I could find," he said. "The more I read, the harder it was to contain my excitement."

It didn't take Zhang or other scientists long to realize that, if nature could turn these molecules into the genetic equivalent of a global positioning system, so could we. Researchers soon learned how to create synthetic versions of the RNA guides and program them to deliver their cargo to virtually any cell. Once the enzyme locks onto the matching DNA sequence, it can cut and paste nucleotides with the precision we have come to expect from the search-and-replace function of a word processor. "This was a finding of mind-boggling importance," Zhang told me. "And it set off a cascade of experiments that have transformed genetic research."

With CRISPR, scientists can change, delete, and replace genes in any animal, including us. Working mostly with mice, researchers have already deployed the tool to correct the genetic errors responsible for sickle-cell anemia, muscular dystrophy, and the fundamental defect associated with cystic fibrosis. One group has replaced a mutation that causes cataracts; another has destroyed receptors that H.I.V. uses to infiltrate our immune system.

The potential impact of CRISPR on the biosphere is equally profound. Last year, by deleting all three copies of a single wheat gene, a team led by the Chinese geneticist Gao Caixia created a strain that is fully resistant to powdery mildew, one of the world's most pervasive blights. In September, Japanese scientists used the technique to prolong the life of tomatoes by turning off genes that control how quickly they ripen. Agricultural researchers hope that such an approach to enhancing crops will prove far less controversial than using genetically modified organisms, a process that requires technicians to introduce foreign DNA into the genes of many of the foods we eat.

The technology has also made it possible to study complicated illnesses in an entirely new way. A few well-known disorders, such as Huntington's disease and sickle-cell anemia, are caused by defects in a single gene. But most devastating illnesses, among them

CRISPR's unprecedented ability to edit genetic code will make possible a new generation of medical treatments. Illustration by Todd St. John

diabetes, autism, Alzheimer's, and cancer, are almost always the result of a constantly shifting dynamic that can include hundreds of genes. The best way to understand those connections has been to test them in animal models, a process of trial and error that can take years. CRISPR promises to make that process easier, more accurate, and exponentially faster.

Inevitably, the technology will also permit scientists to correct genetic flaws in human embryos. Any such change, though, would infiltrate the entire genome and eventually be passed down to children, grandchildren, great-grandchildren, and every subsequent generation. That raises the possibility, more realistically than ever before, that scientists will be able to rewrite the fundamental code of life, with consequences for future generations that we may never be able to anticipate. Vague fears of a dystopian world, full of manufactured humans, long ago became a standard part of any debate about scientific progress. Yet not since J. Robert Oppenheimer realized that the atomic bomb he built to protect the world might actually destroy it have the scientists responsible for a discovery been so leery of using it.

For much of the past century, biology has been consumed with three essential questions: What does each gene do? How do we find the genetic mutations that make us sick? And how can we overcome them? With CRISPR, the answers have become attainable, and we are closing in on a sort of grand unified theory of genetics. "I am not sure what a Golden Age looks like," Winston Yan, a member of Zhang's research team, told me one day when I was with him in the lab, "but I think we are in one."