in my own words

Changing the Code

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Feng Zhang earned his undergraduate degree in chemistry and physics from Harvard College and his Ph.D. in chemistry from Stanford. At 35, he is already recognized as one of the most accomplished scientists of our time for his work on developing CRISPR systems. A core member of the Broad Institute of MIT and Harvard and an investigator at the McGovern Institute for Brain Research at MIT, Zhang discusses the promise of CRISPR and why this is such an exciting time for biotechnology—and for humanity as a whole.

Biology as a tool
I came to the U.S. from China when I was 11. When I was in middle school—I think I was 12—I attended Saturday enrichment classes, and one of them was on molecular biology. At the time, I didn’t really like biology because it was taught to us mostly through memorization of names or by dissecting frogs and trying to identify their anatomical parts. But I liked molecular biology. In this class, they showed the movie *Jurassic Park*, and I remember thinking that it made biology out to be something where you can understand the underlying principles and use them to build things, to repair things, to improve people’s lives. I thought that was really cool.

Science fair foray
The idea that you might be able to program biology was very exciting to me. In the class, they also taught us about DNA, about advances in biotechnology such as gene therapy, and about how, by working with recombinant DNA, you could make new drugs. It was the first time I was exposed to that.

When I was in high school, I volunteered in a gene therapy lab at a nearby hospital, where I did research that involved studying retroviruses to see how retroviral proteins assemble to form a virus. It was the basis for a project for which I eventually won third place in the Intel Science Talent Search. That was a great experience. I was able to share the work I was doing with a broader audience, and it gave me the chance to interact with other students my age with similar interests and experiences. It was also an opportunity to meet professional scientists. I got to go to the NIH and see what research at the highest level is like. It was very stimulating and very inspiring.

A taste for innovation
I knew I wanted to do something in science and technology as a career, but there are many ways to do science. You can be an engineer working in industry, or you can be a scientist and be an entrepreneur and build a product, or you can be a professor and do science and also teach.

As a graduate student, I worked in Karl Deisseroth’s lab. It was a very young lab. I was only the second person to join the lab, which was working on the development of optogenetics, in which light-sensitive proteins are inserted into neurons as a means of activating specific neural circuits. In many ways, it felt very entrepreneurial, like a startup environment where you have to be versatile and apply knowledge from all sorts of fields to move the project forward. It was pretty exciting to be a part of this research that could have such a big impact on neuroscience. It occurred to me that being a professor would be a really good way for me to continue to pursue research.

Manipulating nature to benefit nature
One of the challenges of optogenetics was figuring out how to target this light-sensitive microbial protein to a specific group of cells in the brain. At the time, there weren’t many methods to do that easily. That got me interested in learning more about genome editing, because I knew that if
we could introduce the light-sensitive protein gene into a specific location in the genome, then we could get that gene to express in a subset of neurons, or in a specific circuit in the brain. That could allow us to better understand the mechanisms behind and develop treatments for all kinds of disorders, including PTSD, addiction, and depression.

At the time, however, the only available technologies weren’t very easy to use and didn’t work very well, so I continued to look for and develop new genome editing technologies, including TALEN and CRISPR.

Where the genes are
TALENs, or transcription activator-like effector nucleases, are proteins that you can modify to recognize a new DNA sequence. TALENs use protein modules that recognize one base of DNA at a time, so if you wanted to recognize a longer string of DNA sequence, you would stitch together, say, 15 or 18 of these TALE modules to be able to recognize 15 or 18 DNA bases. Using molecular biology, you can go through a series of steps to put together these protein modules for recognizing a gene that you want to edit in the genome. When you attach a nuclease protein to these DNA-binding modules, the nuclease will make a cut in the DNA and the cell’s own repair machineries will go in and try to repair it. That provides a template for a new sequence, which we can then swap into the genome. But making TALE proteins is a long and cumbersome process.

CRISPR (clustered regularly interspaced short palindromic repeats) systems are used by many bacteria to defend themselves against viruses. They encode proteins and RNA that can recognize a target sequence. That CRISPR proteins, such as Cas9, use RNA to recognize specific DNA sequences made it an appealing tool because it meant you didn’t have to manipulate a protein. CRISPR systems were being studied in bacteria, but we were able to harness CRISPR systems to edit genomes in cells with nuclei—including human cells.

Technology for a better world
There are a lot of genetic disorders, either inherited or caused by mutations, that can lead to diseases such as cancer, sickle cell disease, retinal degeneration, or muscular dystrophy. My lab and many others have been working to develop these genome-editing systems to be able to make corrections to the mutation so that we can one day treat or cure such diseases.

Scientists around the world are already benefiting from the technology. It’s helping them with their research and accelerating the way they can do experiments. In industry, too, CRISPR systems are making it much easier for pharmaceutical and biotech companies to identify good targets for developing drugs to treat disease. And agricultural companies are using CRISPR to either discover new traits for plants for things like drought resistance or virus resistance, or modify plant species to increase crop yields, which will hopefully help us feed a growing population.

Scientists in China have started to test CRISPR systems in clinical settings for the treatment of cancer, and researchers at the University of Pennsylvania are hoping to use it—maybe as early as this year—to treat cancers such as leukemia. Other researchers are working on developing CRISPR in order to treat eye diseases and sickle cell disease. I think we’re going to see a lot of exciting progress in the next few years. Things are happening very quickly.

Controlled progress
Of course, altering an organism’s genetic structure also has the potential to alter the genome of future generations. So while we’re working to try to make the CRISPR system more robust and specific, at the same time, there’s a lot of thought going into how to implement the technology in a way that will allow us to control the editing process.

We’re also sharing these tools with other researchers, because so many people can benefit from them. I think it’s our responsibility to make them accessible. And we’re working to develop ever newer molecular technologies to target these really big problems. It really is a very exciting time to be in this field.

Learn more about Feng Zhang and CRISPR at these sites:
- broadinstitute.org/bios/feng-zhang
- zlab.mit.edu
- mcgovern.mit.edu/principal-investigators/feng-zhang
- newyorker.com/magazine/2015/11/16/the-gene-hackers
- newyorker.com/magazine/2017/01/02/rewriting-the-code-of-life