Meet one of the world's most groundbreaking scientists

- Email

As the dish of steamed chicken feet clattered onto the table, an impish toddler drummed with her chop sticks. Nobody in the noisy restaurant in Boston's Chinatown gave a second glance at the man dressed in a polo shirt and jeans enjoying dim sum with his little girl, wife, and mother.

No one could have guessed that Feng Zhang, at 34, is widely considered the most transformative biologist of his generation, a double threat to win a Nobel Prize in the near future. Or that his discoveries could finally bring cures for some of the greatest causes of human suffering, from autism and schizophrenia to cancer and blindness. Or that he has touched off a global furor over the possibility that a genetics tool he developed could usher in a dystopian age of designer babies.

At that moment, Zhang was simply a young father, husband, and son struggling to explain what drives him, why it isn't unusual for him to arrive home from his lab at 1 or 2 or even 3 in the morning.

He thinks it's important, he told a reporter he had invited to join him for brunch. He enjoys it, he wants to carry on the work of mentors who invested in him, he … "The autumn leaves," his mother, Shujun Zhou, piped up.

Zhang was 11 when he and his mother left China and settled in Des Moines, Iowa. A few years later, when he was in high school, she often waited in her car for hours while he worked late in a gene therapy lab. Driving home in the gathering dark one autumn evening, mother and son were struck by the sight of falling leaves, dead and dying after lives measured in mere months. They spoke about how little time anyone has, she recalled, and how easy it is for a life to disappear without the slightest trace that it had ever been. "It just seemed important to me to try my best to make a difference," Zhang said.

As much as anyone in science, he already has.

STAT has followed Zhang since the summer, accompanying him to standing-room-only talks, interviewing his mentors and lab trainees, and spending hours with Zhang as he talked about his life in more detail than he previously has in public. What emerged is a portrait of a mild-mannered scientist with a brash vision, a striver with an immigrant's ambition to scale the greatest heights in his adopted land, and a researcher who is impatient with the plodding ways of his craft.

Colleagues note his ability to identify promising ideas early, to stoke the creative fires of his junior lab members, and to resist the temptation to pursue likely-to-succeed but incremental advances and instead to take risks. When a member of his lab proposes a project, Zhang asks: Will it be a "hack," clever but inconsequential, or an innovation?

Zhang helped create two revolutionary genetic and neuroscience technologies. As a graduate student, he was a key member of the team that figured out how to light up neurons in the brain, allowing scientists to unravel which circuits control which behaviors and search for the roots of mental illnesses such as schizophrenia and bipolar disorder. Just a few years later, Zhang made the discovery that would vault him into the front ranks of the world's biologists: how to edit the genomes of plants and animals—including humans—quickly, easily, and efficiently.

The tool is already being used in the lab to make human cells impervious to HIV; cure mice of muscular dystrophy, cataracts, and a hereditary liver disease; and improve crops including rice, tomatoes, oranges, tobacco, and wheat. But it also could be used to modify genes in human eggs, sperm, and embryos, raising the specter of parents choosing their baby's traits — personality, athletic ability, looks — like options on a Lexus.

Called CRISPR-Cas9, the technology quickly spawned three companies with hundreds of millions of dollars in venture financing and opened a new era in molecular biology.

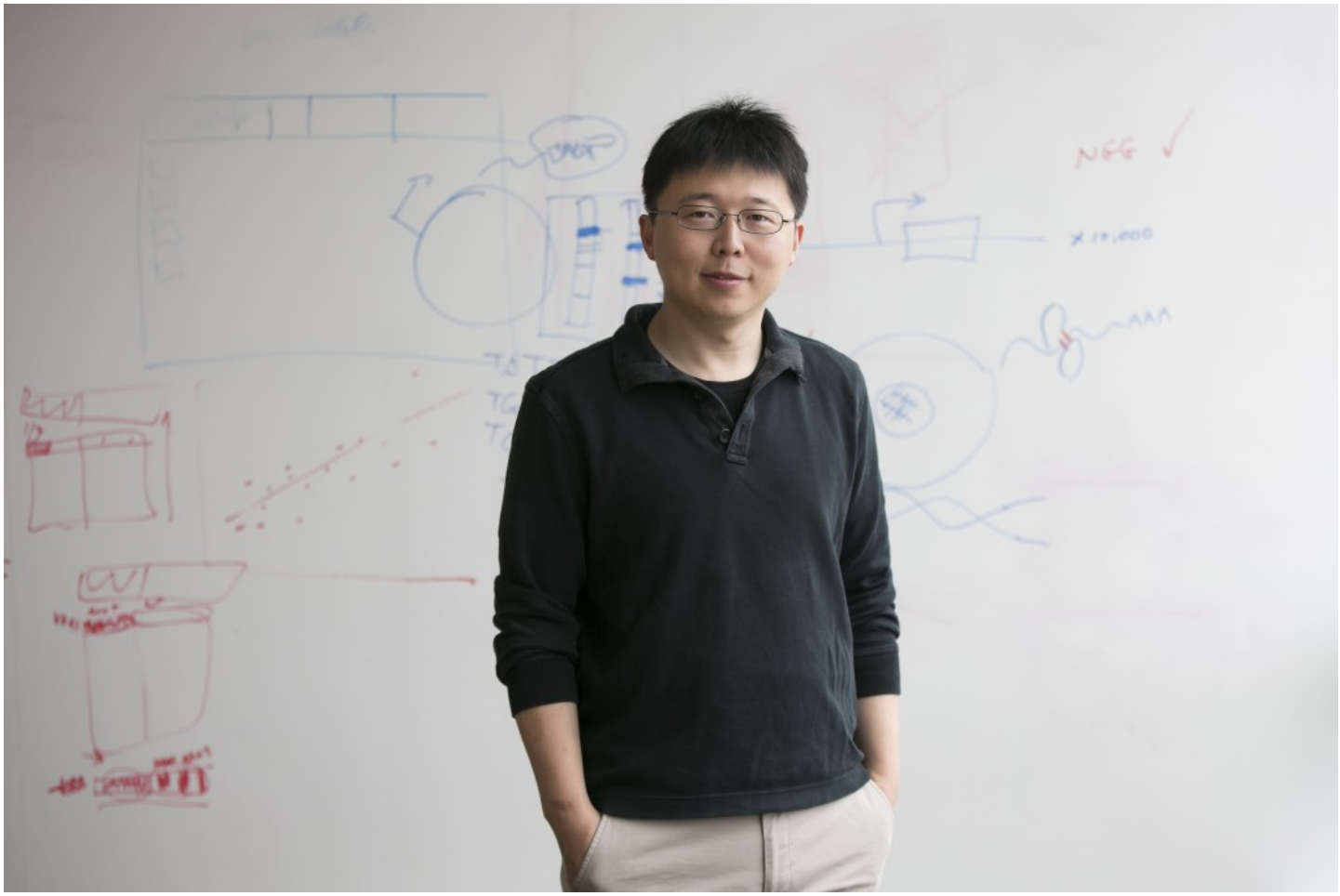
It’s “changing how we do science,” said MIT biologist Phillip Sharp, who shared the 1993 Nobel prize in medicine.

The gene editing tool is so powerful — with such immense implications for the environment and humanity — that science organizations from around the world are convening a global forum next month to craft guidelines for using it responsibly.

Zhang is the youngest head of a lab at the Broad Institute in Cambridge, Mass., a high-powered genomics research center affiliated with MIT and Harvard, where he is one of only eight “core faculty.” Many of his post-doctoral fellows and graduate students are older. Rarely without a smile, he regularly bounds into the office of the Broad’s director, Eric Lander, showing him his latest “cool” data.

Exactly how much credit Zhang deserves for the development of CRISPR is the focus of a bitter patent fight, but if he and the Broad prevail, he stands to become the latest of MIT’s wealthy scientist-entrepreneurs. It’s a future Zhang could never have imagined as a child in Iowa. After arriving from China, he and his mother initially got by on what she earned in menial jobs such as a motel housekeeper — though she was a computer engineer. His father, an administrator at a science and technology university, did not join them for several years.

Then his life changed thanks to the most mundane of experiences. Zhang went to the movies.



Katherine Taylor/STAT

Feng Zhang at the Broad Institute in Cambridge, Mass.

Life might be programmable

In Des Moines, middle-school biology class meant dissecting frogs stinking of formaldehyde. But Zhang was rescued by a Saturday enrichment program in molecular biology, where the instructors, not being fools, figured that a reasonable way to keep a bunch of teenagers engaged was to show them *Jurassic Park*.

“Both of my parents work in computer science, so I was always interested in programming,” Zhang recalled. The

1993 film, in which hubristic researchers merged dinosaur and frog DNA to bring back the extinct reptiles, “told me that biology might also be a programmable system.”

A seed had been planted in his mind. An organism’s genetic instructions, he realized, could be overwritten to change its characteristics, just as his parents wrote computer code.

He got his first chance to program a living thing in 1995, as a sophomore at Theodore Roosevelt High School. The head of a program for gifted students asked Zhang if he’d like to volunteer after school in a gene therapy lab at nearby Methodist Hospital. “I said it sounds great,” Zhang recalled, and although he “knew zero” about advanced biology, the head of the lab, Dr. John Levy, didn’t blanch at his inexperience.

Every afternoon, Levy would sit in a break room drinking tea and scribbling on a pad to explain concepts in molecular biology. Zhang was a quick study, learning key techniques and succeeding in his warm-up project: using viruses to slip jellyfish genes for a glow-in-the-dark molecule called green fluorescent protein into human melanoma cells.

It wasn’t resurrecting dinosaurs, but he had engineered cells of one species to express genes from another, and the eerie emerald light emanating from the cells was proof. “They glowed!” Zhang recalled with an excitement he still retains 20 years later.

Zhang spent the rest of the year studying whether the fluorescent protein, which absorbs ultraviolet light, might protect DNA from the damaging and cancer-causing effects of ultraviolet light. He discovered that it does, and the experiment became his Iowa state science fair project, which had the added attraction of drawing “kids like me,” Zhang said: “geeky.”

He did another genetics project under Levy’s mentorship his junior year, in viruses, which earned him third place nationally and a $50,000 scholarship in the 2000 Intel Science Talent Search competition.

It “made me want to go out and cure HIV,” Zhang said. That wasn’t exactly in the cards for a high school student; neither was extending his fluorescent protein work to see if, by blocking ultraviolet light, it could help prevent melanoma. But he had learned a valuable lesson: intriguing scientific discoveries often go nowhere.

Admitted to Harvard with a full scholarship, Zhang conducted influenza-virus research in the lab of chemist Xiaowei Zhuang while majoring in chemistry and physics. The research led to a 2004 paper in a top journal on how flu viruses enter cells. Key to the discovery: the glowing jellyfish protein Zhang had first played with in Iowa.

Zhang was a bit of a Julia Child in the lab, able to get wondrous results but prone to the laboratory version of dropping turkeys onto the floor. In organic chemistry, he forgot that putting acid into a certain hot reaction is a no-no. “Everything foamed up and exploded inside the chemical hood,” he recalled. He and his partner fled.

Another experience had a more lasting impact. When a close friend and fellow student developed major depressive disorder, Zhang spent hours trying to help and making sure he was not suicidal. The friend was so deep in the abyss of depression as to be unreachable, however, and had to take a year off from Harvard. Zhang was deeply touched and dedicated himself to developing better treatments for mental illness.

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Albert Einstein is renowned for having published five mind-bending discoveries in a single year. Zhang was about to embark on a period almost as fertile. After graduating from Harvard in June 2004, Zhang headed to graduate school at Stanford, joining the lab of a rising young neuroscience professor named Karl Deisseroth. With graduate student Ed Boyden, the trio invented optogenetics, in which light-sensitive proteins are slipped into neurons so light can activate specific neural circuits. Zhang’s contribution was developing a system for using viruses to ferry foreign genes into neurons and get the genes to churn out light-sensitive proteins.

In 2007, with reporters scheduled to visit, Deisseroth had Zhang engineer a mouse with light-sensitive neurons in its motor cortex. Sure enough, light turned on the neurons and the mice walked in circles. Today, optogenetics is

considered one of the seminal achievements in neuroscience, used by researchers worldwide to map neural circuitry, including that underlying schizophrenia, depression, or autism.

Doctorate in hand, Zhang "started thinking about how I could insert genes easily into animals," much as he did for optogenetics but in ways that would work for every kind of animal and every kind of gene. In 2009 he received a position at Harvard's Society of Fellows, a prestigious perch "for people who are preternaturally independent and creative," said Broad neuroscientist and former Harvard provost Steven Hyman. "Feng is both."

The position didn't come with a lab, however. Zhang begged and borrowed space in labs of senior Harvard scientists. He began with the then-leading gene editing technique, in which proteins studded with structures called "zinc fingers" recognize a specific DNA sequence and cut it. Cells naturally repair such cuts and, if foreign DNA has also been slipped into the cell, incorporate the substitute DNA. Presto: an edited genome. The trouble is, zinc fingers are "remarkably difficult to work with," Zhang said.

Scientists unveiled another gene-editing technique, called TALEs, in 2009. But TALEs, like zinc fingers, are difficult-to-make proteins. "I was teaching students to build TALEs and it would take three months before they could even use it," Zhang recalled. He was the lead author on a study that involved creating TALEs able to home to specific DNA sequences in human and mouse cells and turn genes on or off. But he wasn't satisfied. "I thought there must be better ways to do gene editing," he said.

His Fellows appointment nearing an end, Zhang needed a job. A neuroscientist at MIT's McGovern Institute for Brain Research had heard Deisseroth sing the praises of "this amazing superstar," recalled McGovern director Robert Desimone. In a collaborative enterprise like science, where it's not unusual for papers to have a dozen authors, "you always wonder who did what," Desimone said. The McGovern asked around and was assured "that Feng played a key role" in developing optogenetics, said Desimone. Zhang's list of papers, he added, "was the strongest publication history of anyone [at this stage of a career] in the history of neuroscience." Zhang was hired, by both MIT and the Broad.

In February 2011, a visiting scientist told a meeting of the Broad's advisory board about his research on bacterial genomes containing an immune system called CRISPR. "I was sitting in the back of the room and my mind had been drifting," Zhang recalled, but the odd acronym immediately sparked his curiosity.

"I had no idea what CRISPR was, but I looked it up on Google and became really excited. Fortunately, the field was young and there were not a lot of papers to read." He spent much of a scientific meeting in Miami a few days later holed up in his hotel room poring over CRISPR papers.

What he learned was that CRISPR — Clustered Regularly Interspaced Short Palindromic Repeats — had been discovered by microbiologists in bacteria, where they defend against viruses. The CRISPR system consists of a search-and-destroy duo: Genetic material called RNA homes in on a specific stretch of DNA; an enzyme called Cas9 cuts that DNA. Since CRISPR can destroy viruses "that make yogurt taste funny," Zhang said, "the field was focused on using CRISPR to make better yogurt."

Zhang had bigger goals. "We wanted to see, 'Can we make it work in human cells?'," he recalled. He e-mailed graduate student Le Cong: "This could be really big."

It was an audacious aim. Sticking to TALEs—a more established technology—was the safer course, Cong reflected later, but "we decided to give CRISPR a try. It was worth taking the risk."

Katherine Taylor/STAT

Feng Zhang arrives for work at the Broad Institute.

Working like crazy

Back in Cambridge, Cong “immediately recognized why Feng was excited,” he said. TALEs had driven them crazy, as they laboriously synthesized protein after protein only to find that it wouldn’t home in on the stretch of DNA they wanted. But CRISPR used RNA, not proteins, to recognize specific DNA sequences in a genome. If synthesizing proteins is as complicated as making a roller coaster out of K’nex, then constructing RNAs is as simple as stringing beads on thread.

Instead of warming up by studying CRISPR in bacteria, as other scientists were, the duo jumped to human and mouse cells, figuring that only if CRISPR worked in these higher-order cells would it be medically important. On a whiteboard in his office, Zhang listed individual experiments they would need to do and split them up.

“It was initially Feng and myself, and we were working like crazy,” Cong said. The scientists spent months testing Cas9 enzymes, in particular monitoring whether they got to the nuclei of human cells, where the genes reside. Bacteria, where the CRISPR system originated, do not have nuclei, so there was no guarantee that it would work in cells that do. “We wanted to show that CRISPR was better than TALEs, that it was revolutionary and the system of choice for genome editing,” Cong said.

They often worked until 11 p.m. or later — Zhang had classes to teach, and couldn’t start his experiments until late afternoon. They took breaks for ramen noodles, Chinese take-out or burritos and, once, to crash a party at Zhang’s apartment complex and try their first tequila shots. (Only one each; they returned to the lab that night, too.)

The scientists wanted to demonstrate at least two crucial things: that CRISPR edited the genome in mouse and human cells, and that the edited genome functioned. They’d targeted the gene for green fluorescent protein,

Zhang's sentimental favorite from high school, and used microscopes and fancy cameras to study the green glow: The less the cells glowed green, the more CRISPR had edited out the fluorescence gene.

Once the basics worked, by the spring of 2012, they had enough data for a paper, Zhang said. But it would have been only a so-so paper. "I didn't want to submit the paper just because the result was publishable," he said. "I want to wait until we have a paper that can make a significant difference, not just to be first with something."

"We thought we had the luxury of time," Cong recalled. "We didn't know about the competition."

But competition there was. In June 2012, scientists led by Emmanuelle Charpentier, then at Umea University in Sweden, and Jennifer Doudna of the University of California, Berkeley, reported using CRISPR-Cas9 to cut target DNA sequences in test tubes, raising the "potential . . . for RNA-programmable genome editing," they wrote in their paper in the journal Science.

Zhang didn't feel he had been scooped, he said: many biochemical tricks work in test tubes but fail in human cells. Before the Charpentier-Doudna paper was published, Cong recalled, they had come up with "a completely independent and different way of using Cas9 for genome editing than the strategy proposed" in that June paper: "We had these details figured out before [it] was published," Cong said, and Zhang included those details in grant applications he submitted, also before June.

Moreover, when they read their rivals' paper, Cong said, they saw that it described the use of two molecules that were "very different" from the CRISPR-Cas9 system Zhang's team had designed and lacked "critical components" for making the genome-editing system work in living cells as opposed to test tubes.

The team therefore pressed on through late summer, amassing data showing their system could not only target genes inside human and mouse cells but edit several at once. During the final sprint, Zhang recruited additional members of his growing lab, an approach his colleagues compare to that at tech start-ups: he recognizes a killer app and throws bodies into the fray like a general calling up infantry. "We"—a word Zhang emphasized—"showed we could edit the human genome."

He sent the paper to Science on Oct. 5. It was published online in early January 2013, along with a similar paper from the lab of Harvard's George Church, where Zhang had worked during his Harvard fellowship. Asked if he knew his old mentor was also in the CRISPR race, Zhang said he had no idea.

CRISPR "is changing how we do science."

Phillip Sharp, MIT biologist and Nobel laureate

Zhang has received some bad press and is the occasional target of Twitter barbs, because MIT paid a $70 fee for accelerated review when it applied for a CRISPR patent. That has been portrayed by rivals as somehow jumping the line, since the Doudna-Charpentier patent application was submitted months earlier, but it's not clear it made any difference in the patent decision.

At the time, the patent office used a system that awards patents to whoever first invented or conceived of something novel; Zhang has submitted lab notebooks meant to show that his lab was indeed first, which will ultimately carry more weight than the expedited review. Under the current "first to file" system, the patent might have gone to Doudna and Charpentier. But with the old first-to-invent system in effect, MIT received a key patent for the use of CRISPR to edit plant and animal genomes, with Zhang listed as inventor, in April 2014.

Berkeley has appealed that decision. The university contends that Doudna and Charpentier achieved the key CRISPR breakthroughs — in particular, identifying the three molecules that are crucial to making CRISPR work — and that Zhang's success in animal cells was just an extension of their work.

Zhang rejects that characterization, arguing that Doudna and Charpentier's 2012 paper "showed that you can cut DNA in test tubes." If extending that to plant and animal cells was "obvious," as critics of the Broad contend, "then why would our paper be published in Science?," one of the world's top journals, he asked. He had the idea of using Cas9 to edit animal genomes in 2011, he said, and to get it to work in human cells he used a different desigr

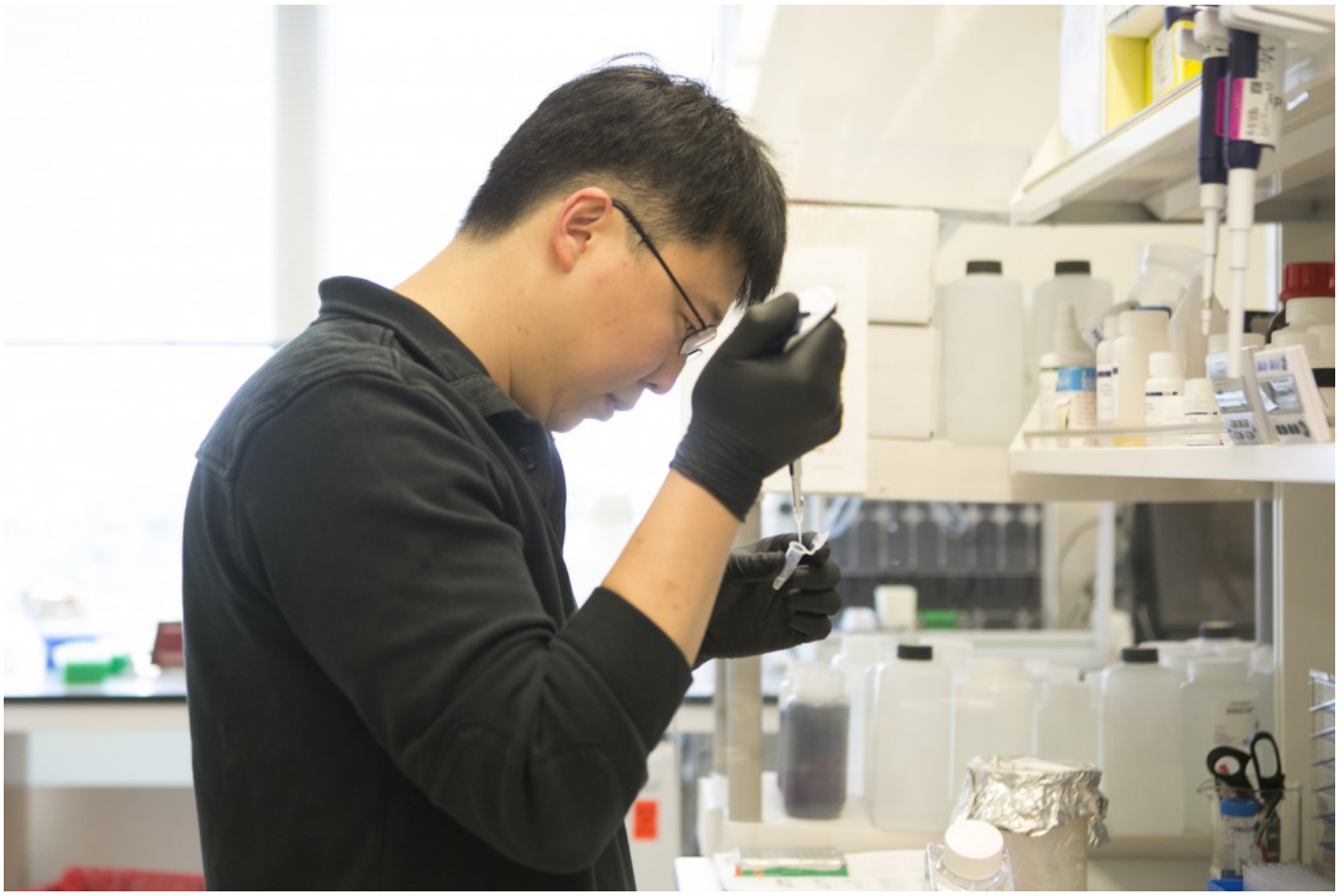
of RNA than the one Doudna and Charpentier described.

Zhang's breakthrough helped open the floodgates: The number of scientific papers with CRISPR in their title rose from 90 in 2012 to 741 (and counting) this year. That was partly Zhang's doing: he has been using a non-profit called AddGene to distribute genetic and other material, called reagents, to biologists around the world.

The intense interest reflects the astonishing power of CRISPR for both basic and commercial research. It is the rare media mention of CRISPR that does not include the phrase "designer baby," however. The technology works in essentially any cell, including human eggs, sperm, and embryos. Someone who developed from such "germline engineering" would carry Genome 2.0. So would his or her descendants. That has led to fevered speculation about editing genes to enhance personality, cognitive, behavioral, and physical traits.

In April, when scientists in China reported using CRISPR to edit the genomes of non-viable embryos created through in vitro fertilization, it created a furor. The U.S. National Academies will hold an international summit on genome editing—its promise, risk, and need for oversight—next month.

Zhang described his work to the Academies in October, emphasizing that his lab and the company he co-founded, Editas Medicine, are developing CRISPR-based therapies for non-germline cells—editing genes in blood cells, for instance, to cure sickle-cell disease. The possibility of changing one individual at a time, he says, would be sufficiently revolutionary.



Katherine Taylor/STAT

Feng Zhang runs an experiment with DNA and RNA in his lab.

'Everything goes faster in this lab'

More than anything, what stands out about Zhang is his productivity. Since his breakthrough CRISPR paper in 2013, he has had 38 more publications. His lab hums into the night, with Zhang often right there beside his junior

colleagues, happily pipetting. “He comes back after eating dinner with his family” — his wife, his toddler daughter, and his parents squeeze into an apartment about a mile from the Broad — “because he genuinely can’t wait until morning to know the answer” from the experiment his team is running, said post-doctoral fellow Naomi Habib. “He leads by example. He doesn’t measure people’s hours, but infects us with his passion.”

When Habib told him she was expecting her second child—news that many lab heads, male and female, would greet with annoyance or even anger—Zhang arranged for a technician to get up to speed on her experiments and keep them going during her absence.

He gives credit to other scientists, even those on the bottom rungs of the lab hierarchy. When he and colleagues engineered a new CRISPR-related protein in 2014, he named it SAM—ostensibly for “synergistic activation mediators,” but really for the initials of three students who did the work. “We had to come up with a fancy name to please the reviewers,” Zhang said, “but SAM was really for them.”

He has an uncanny ability to recognize the potential of an idea, much as he did when he first heard of CRISPR. In May, a scientist attending a genome engineering meeting at the Broad mentioned that some bacteria might use DNA-cutting enzymes other than Cas9. Afterward, Zhang casually walked over to one of his graduate students, Bernd Zetsche, and asked, “Are you busy?” Zetsche um’ed and ah’ed, since of course he was in the middle of a project, but Zhang redirected him to his latest brainstorm.

By September they had a published paper describing some members of a new family of molecular scissors that can be used to edit human and other genomes. “Somehow,” said Zetsche, still somewhat at a loss to explain the astonishingly fast turnaround, “everything goes faster in this lab.”

Although Zhang is known for CRISPR, he views that as only a means to his true goal: using genetics to understand and, ultimately, treat diseases of the mind. Half his lab is focused on brain research. It’s the possibility of making a real difference in autism, depression, schizophrenia, and other serious disorders that drives him, Zhang said. All the things such illnesses take away, he said —the ability to feel joy, to make meaningful social connections, to think clearly and deeply—are “a very essential part of being human.”

At a recent lab meeting, Habib was showing three dozen people at a long conference table PowerPoint slides of results from an experiment measuring which of thousands of genes are active in which brain cells. Zhang, although not dominating the conversation, was laser-focused on making sure the significance of their findings were communicated to the public.

“Figure 1 is not punchy enough,” he said. “It would be really nice if Figure 1 said, ‘We can do this and it’s important.’ ” Think of your audience “as a high school biology class and not your peers,” he suggested.

If the world doesn’t know you made a breakthrough, he told his colleagues, then for practical purposes you didn’t.

CORRECTION: An earlier version of this story incorrectly described Zhang’s relationship with AddGene, the non-profit he is using to share CRISPR tools, and the fee the Broad Institute paid for expedited review of its patent application.

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