FIELDS OF DREAMS

China bets big on genome editing of crops

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PHOTO: STEFEN CHOW

Published by AAAS

In a lab chamber in Beijing, Gao Caixia grows CRISPR-modified wheat plants that she hopes will have a higher yield.

If Gao Caixia were a farmer, she might be spread a little thin. Down the hall from her office at a branch of the Chinese Academy of Sciences (CAS) here in Beijing, seeds from a strain of unusually soft rice and a variety of wheat with especially fat grains and resistance to a common fungus sprout in a tissue culture room. A short stroll away, wild tomato plants far hardier than domestic varieties but bearing the same sweet fruit crowd a greenhouse, along with herbicide-resistant corn and potatoes that are slow to brown when cut. In other lab rooms Gao grows new varieties of lettuce, bananas, ryegrass, and strawberries.

But Gao isn't a farmer, and that cornucopia isn't meant for the table—not yet, anyway. She is a plant scientist working at the leading edge of crop improvement. Every one of those diverse crops has been a target for conventional plant breeders, who have slowly and painstakingly worked to endow them with traits to make them more productive, nutritious, or hardy. But Gao is improving them at startling speeds by using the genome editor CRISPR.

Gao is one face of the Chinese government's bet that CRISPR can transform the country's food supply. A natural bacterial immune system, CRISPR was turned into a powerful genome editor just a few years ago in U.S. and European labs. Yet today, China publishes twice as many CRISPR-related agricultural papers as the second-place country, the United States. The explanation? "Because I'm here," jokes Gao, who punctuates much of her speech with robust, giddy, infectious laughter.

This story was supported by the Pulitzer Center.

In August 2013, her group modified plant DNA with CRISPR, a first, and the 50-year-old researcher has since written three dozen publications that describe using the genome editor on various crops. Daniel Voytas, a plant geneticist at the University of Minnesota in St. Paul who invented an earlier genome-editing system and who has also adopted CRISPR, says Gao is an "outstanding cell biologist [who] jumped on CRISPR early on and has just been riding the crest of the wave."

But she is far from alone in China. Her team is one of 20 groups there seeking to use CRISPR to modify crop genes. "All the labs use CRISPR for basic research," Gao says. "They cannot live without CRISPR." China also expanded its efforts beyond its borders in 2017, when the state-owned company ChemChina bought Switzerland-based Syngenta—one of the world's four largest agribusinesses, which has a large R&D team working with CRISPR—for $43 billion. That was the most China has ever spent on acquiring a foreign company, and it created an intimate relationship between government, industry, and academia—a "sort of a ménage à trois" that ultimately could funnel intellectual property from university labs into the company, says plant geneticist Zachary Lippman of Cold Spring Harbor Laboratory in New York.

Chinese leaders "want to strategically invest in genome editing, and [by that] I mean, catch up," says Zhang Bei, who heads a team of 50 scientists at the Syngenta Beijing Innovation Center and works closely with a sister R&D facility in Durham. "And they also want to be the global leader as well in this area."

China may one day need CRISPR-modified plants to provide enough food for its massive population, notes rice researcher Li Jiayang, former president of the Chinese Academy of Agricultural Sciences in Beijing and vice minister of agriculture. "We have to feed 1.4 billion people with very limited natural resources," says Li, who works at the same CAS campus as Gao, the Institute of Genetics and Developmental Biology. "We want to get the highest yield of production with the least input on the land from fertilizers and pesticides, and breed super-varieties that are pest and disease resistant as well as drought and salt tolerant. All this means we need to find the key genes and to work with them."

Before the harvest of that effort can move from labs to farms and

Gao Caixia's team grows CRISPR-modified rice strains in experimental paddies near its lab in Beijing.

tables, however, China needs to resolve how it will regulate CRISPR-engineered crops—a divisive issue in many countries. In a 2018 decision that rocked big agriculture, a European court ruled that such crops are genetically modified organisms (GMOs) that need strict regulation. In contrast, the U.S. Department of Agriculture (USDA) exempts genome-edited plants from regulations covering GMOs as long as they were produced not by transferring DNA from other species, but by inducing mutations that could have occurred naturally or through conventional breeding.

Chinese consumers are wary of GM food. The country strictly limits the import of GM crops, and the only GM food it grows are papayas for domestic consumption. But for CRISPR, many plant researchers around the world, Lippman included, assume China will follow in the United States's footsteps.

Whatever the outcome of China's regulatory decision, it won't address CRISPR's own limitations, especially for changing crop traits influenced by multiple genes. "We still have to tackle a lot of those challenges," Voytas says. But he expects China's major academic and industrial push into CRISPR to pay off in improved techniques as well as new crops. "China definitely has the foundation to contribute and make discoveries on those frontiers, particularly now that such a big investment has been made."

GAO DOESN'T HAVE a farming background, and as a teenager she did not dream of becoming a plant scientist. "If I said that, I'd be lying," Gao says, laughing again.

High school students in China take a standard exam, the *gaokao*, and their performance leads to offers in specific majors at specific universities. "I thought it would be very nice to be a doctor, but I was not really at that level," Gao says. She was offered a slot at an agricultural university. "I thought that was fine because otherwise I'd be quite embarrassed to go back to high school for another year to take the exam again."

Whatever the downsides of an educational system that puts the country's needs above individual desires, it has helped build a strong agriculture research community for China. And the nation backs it with money. In 2013, the most recent year for which USDA has comparative figures, China's public funding of agricultural research approached $10 billion—more than twice what the U.S. government spent—and it supported more than 1100 agricultural research institutes. "I of course need to apply for all my grants, but the percentage of my proposals that get funded seems higher than the rest of the world," Gao says.

Gao did not immediately embrace CRISPR after reading the landmark study in June 2012 that showed how to transform the bacterial system into a tool for altering genomes. Her lab at the time was having steady success with a more cumbersome genome editor, transcription activator-like effector nuclease (TALEN), the system Voytas invented. "We had knocked out more than 100 genes with TALEN, and we were so proud of it," Gao says. "And you think, 'a new technology, arrrgh, should we try it or not?'"

Gao's first CRISPR success—her proof-of-principle editing of plant DNA—was with rice, which has a genome one-eighth the size of the one in humans. But she soon tackled wheat, which has six sets of chromosomes and a genome nearly six times larger than the human one. In a tour de force experiment published in *Nature Biotechnology* in July 2014, Gao's group showed how either TALEN or the much simpler CRISPR could cripple production of a protein that makes wheat susceptible to powdery mildew, a fungal disease that extensively damages harvests. With conventional breeding, "that would have been a nightmare, if not impossible," Lippman says, because wheat has six copies of the key gene, and knocking out all of them would have taken multiple generations.

CRISPR can easily modify several genes in one step, and it is faster and simpler than TALEN. But CRISPR has its limits: In a paper in the 19 April issue of *Science*, Gao's lab showed that one popular CRISPR variation called base editors makes many unintended "off-target" mutations. And although CRISPR efficiently knocks out existing genes, putting many plant traits within its reach, it can't efficiently add new genes. "We are not so good at it," Gao says. No one is. Gao notes her lab succeeds only about 1% of the time, but it—and the rest of the plant CRISPR world—is trying to improve those odds.

CRISPR researchers are also looking for easier ways to get the components of the genome editor—typically two or more genes—through the tough walls that protect plant cells. For now, scientists depend on cumbersome injection devices known as gene guns or on growing specialized plant-infecting bacteria to deliver the CRISPR apparatus. But China's new acquisition, Syngenta, may have a more elegant approach. Its North Carolina unit has engineered corn pollen to deliver the CRISPR machinery into cells, where it makes an edit and then disappears. Preliminary evidence, reported in the April issue of *Nature Biotechnology*, shows the strategy works in wheat and a few vegetable species.

Most of all, scientists still need to identify the right genes to manipulate, says geneticist Catherine Feuillet, who previously headed crop science at Bayer and now is chief scientific officer of Inari Agriculture, a startup in Cambridge, Massachusetts. (The firm has licensed Lippman's technology and he is a consultant.) Changing a single gene to control pests or a fungus has been the "bread and butter of biotech," Feuillet says, but multiple genes—often unidentified—affect prized traits such as yield, drought tolerance, or the ability to survive without agrochemicals. "The person who can predict that 'if you do this edit, this is the performance you have' is the winner of the whole game," Feuillet says.

ALTHOUGH GAO, Bei, and the rest of China's CRISPR plant community are ready to unleash a bounty of edited crops, their government first has to clarify its regulatory policies. Many agricultural industry observers think it's waiting to see how the public reacts in the United States as companies there tiptoe into that future. In February, Calyxt—a Minneapolis, Minnesota, company that Voytas co-founded—brought to the U.S. market the first gene-edited food product, a "healthier" soybean oil created with TALEN that it sells to the food industry. Calyno oil, the company boasts, has zero trans fats, 80% oleic acid, and "three times the fry life and extended shelf life."

Corteva, of Wilmington, Delaware, will likely bring the first CRISPR crop to market, and it, too, is far from one that will help feed the world. Corteva—DowDuPont's agricultural arm, now rebranded with a consumer-friendly name—deleted a gene in order to improve what's known as waxy corn, which industry uses to make shiny paper and to thicken food. Neal Gutterson, Corteva's chief technology officer, says the company hopes its new, even waxier corn will help the public become more comfortable with the concept of CRISPR-altered food. "People don't like the combination of technology and food in the same sentence, certainly not in the same phrase," he says.

For Corteva, Syngenta, and the other two big ag companies—BASF and Bayer (which acquired Monsanto last year)—the long game is to use CRISPR to develop better versions of their serious moneymakers, the "elite" varieties of a wide range of crops that have big commercial markets. They sell dozens of kinds of elite corn seeds—for example, inbred strains that consistently have high yields or reliable resistance to herbicides. Creating the genetic purity needed for an elite variety typically takes traditional breeding of many generations of plants, and CRISPR is seen as the cleanest way to improve them quickly. The earlier methods of engineering a plant can lead to unwanted genomic changes that must be laboriously culled.

A lab technician at Syngenta's Beijing Innovation Center moves genome-edited soybean sprouts into fresh growth media.

PHOTO: JON COHEN/*SCIENCE*

The Chinese government signaled it would back modern genome editing of plants in a 5-year plan issued in 2016, and to many observers the purchase of Syngenta confirmed that. "They have had a plan for years now, and I think the Syngenta acquisition was part of that plan at the outset," says food scientist Rodolphe Barrangou, a pioneering CRISPR researcher who previously headed genomics R&D at DuPont and now is at North Carolina State University in Raleigh.

Barrangou suggests the Chinese government is reticent about how it will regulate CRISPR-modified plants for strategic reasons. "In terms of gamesmanship, is it not possible that they will make the announcement when they're ready to give the green light at the same time with their own products?"

It's too soon to say which CRISPR crop Syngenta will try to take to market first if China gives the green light, says Wu Gusui, who heads seed research at the company's North Carolina facility. "It could be tomato, could be corn, depending on the progress of the next 2 or 3 years." But he says Syngenta sees CRISPR-modified corn as a big opportunity in China, which grows more hectares of corn than any other crop. Yields per hectare are only 60% of those in the United States because corn ear worms often weaken Chinese crops. A fungus thrives in the weakened plants, producing a toxin that makes the resultant ears unfit for animal feed. As a result, China must import a great deal of corn. (According to USDA, 82% of U.S.-grown corn has been engineered to have a bacterial gene that makes it resistant to ear worms.)

CRISPR could allow Syngenta to quickly modify the corn genomes to introduce insect resistance or other traits, bolstering China's food supply while transforming agribusiness there. The country's seed marketplace has some 3000 companies, and none has more than a 10% share of corn, Wu says. "Syngenta is putting a lot of emphasis to grow in China to become the leading seed company. The China market as a whole, if it modernizes as the U.S. has modernized, can be as big as the U.S. market."

Gao has her own contenders to be China's first CRISPR crops: different kinds of aromatic rice—"it's easy to make and very popular," she says—and wheat that's resistant to powdery mildew. Regardless of which crops make it to farmers first, Gao says, they likely will arrive long before any CRISPR-derived medical treatment reaches a doctor's office or an animal product comes to market. Crops may have a lower profile, but the research also presents fewer risks and ethical dilemmas. Propelled by China's vast investment, it is also much further along.

Just ask Gao. If Chinese regulators do open the door for CRISPR-engineered food, how long would it take before something in one of her culture rooms or greenhouses might be ready for planting on a commercial farm? "Six months," she says. "That's why we work with CRISPR."

And Gao doesn't laugh when she says that. ■

Science

Fields of dreams

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Science **365** (6452), 422-425.
DOI: 10.1126/science.365.6452.422

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