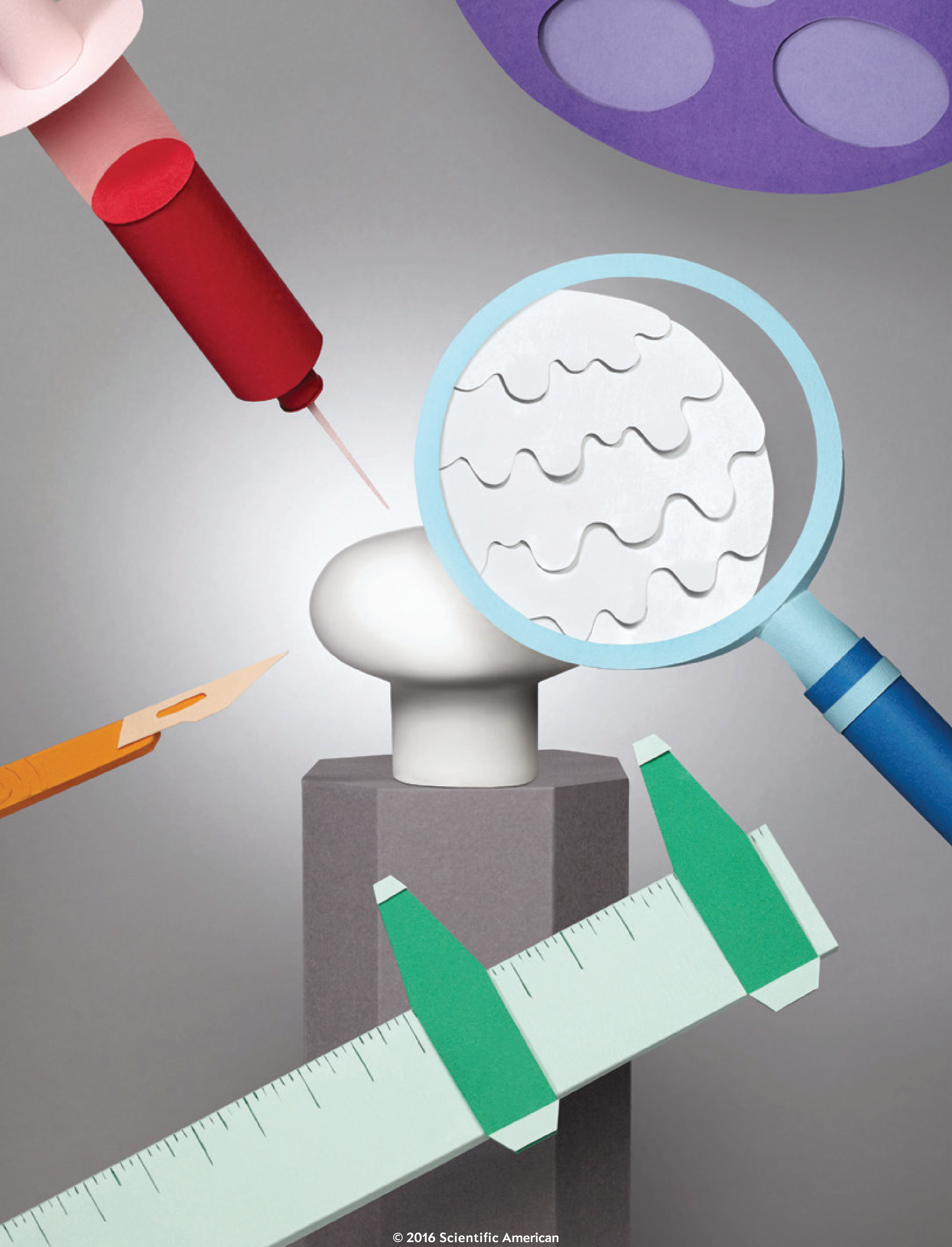

editing the mushroom

A powerful new gene-editing tool is sweeping agriculture. It could transform the debate over genetic modification

By Stephen S. Hall

THE HUNDRED OR SO FARMERS crowding the ballroom of the Mendenhall Inn in Chester County, Pennsylvania, might not have had a background in gene editing, but they knew mushrooms. These local growers produce a staggering 1.1 million pounds of mushrooms on average every day, which is one reason Pennsylvania dominates the annual $1.2-billion U.S. market. Some of the mushrooms they produce, however, turn brown and decay on store shelves; if you've ever held a slimy, decomposing, formerly white mushroom in your hand, you know why no ones buys them. Mushrooms are so sensitive to physical insult that even careful "one-touch" picking and packing can activate an enzyme that hastens their decay.

IN BRIEF

The gene-editing tool called CRISPR allows scientists to alter an organism's genome with unprecedented precision.

CRISPR has the potential to put powerful genetic-modification capabilities into the hands of small agricultural firms, rather than big agribusinesses, because it is easy and inexpensive to use.

Proponents say it is less biologically disruptive than traditional plant-breeding techniques practiced for thousands of years. Regulators tend to agree.

CRISPR could transform the debate over genetically modified foods—or be seen as the latest Frankenfood.

PHOTOGRAPH BY EMMA TODD

Illustration by Owen Gildersleeve

On a foggy morning last fall, at a continuing education seminar on mushrooms, a biologist named Yinong Yang took the podium to deliver news of a possible solution for the browning problem. Yang, a cheerfully polite professor of plant pathology at Pennsylvania State University, is not an expert in the field. ("The only thing I know about mushrooms is how to eat them," he says.) But he edited the genome of *Agaricus bisporus,* the most popular dinner-table mushroom in the Western world, using a new tool called CRISPR.

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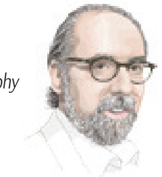


The mushroom farmers in the audience had probably never heard of CRISPR, but they understood it was a big deal when Yang showed a picture of actress Cameron Diaz awarding inventors Jennifer Doudna and Emmanuelle Charpentier the Breakthrough Prize in November 2014, which came with a check for $3 million each. And they understood the enormous commercial implications when Yang showed them photographs comparing brown, decayed mushrooms with pristine white CRISPR-engineered *A. bisporus,* the all-purpose strain that annually accounts for more than 900 million pounds of white button, cremini and portobello mushrooms. (Penn State understood the commercial implications, too; the day before Yang's talk, the university filed for a patent on the mushroom work.)

In its brief three years as a science story, CRISPR has already generated more fascinating subplots than a Dickens novel. It is a revolutionary research tool with dramatic medical implications, thorny bioethical conundrums, an awkward patent spat and, floating over it all, billion-dollar commercial implications for medicine and agriculture. The technique has blown through the basic research community like an F5 tornado. Academic laboratories and biotech companies are chasing novel treatments for diseases such as sickle-cell anemia and beta-thalassemia. And there has even been speculation about DIY artists and bioentrepreneurs creating everything from purple-furred bunnies to living, breathing gene-edited tchotchkes, like the miniaturized pigs recently made in China as pets. The prospect of using CRISPR to repair embryos or permanently edit our DNA (a process known as human germ-line modification) has sparked fevered talk of "improving" the human species and calls for international moratoriums.

The CRISPR revolution may be having its most profound—and least publicized—effect in agriculture. By the fall of 2015 about 50 scientific papers had been published reporting uses of CRISPR in gene-edited plants, and there are preliminary signs that the U.S. Department of Agriculture, one of the agencies that assesses genetically modified agricultural products, does not think all gene-edited crops require the same regulatory attention as "traditional" genetically modified organisms, or GMOs. With that regulatory door even slightly ajar, companies are racing to get gene-edited crops into the fields and, ultimately, into the food supply.

The transformative aspect of CRISPR lies in its unprecedented precision. CRISPR allows you to knock out any gene or, with a little more effort, to add a desirable trait by inserting a gene in a specific place in a genome. This makes it, according to its practitioners, the least biologically disruptive form of plant breeding that humans have ever devised—including the "natural" breeding techniques that have been practiced for thousands of years. It also enables scientists to sidestep, in many cases, the controversial techniques of inserting DNA from other species into plants; these "transgenic" crops, such as the Monsanto-made corn and soybeans that are resistant to the herbicide Roundup, have aroused particular ire in GMO critics and led to public distrust of the technology. Yet some scientists are optimistic that CRISPR crops are so fundamentally different that they will change the tenor of the debate over GMO foods. "The new technology," says Daniel F. Voytas, an academic and company-affiliated scientist, "is necessitating a rethinking of what a GMO is."

Will consumers agree? Or will they see CRISPR crops as the latest iteration of Frankenfood—a genetic distortion of nature in which foreign (and agribusiness-friendly) DNA is muscled into a species, with unpredictable health or environmental consequences? Because CRISPR is only now being applied to food crops, the question has not yet surfaced for the public, but it will soon. Farmers such as Yang's mushroom growers will be the first to weigh in—probably in the next year or two.

Moments after Yang's talk, an industry scientist confronted him with the central challenge of CRISPR food. The researcher conceded Yang's point that the improved mushrooms required minimal tinkering with DNA compared with conventional GMOs. "But," the scientist said, "it *is* genetic modification, and some people will see it as we are playing God. How do we get around that?"

How well Yang and other scientists applying these gene-editing techniques to food can answer that question will determine whether CRISPR is a potentially transformational tool or one that will be stymied by public opposition.

"WOW, THAT'S THE ONE!"

THE TELLTALE SIGN of any transformational technology is how quickly researchers apply it to their own scientific problems. By that standard, CRISPR ranks among the most powerful additions to biology's tool kit in the past half a century. The gene-edited mushroom is a case in point.

Yinong Yang—his first name means "also practices agriculture" in Chinese—never worked with mushrooms until 2013, but you might say he was to the task bred. Born in Huangyan, a city south of Shanghai known as the citrus capital of China, he dabbled with some primitive gene-editing enzymes in the mid-1990s as a graduate student at the University of Florida and later at the University of Arkansas. He vividly remembers opening the August 17, 2012, issue of *Science,* which contained a paper from Doudna's lab at the University of California, Berkeley, and Charpentier's lab describing CRISPR's gene-editing potential. "Wow," he thought. "That's the one!" Within days he was hatching plans to improve traits in rice and potato plants through gene editing. His lab published its first CRISPR paper in the summer of 2013.

He was not alone. Plant scientists jumped on CRISPR as soon as the technique was published. Chinese scientists, who quickly embraced the technology, shocked the agricultural community in 2014 when they showed how CRISPR could be used to make bread wheat resistant to a long-standing scourge, powdery mildew.

The gene-editing revolution had begun before the arrival of CRISPR, however. For people like Voytas, CRISPR is merely the latest chapter in a much longer scientific saga that is just now bearing fruit. He first attempted gene editing in plants 15 years ago, while at Iowa State University, with a technology known as zinc fingers; his first gene-editing company foundered on patent issues. In 2008 he moved to the University of Minnesota and in 2010 patented, with former Iowa State colleague Adam Bogdanove, now at Cornell University, a gene-editing system in plants based on TALENs, a subsequent gene-editing tool. That same year Voytas and his colleagues started a company now known as Calyxt. Without the hoopla of CRISPR, agricultural scientists have used TALENs to produce gene-edited plants that have already been grown in fields in North and South America. Calyxt, for example, has created two strains of soybean modified to produce a healthier oil, with levels of monosaturated fats comparable to olive and canola oils. And the company has gene-edited a potato strain to prevent the accumulation of certain sugars during cold storage, reducing the bitter taste associated with storage, as well as the amount of acrylamide, a suspected carcinogen, produced when potatoes are fried.

Because these genetic modifications did not involve the introduction of any foreign genes, the USDA's Animal and Plant Health Inspection Service (APHIS) decided last year that the crops do not need to be regulated as GMOs. "The USDA has given regulatory clearance to plant a potato variety and two soybean varieties, so the potato and one of the soybean varieties are in the field this year," Voytas told me last October. "They basically considered these as just standard plants, as if they were generated by chemical mutagens or gamma rays or some nonregulated technology. The fact that we got regulatory clearance and can go almost immediately from the greenhouse to the field is a big plus. It allows us to really accelerate product development."

Animal scientists have also jumped on the gene-editing bandwagon. Researchers at the small Minnesota-based biotech firm Recombinetics have genetically blocked the biological signal that governs the growth of horns in Holstein cows, the workhorse of the dairy industry. They accomplished this by using gene editing to replicate a mutation that naturally occurs in Angus beef cattle, which do not grow horns. Ag scientists tout this application of gene editing as a more humane form of farming because it spares male Holstein cows from a gruesome procedure during which dairy farmers physically gouge out and then cauterize developing horns (the procedure is done to protect both dairy cattle and dairy farmers from injury). Scott Fahrenkrug, the company's CEO, says the process does not involve transgenes, just the introduction of a few letters of DNA "to match the food we already eat." Korean and Chinese scientists, meanwhile, have teamed up to produce a pig with much more muscle mass, by using gene editing to knock out a gene called myostatin.

The speed, ease and thrift of CRISPR make it an even more attractive technique than TALENs. "Without a doubt," Voytas says, in the future CRISPR "is going to be the plant-editing tool of choice." But the murky patent situation—both the University of California and the Broad Institute (run jointly by the Massachusetts Institute of Technology and Harvard University) claim to have invented CRISPR—may slow commercial agricultural development. DuPont recently reached a "strategic alliance" with Caribou Biosciences, a biotech associated with U.C. Berkeley, to use CRISPR applications in agriculture, but executives at two small biotechs told *Scientific American* that they were wary of developing CRISPR-related products while the patent dispute remains unresolved.

That's not a big issue for academic labs. The mushroom story took a decisive turn in October 2013, when a Penn State alum named David Carroll popped into Yang's lab. Carroll, who happened to be president of Giorgi Mushroom, wondered if new gene-editing techniques could be used to improve mushrooms. Emboldened by the power of CRISPR to create highly precise mutations, Yang replied, "What kind of trait do you want?" Carroll suggested antibrowning, and Yang immediately agreed to try it.

Yang knew exactly which gene he wanted to target. Biologists had previously identified a family of six genes, each of which encode an enzyme that causes browning (the same class of genes also triggers browning in apples and potatoes, both of which have been targeted by gene editors). Four of the so-called browning genes churn out that enzyme in the fruiting body of mushrooms, and Yang thought that if he could shut down one of them through a gene-editing mutation, he might slow the rate of browning.

The brilliant ease of CRISPR derives from the fact that it is straightforward for biologists to customize a molecular tool—a "construct"—that creates such mutations. Like a utility knife that combines a compass, scissors and vise, these tools excel at two tasks: homing in on a very specific stretch of DNA and then cutting it (the vise, or scaffolding, holds everything in place during the cutting). The homing is accomplished by a small piece of nucleic acid called the guide RNA, which is designed to mirror the DNA sequence in the target area and attach to it using the unique and specific attraction of DNA base pairs made famous by James Watson and Francis Crick (where As grab onto Ts and Cs grab onto Gs). If you make a piece of guide RNA that is 20 letters long, it will find its mirror sequence of DNA—with GPS-like precision—amid the string of 30 million letters that spell out the *Agaricus* mushroom genome. The cutting is then accomplished by the Cas9 enzyme, originally isolated from bacterial cultures in yogurt, which rides in on the back of the guide RNA. (The term "CRISPR/Cas9" is a bit of a misnomer now because CRISPR refers to *c*lustered *r*egularly *i*nterspersed *s*hort *p*alindromic *r*epeats, patches of DNA that occur only in bacteria. It is the Cas9 protein, loaded with an RNA targeting sequence, that edits plant, fungal and human DNA, even though no CRISPRs are involved.)

Once gene editors cut DNA at the desired spot, they let nature perform the dirty work of mutation. Any time the double helix of DNA is cut, the cell notices the wound and sets out to repair the break. These repairs are not perfect, however, which is exactly what makes CRISPR so powerful at creating mutations. During the repair process, a few letters of DNA usually get deleted; because a cell's protein-making machinery reads DNA in three-letter "words," deleting a couple of letters subverts the entire text and essentially inactivates the gene by creating what is known as a reading frame shift. That is precisely what happened with the gene-edited mushroom. In Yang's work, a tiny deletion of DNA inactivated one of the enzymes that promote browning—a mutation that Yang and his colleagues confirmed with DNA analysis. Editing complete. According to Yang, a skillful molecular biologist could in about three days build a custom-designed mutation tool to edit virtually any gene in virtually any organism.

That sentiment echoes the mantra scientists constantly in-

PLANT BREEDING

Genetic Modification by Any Other Name

People have been cultivating crops for thousands of years, and for all that time they have aimed to identify and incorporate beneficial traits (higher yields, for example, or disease resistance) into existing plant varieties. First they used conventional crossbreeding. In the early 20th century scientists learned to deliberately mutate the DNA of existing plants and hope for desirable traits to appear at random. Today new "precision breeding" techniques such as CRISPR enable scientists to mutate specific genes or insert new genetic traits with unprecedented precision. Yet *all* these techniques alter the DNA of the plants, so what counts as a genetically modified organism (GMO), anyway?

Key Concepts

Mutagenesis Since the 1920s agricultural scientists have deliberately mutated the DNA of plant seeds with x-rays, gamma rays or chemicals and then grown the plants to see if they have acquired beneficial traits. If so, the mutated plants can be crossbred with existing varieties. Plants created this way are not considered GMOs by the U.S. Department of Agriculture.

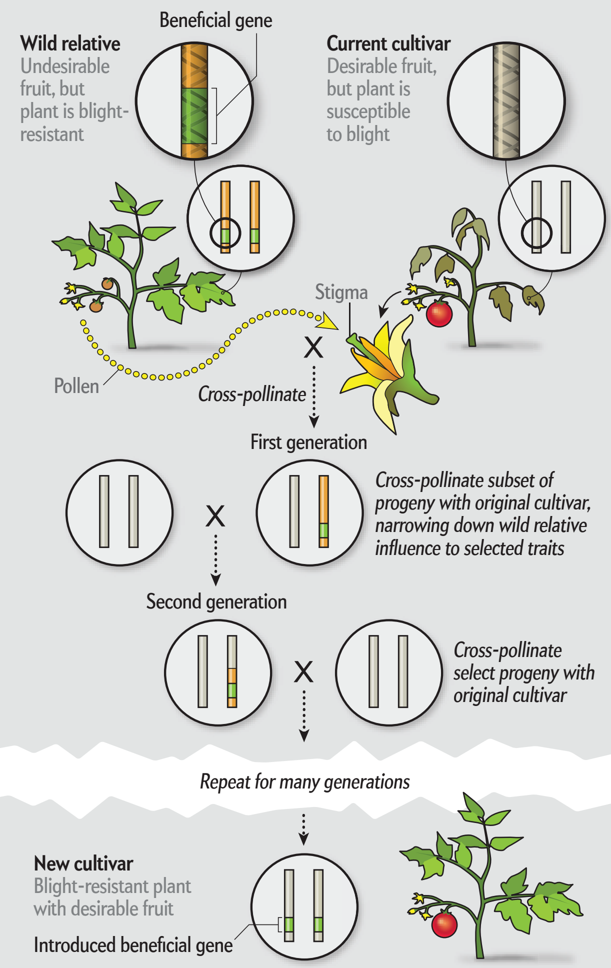
Gene Silencing For the past decade scientists have been able to turn off genes that confer unwanted traits by introducing a disruptive form of RNA into plant cells. This "interfering" RNA (or iRNA) is engineered to disrupt a specific sequence of DNA underlying an undesirable trait. Several food crops, including nonbrowning potatoes and apples, have been created in this way. The USDA does not call them GMOs.

Cisgenesis This process involves introducing a specific gene from a related plant species. The transfer is typically accomplished by a plant-infecting microbe called *Agrobacterium tumefaciens*, which can insert the gene into a semirandom spot in the plant's DNA. The USDA reviews cisgenic plants on a case-by-case basis to determine their regulatory status.

Transgenesis The technique involves the transfer of foreign DNA encoding a desired trait into an unrelated plant species. As in cisgenesis, *A. tumefaciens* is used to smuggle in the foreign DNA when the bacterium infects a plant cell. Examples of transgenic crops include corn into which a herbicide-resistant gene has been inserted. Ninety percent of all soybeans grown in the U.S. are transgenic; the USDA considers transgenic plants to be GMOs.

Conventional Crossbreeding

Includes selective breeding and crossbreeding following mutagenesis. During natural breeding, large segments of chromosomes—up to millions of base pairs—are introduced along with the desired trait into a domesticated cultivar. Subsequent crosses typically reduce the amount of transferred DNA, but the insert often remains hundreds of thousands of base pairs long and can drag along undesirable genes ("linkage drag") in the process. A 2010 genomic analysis of *Arabidopsis* (considered the "mouse model" of plants) showed that conventional breeding introduced approximately seven spontaneous new mutations per billion base pairs of DNA in each generation.

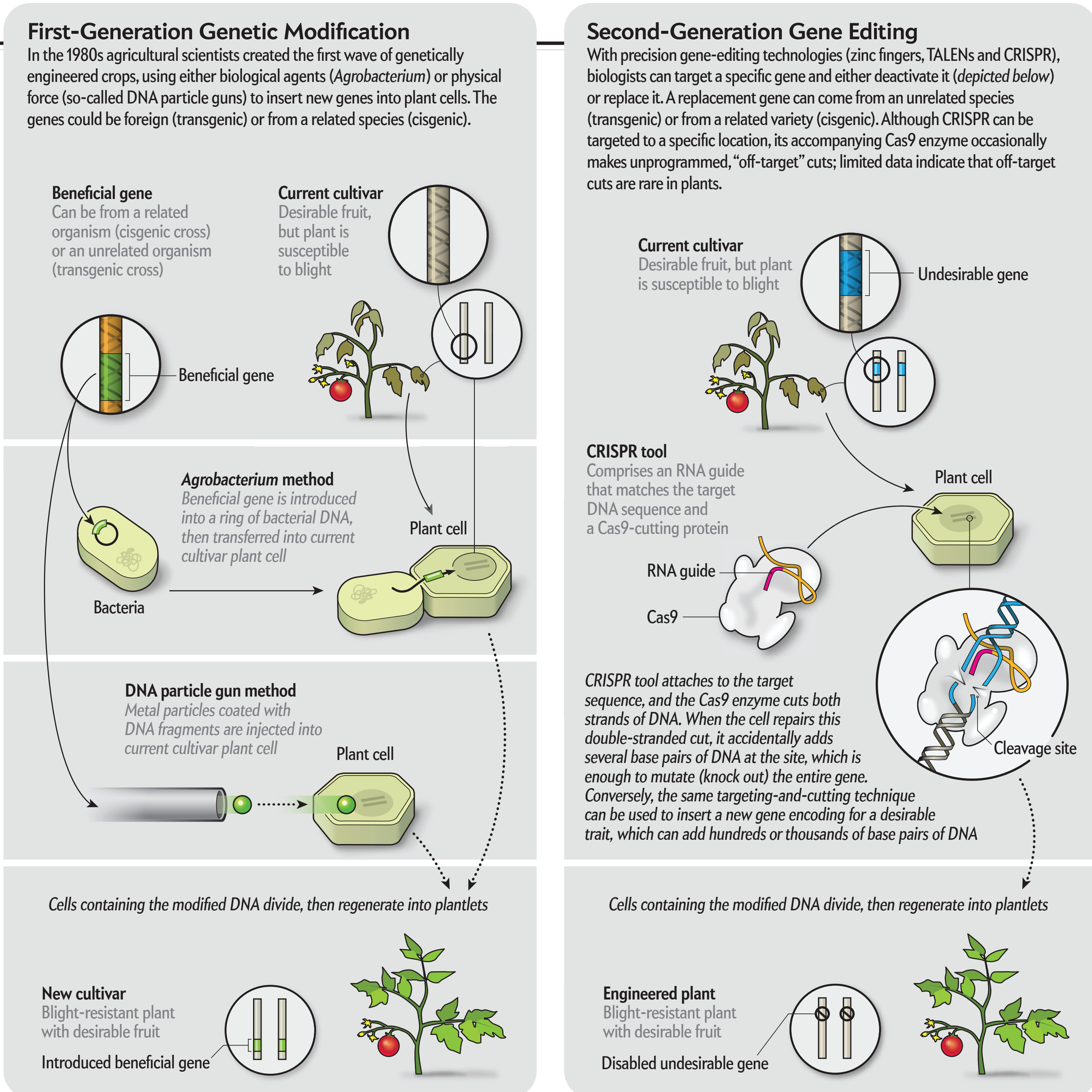


voke about CRISPR: it is fast, cheap and easy. It took about two months of lab work to create the antibrowning mushroom; Yang's demeanor suggested that the work was routine, if not ridiculously easy. And it was remarkably inexpensive. The trickiest step, making the guide RNA and its scaffolding, cost a couple of hundred dollars; a number of small biotech firms now make custom-order CRISPR constructs to edit any gene desired. The biggest cost is manpower: Xiangling Shen, a postdoctoral fellow in Yang's lab, worked on the project part-time. "If you don't consider manpower, it probably cost less than $10,000," Yang says. In the world of agricultural biotech, that is chump change.

And that doesn't begin to hint at the potentially game-changing thrift of CRISPR in the regulatory arena. Last October, Yang gave an informal presentation of the mushroom work to federal regulators at the USDA's APHIS, which decides if genetically modified food crops fall under government regulatory control (in short, whether they are considered a GMO); he came away from the meeting convinced that USDA regulators did not believe the CRISPR mushroom would require special or extended regulatory review. If true, that may be the most important way CRISPR is cheaper: Voytas has estimated that the regulatory review process can cost up to $35 million and take up to five and a half years.

Another advantage of the mushroom as a proof of principle for CRISPR in agriculture is the speed at which fungi grow: from spawn to maturity, mushrooms take about five weeks, and they can be grown year-round in windowless, climate-controlled facilities known as mushroom houses. The gene-edited soybeans and

Illustrations by Jen Christiansen



potatoes created by Calyxt, in contrast, take months to field-test, which is why the company sought, and received, regulatory clearance to grow its soybeans in Argentina last winter (2014–2015). "You bop back and forth over the equator," Voytas says, "so you can get multiple plantings in a year." Calyxt harvested its first North American gene-edited crops from the field last October.

One of the long-standing fears about genetic modification is the specter of unintended consequences. In the world of biotech foods, this usually means unexpected toxins or allergens making modified foods unhealthy (a fear that has never been documented in a GMO food) or a genetically modified crop running amok and devastating the local ecology. CRISPR is even making people such as John Pecchia think about unintended economic consequences. One of two mushroom professors at Penn State, Pecchia spends a lot of time in a low-slung cinder-block building situated on the outskirts of the campus, which houses the only center of academic mushroom research in the U.S. In the spring of 2015 Pecchia took some of Yang's starter culture and grew up the first batch of gene-edited mushrooms. Standing outside a room where a steamy, fetid mix of mushroom compost was brewing at 80 degrees Celsius, he notes that a mushroom with a longer shelf life might result in smaller demand from stores and also enable unexpected competition. "You could open up the borders to foreign mushroom imports," he adds, "so it's a double-edged sword."

In the tortuous path of genetically modified foods to market, here is one more paradox to chew on. No one knows what the gene-edited mushroom tastes like. They've been steamed and boiled, but not for eating purposes. Every mushroom created so far has been destroyed after Yang conducted browning tests. Once proof of principle has been established, Pecchia says, "we just steam them away."

TRANSGENE-FREE MODIFICATION

WILL THE PUBLIC STEAM, sauté or otherwise welcome gene-edited food into their kitchens and onto their plates? That may be the central question in the most intriguing chapter in the CRISPR food story, which coincides with a crucial juncture in the tumultuous, 30-year debate over genetically modified crops.

When Yang described his mushroom project to the Pennsylvania farmers—and to officials at the USDA last October—he used a telltale phrase to describe his procedure: "transgene-free genetic modification." The phrase is a carefully crafted attempt to distinguish the new, high-precision gene-editing techniques like CRISPR from earlier agricultural biotech, where foreign DNA (transgenes) were added to a plant species. For Yang and many others, that delicate wording is important in recasting the GMO debate. Indeed, the acronym "GEO" (for gene-edited organism) has begun to crop up as an alternative to "GMO" or "GM."

New technologies like CRISPR are forcing some governments to reconsider the definition of a genetically modified organism.

The reframing is as much philosophical as semantic, and it is unfolding as the Obama administration is overhauling the system by which the government reviews genetically modified crops and foods. Known as the Coordinated Framework for Regulation of Biotechnology, this regulatory process, which has not been updated since 1992, defines roles for the USDA, the Food and Drug Administration, and the Environmental Protection Agency. The power of CRISPR has added urgency to the regulatory rethink, and scientists are using the opportunity to revisit a very old question: What exactly does "genetically modified" mean? Voytas, whose track record of publications and patents in gene-edited food crops makes him a sort of editor in chief of small agricultural biotechs in the U.S., answered with a grim little laugh when asked that question: "The GM term is a tricky one."

What's so tricky about it? Most critics of biotech food argue that any form of genetic modification is just that, genetic modification, bringing with it the possibility of unintended mutations or alterations that could pose risks to human health or the environment. Scientists such as Voytas and Yang reply that *all* forms of plant breeding, dating all the way back to the creation of bread wheat by Neolithic farmers 3,000 years ago, involve genetic modification and that the use of traditional breeding techniques is not a biologically benign process. It creates, as Yang put it, "huge" genetic disruptions. (Nina Fedoroff, a plant biologist and former president of the American Association for the Advancement of Science, has referred to domesticated versions of bread wheat, created by traditional breeding, as "genetic monstrosities.")

Before the era of recombinant DNA in the 1970s, which allowed first-generation agricultural biotech, plant breeders typically resorted to brute-force methods (x-rays, gamma rays or powerful chemicals) to alter the DNA of plants. Despite this blunderbuss approach, some of these random, man-made mutations modified genes in a way that produced desirable agricultural traits: higher yields, or more shapely fruit, or an ability to grow in adverse conditions such as drought. These beneficial mutations could then be combined with beneficial traits in other strains but only by crossing—or mating—the plants. That type of crossbreeding takes a lot of time (often five to 10 years), but at least it is "natural."

But it is also very disruptive. Any time DNA from two different individuals comes together during reproduction, whether in humans or plants, the DNA gets scrambled in a process known as chromosomal reassortment. Spontaneous mutations can occur in each generation, and millions of base pairs of DNA can be transferred when breeders select for a desired trait. It is natural, yes, but also "a big mash-up," according to Voytas. "In that process, you don't just move one gene," he says. "You often move a pretty big chunk of DNA from the wild species." Moreover, the desirable trait often drags along with it an undesirable trait on the same piece of DNA during the process of breeding; this "linkage drag" can actually harm the naturally bred plant. On the basis of several recent findings on the genetics of rice plants, some biologists hypothesize that domestication has inadvertently introduced "silent" detrimental mutations as well as obvious beneficial traits.

Although CRISPR is more precise than traditional breeding, the technique is not infallible. The precision cutting tool sometimes cuts an unintended region, and the frequency of these "off-target" cuts has raised safety concerns (it is also the main reason that gene editing of human sperm and egg cells is still considered unsafe and unethical). Jennifer Kuzma, a policy analyst at North Carolina State University, who has followed the science—and politics—of GMO agriculture since its inception, says, "That precision has merit, but it doesn't necessarily correlate with risk reduction," adding that off-target cuts "may introduce a different pathway to hazard." Feng Zhang of the Broad Institute (which holds the patent that is now being disputed) has published several refinements in the CRISPR system that improve specificity and reduce off-target hits.

The ease and relative thrift of CRISPR have also allowed academic labs and small biotechs back into a game that has historically been monopolized by big agribusinesses. Only deep-pocketed companies could afford to run the costly regulatory gauntlet in the beginning, and to date, almost every crop modification created by genetic engineering was done to enhance the economics of food production for farmers or companies, be it the increased yields of Monsanto's herbicide-resistant field crops or the shipping hardiness of Calgene's ill-fated Flavr-Savr tomato. Those genetic crop modifications were more appealing to agribusiness than consumers, and they were not very food-centric.

SCIENTIFIC AMERICAN ONLINE For more coverage of CRISPR, go to ScientificAmerican.com/mar2016/crispr

As a group of agricultural policy experts at the University of California, Davis, recently observed, “the multinational corporations that have dominated the field for the past decade and a half do not have a glowing record in terms of innovation beyond traits for pesticide and herbicide resistance.”

The new players have brought a different kind of innovation to agriculture. Voytas, for example, argues that the precision of gene editing is allowing biotech scientists to target consumers by creating healthier, safer foods. Voytas and his colleague Caixia Gao of the Chinese Academy of Sciences have pointed out that plants have many “antinutritionals”: noxious self-defense substances or outright toxins that could be gene-edited away to improve nutritional and taste traits. Calyxt’s gene-edited potato, for example, reduces a bitter taste trait associated with cold storage of the tubers.

But Voytas goes even further. He believes the Calyxt soybean could be sold to farmers as a non-GMO product because, unlike 90 percent of soybeans grown in the U.S., the gene-edited strains do not have any transgenes. “A lot of people don’t want GM products,” he says. “We could maybe make non-GM soybean oil and non-GM soybean meal with our product.”

Like any powerful new technology, CRISPR has inspired some agricultural dreamers to envision almost science-fiction scenarios for the future of farming—scenarios that are already making their way into the scientific literature. Michael Palmgren, a plant biologist at the University of Copenhagen, has proposed that scientists can use the new gene-editing techniques to “rewild” food plants, that is, to resurrect traits that have been lost during generations of agricultural breeding. A number of economically significant food crops—notably rice, wheat, oranges and bananas—are highly susceptible to plant pathogens; the restoration of lost genes could increase disease resistance. The idea, Palmgren and his Danish colleagues recently noted, aspires to “the reversal of the unintended results of breeding.”

Attempts at rewilding are already under way but with a twist. Rather than restoring lost wild traits to domestic breeds, Voytas says his University of Minnesota lab is attempting what he calls “molecular domestication”: transferring agriculturally desirable genes from existing hybrids back into wild species that are hardier and more adaptable, such as the ancestral form of corn, and potatoes. “It’s usually only a handful of critical changes that occurred—five, six or seven genes—that allowed a weedy species to become desirable, such as changes in fruit size or corn ear number, those sorts of things,” Voytas says. Rather than crossing the wild varieties with the domesticated strains, which would require a 10-year breeding regime, he says, “maybe we can just go in and treat those genes and domesticate the wild variety.”

There are early signs that gene editing, including CRISPR, may also enjoy a speedier regulatory path. So far U.S. regulators appear to view at least some gene-edited crops as different from transgenic GMO crops. When Calyxt first asked the USDA if its gene-edited potatoes required regulatory review, federal officials took about a year before concluding, in August 2014, that gene editing did not require special consideration; when the company went back to the USDA last summer with its gene-edited soybeans, government reviewers took only two months to reach a similar conclusion. To companies, this suggests that U.S. authorities view the new techniques as fundamentally distinct from transgenic methods; to critics, it suggests a regulatory loophole that companies are exploiting. Yang’s mushrooms may be the first CRISPR food considered by the USDA.

And new technologies like CRISPR are forcing some governments to reconsider the definition of a GMO. Last November the Swedish Board of Agriculture decreed that some plant mutations induced by CRISPR do not meet the European Union’s definition of a GMO, and Argentina has similarly concluded that certain gene-edited plants fall outside its GMO regulations. The E.U., which has historically restricted genetically modified plants, is currently reviewing policy in light of the new gene-editing techniques, but its oft-delayed legal analysis will not be made public until the end of March at the earliest. While there is not much middle ground, Voytas and others have suggested one potential compromise: gene editing that causes a mutation, or “knock out,” should be viewed as analogous to traditional forms of plant breeding (where x-rays, for example, are used to create mutations), whereas gene editing that introduces new DNA (a “knock in”) deserves regulatory scrutiny on a case-by-case basis.

The day of food-market reckoning for gene-edited crops may not be too far off; Voytas estimates that Calyxt will have a “small commercial launch” of its soybeans by 2017 or 2018. “It’s going to take some time to get enough seed for, say, half a million acres,” he says. “But we’re pushing as hard and fast as we can.”

How will the public respond? Kuzma predicts that people who have historically opposed genetic modification will not be drinking CRISPR Kool-Aid anytime soon. “The public that opposed first-generation GMOs is not likely to embrace this second generation of genetic engineering, just because you’re tweaking a little bit of DNA,” she says. “They’re just going to lump it together with GMOs.” Kuzma is more concerned about the need to revamp the overall regulatory structure and bring more voices into the review process, at an “inflection point” at which more and more gene-edited foods are wending their way to the marketplace.

And what about the mushroom? Beyond polite applause at the end of Yinong Yang’s talk, the reaction of mushroom farmers remains unclear. Yang acknowledged as much when he told the farmers, “Whether this can be commercialized, that’s up to you guys.” For now, the antibrowning mushroom is just a lab project, a proof of principle. If growers are unconvinced of the value of the antibrowning mushroom or fear consumers will shun it, the well-edited mushroom may never see the light of day. That’s usually a good thing for a mushroom, which grows in the dark, but is perhaps more ominous for a new and potentially transformative technology. SA

MORE TO EXPLORE

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