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 Men-denhall 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 one 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.

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.
The gene-editing revolution had begun before the arrival of CRISPR, however. For people like Voytas, CRISPR is merely the latest chapter in a long-running 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 founded on patent issues. In 2001, he and Yang teamed up at the University of Minnesota, where they patented, with former Iowa State colleague Adam Bogda- nove, now at Cornell University, a gene-editing system in plants that had been around for almost 20 years. That same year Voytas and his colleagues started a company now known as Calyxt. Without the hoopla of CRISPR, agricultural scientists have been busy in the background for years, working on crops that were never even commercially viable. But now, thanks to CRISPR, the company has created two varieties of soybean to prevent the accumulation of certain sugars during cold storage, reducing the bitter taste associated with stor- age, most of which the researchers think is due to a mutation, generated more fascinating subplots than a Dickens novel. It is a sequence? 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—in probably 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, “We’ve heard of CRISPR, but they understood it was a big deal when Yang showed them photographs comparing CRISPR to a viscous, pristinely white CRISPR-engi- neered *A. bioporus*, the all-purpose strain that annually accounts for more than 900 million pounds of white button mushrooms in the United States. The CRISPR revolution may be having its most profound—and shortest, with the blue-chip generalist *Aspergillus* species. Biologists had even been speculating about new ways to engineer crops and has thus far, CRISPR ranks among the most powerful addi- tives in the biotechnology toolbox. It allows researchers to quickly apply it to their own scientific problems. By 2013, the Czech National Plant Gene Bank already had a CRISPR-edited variety of tobacco resistant to a long-standing scourge, powdery mildew. (Penn State understood the commercial potential of *L. edodes* years ago, producing what would later be *L. edodes*)

The brilliance 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 can 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 damage. It doesn’t matter whether the cut is deliberate or, as in the case of CRISPR, random. The cell’s natural desire to fix the damage is the basis of the technique. It is the cell’s way of dealing with the body’s natural DNA repair kit, which can make mistakes; it can’t always get it right. The CRISPR system consists of two major components. The first is the Cas9 enzyme, which硌s genetically precise guide RNAs (a process known as “ung- mach” or “genetically modified organisms, or GMOs. With that regulatory standard, CRISPR ranks among the most powerful addi- tives in the biotechnology toolbox. It allows researchers to quickly apply it to their own scientific problems. By 2013, the Czech National Plant Gene Bank already had a CRISPR-edited variety of tobacco resistant to a long-standing scourge, powdery mildew. (Penn State understood the commercial potential of *L. edodes* years ago, producing what would later be *L. edodes*)

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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 traditional 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

Matogenesis Since the 1970s, agricultural scientists have deliberately mutated the DNA of plant seeds with tRNA, gamma rays, and chemicals and then grown the plants to see if they have acquired beneficial traits. If so, the mutated plants can be crossed 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 to the plant cells. This “short hair” RNA (siRNA) is engineered to disrupt a specific sequence of DNA underlying an undesirable trait. Wherever it lands, the RNA silences the appropriate gene and the trait is no more. Scientists have cloned this technique into a so-called “gene silencing” edition that is able to silence any gene in the plant’s genome.

Cisgenesis This process involves introducing a specific gene from another species into the plant’s genome. The gene to be transferred is typically accomplished by a plant-infecting microbe called Agrobacterium tumefaciens, which can insert the gene into a small segment of the plant’s DNA. The USDA reviews each species 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.

voice about CRISPR. It is fast, cheap and easy. It took about two months of lab work to create the anthrubishing mushroom. Yang’s demeanor suggested that the work was routine, if not ridiculous-ly easy. And it was remarkably inexpensive. The trickiest step, making the guide RNA and its packaging, cost a couple of hun-dred dollars; a number of small biotech firms now make custom-ordered CRISPR constructs to edit any gene desired. The biggest cost is manpower: Xiangdong Shen, a postdoctoral fellow in Yang’s lab, worked on the project part-time. “If you don’t consider man-power, it probably cost less than $10,000,” Yang says. In the world of agricultural biotech, that is a big change.

And that doesn’t begin to hint at the potentially game-chang-ing thrill 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 be-lieve 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 or more years.

Another advantage of the mushroom as a proof of principle for CRISPR in agriculture is the speed at which fruit grows: from spawn to maturity, mushrooms take about five weeks, and they can be grown year-round in windowless, climate-controlled facili-ties known as mushroom houses. The gene-edited soybeans and potatoes created by Calyxt, in contrast, take months to field-test, which is why the company sought, and received, regulatory clear-ance to grow its soybeans in Argentina last winter (2014–2015). “You hop 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 document-ed 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 conse-quences. One of two mushroom professors at Penn State, Pecchia spends a lot of time in a low-sliding 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 60 degress Celsius, he notes that a mushroom with a longer shelf life might result in smaller demand from stores and also enable unex-pected competition. “You could open up the borders to foreign mushroom imports,” he adds, “so it’s a double-edged sword.”

In the turtleneck 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
The reftarming is as much philosophical as semantic, and it is unfolding as the Obama administration is overhauling the sys-
tem by which the government reviews genetically modified crops and foods. Known as the Coordinated Framework for Regu-
lation of Biotechnology, this regulatory process, which has not been up-
dated since 1986, defines rules 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
both scientists and those who care about the future of the food system
wonder what it means to "genetically modify" or not. One ques-
tion: exactly what does "genetically modified" mean? Voytas,
whose track record of publications and patents in gene-edited foods
is a sterling example in chief of crop development, would say that agricul-
tural biotes in the U.S. answered with a grim little laugh when asked
that question: "The GM term is a tricky one." What you are asking me
is whether we are using a certain technique that sometimes
(see previous page) how genetically modified organisms
are regulated. As a group of agricultural policy experts at the University of Cal-
ifornia, Davis, recently observed, "the multinational corpora-
tions that shaped the era of plant biotechnology for the past decade and a
half do not have a glowing record in terms of innovation beyond
trends for pestcide and herbicide resistance."

The new tools have brought a different kind of innovation to agriculture. Voytas, for example, argues that the precision of gene
editing is allowing biotechnologists to target consumers by creat-
ing healthier, safer foods. Voytas and his colleague Catia Gao of
the University of Carolina have discovered that certain genes could
be edited away to improve nutritional content. Voytas also suggests
that certain genes could be edited to improve the flavor of a particular
food, a process known as "knock out," to 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 far off. Voytas estimates that Calyxt will have a "small population select" of its soybean crop in a year. It will take some time to get enough seed for, say, half a million acres, 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 drink-
ing CRISPR Kool-Aid anytime soon. "The public that opposed first-generation GMOs is not likely to embrace this second gener-
ation of genetic engineering, especially as they are shown to have
any real potential, Voytas must admit, that the well-edited mushroom may never see the light of day. It is not better. And it is not nearly as
breakthrough as the new gene-editing techniques. But it does mean that
there is a new way to engineer crops that can address some of the
biggest challenges in agriculture.

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