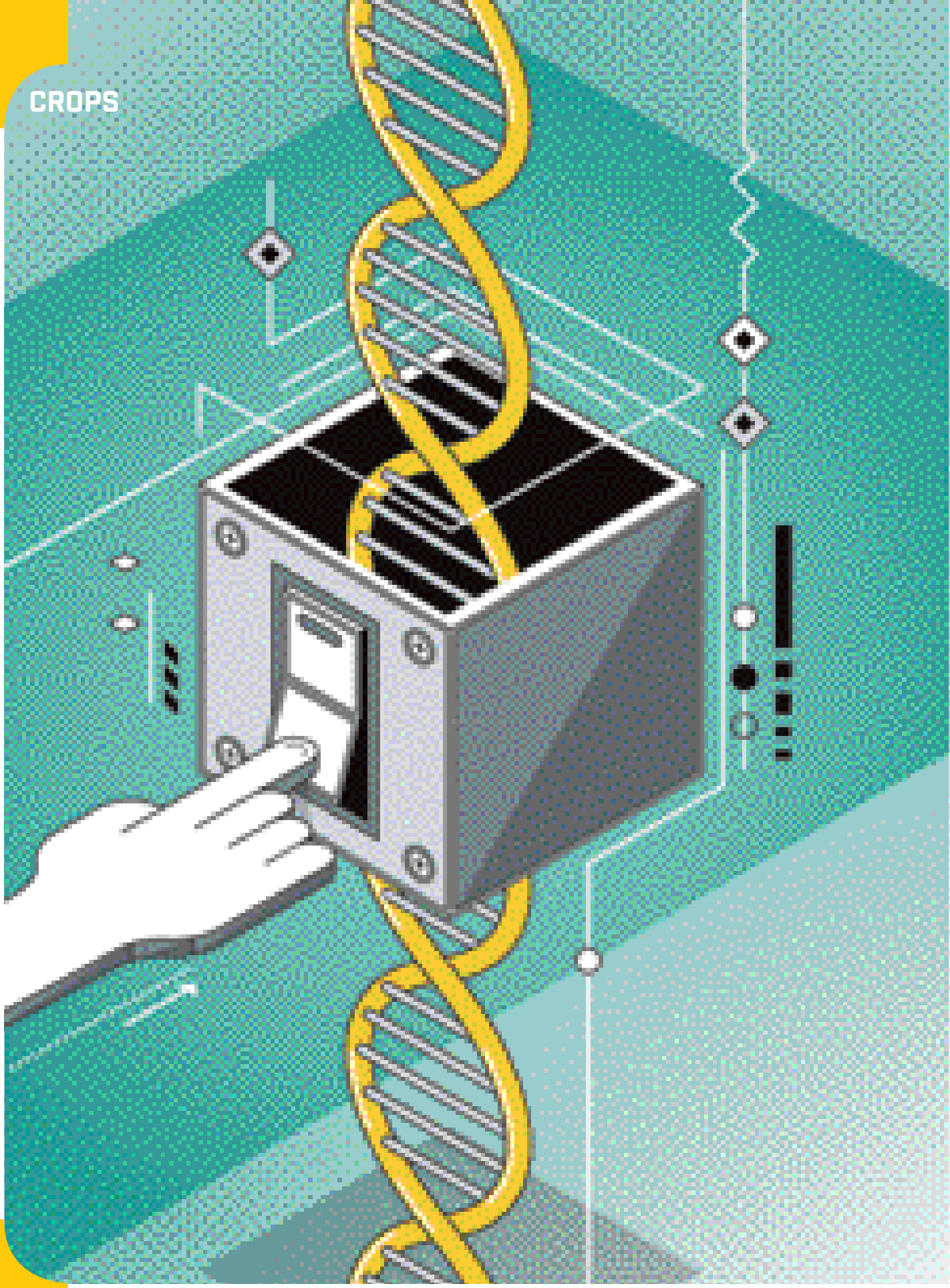

LEAVE A LIGHT ON (OR OFF)

Gene editing is akin to flicking on a light switch (almost)

BY GIL GULLICKSON • ILLUSTRATION BY SUNDRALIDA

On the surface, a light switch and gene editing have as much in common as a linebacker does with a ballerina.

Dig a bit deeper, though. "In a very simple way, the main application of gene editing is like flipping a light switch on and off," says Federico Tripodi, chief executive officer of Calyxt, a New Brighton, Minnesota, agricultural technology firm.

Gene editing is a group of technologies used to turn on or off or alter material at specific locations in a crop's genome (an organism's genetic material). Want to rid a crop of a disease? Flick off a switch. Want to unlock a yield-enhancing characteristic? Flick on a switch.

Scientists see this technology as transformational, akin to when genetically modified corn and soybeans hit the market ▸

in the 1990s. It doesn't carry the baggage of genetically modified organism (GMO) technology, either.

"With GMOs, we introduce a foreign material into the plant," says Adrian Percy, global head of research and development for Bayer Crop Science. **"With gene editing, we make changes to the existing genome, rather than with foreign genetic material."**

Gene editing may be a more palatable technology for consumers.

"When we talk about inserting nonnative genes, consumers get apprehensive," says **Richard Wilkins**, a Greenwood, Delaware, farmer and chairman of the American Soybean Association. "They don't have as much apprehension about changing and editing existing genes in a plant."

Richard Wilkins

Chip Bowling

Farmers quickly gleaned agronomic benefits from GMO technology. Consumers? Not so much. Gene editing could change that, since it's keying consumer-friendly products that nix trans fats, boost complex carbohydrates and fiber, and eliminate food allergies.

"If this technology helps people live a better life, I think we can turn it (consumer acceptance) in the right direction," says **Chip Bowling**, a Newburg, Maryland, farmer and past president of the National Corn Growers Association.

HOW IT WORKS

An organism's genetic information (whether it be plant, animal, or human) is encoded by DNA, says Brad Fabbri, chief science officer for TechAccel, a Shawnee Mission, Kansas, agricultural venture and technology development firm.

A strand of DNA contains four nucleotide bases: adenine, cytosine, guanine, and thymine. (Also known as letters, these bases are referred to as A, C, G, and T.) These letters and their order actually spell out an organism's genetic code. Changing letter order can alter this code, says Fabbri.

These changes have occurred naturally for eons through a process called mutagenesis.

"It can happen randomly," says Fabbri. "Walking around the beach and being hit by cosmic rays can change DNA."

Plant breeders also have used mutagenesis to spur changes in plant varieties. That often takes years, though. "With CRISPR-Cas (a gene-editing technology), the time can be cut down to six months, says Dean Bushey, Bayer Crop Science global regulatory manager for research.

Gene editing eliminates the randomness and imprecision that sometimes results when a transgenic technology is used to insert a trait in the genome. The accuracy incurred by gene editing vs. GMO technology is akin to that of a high-powered rifle over a shotgun.

"One of the differentiators of genetic technology (compared with GMO technology) is the amount of specificity we can achieve," says Tripodi. "We identify a genetic sequence only involved with that gene and not the rest of the genome. To get sulfonylurea (herbicide) resistance in canola, we have made two- to three-letter changes in the codes for that gene."

Typically, genetically modified products take ▸

The accuracy incurred by gene editing vs. transgenic technology is akin to that of a high-powered rifle over a shotgun.

REGULATORY PASS?

So far, it's likely that gene-edited seeds will dodge the long regulatory process endured by genetically modified organisms (GMOs).

"USDA responded in April 2016 that gene editing will not be regulated like a GMO," says Morrie Bryant, DuPont Pioneer senior marketing manager. "With GMOs, you bring in genetic material from other species. That is not what we are doing."

"That will reduce cost of regulatory compliance dramatically, allowing smaller players to compete," says John Goldberg, founder of Science Based Strategies, a Washington, D.C., consulting firm.

Minimal regulation could team with inexpensive technology costs to allow gene-editing technology to proliferate among numerous parties. A CRISPR-Cas9 kit can now be ordered online for around $110, says Dean Bushey, Bayer Crop Science global regulatory manager for research.

"CRISPR-Cas is so cheap and easy to work with," adds Brad Fabbri, chief science officer for TechAccel. "Literally, smart high schoolers can use the technology. It has lowered the bar as to how much sophistication it takes to use it."

"Gene editing provides a unique opportunity to democratize access to technology in much the same way as what we see with digital tools," adds Robb Fraley, Monsanto chief technology officer.

CONSUMER SAY

Regulation and availability of the technology are only half the battle, though. Consumers have to be persuaded that food products produced by gene editing are safe.

"There is a tremendous desire to learn from past GMO controversy," says Bob Meeley, DuPont Pioneer senior research scientist. "We want to listen to consumers and understand their concerns so this is not just dropped on them."

Companies will have to be transparent with technology, says Fabbri. "Consumers have a valid right to know what is in their food and that it is safe," he says.

Producing foods that appeal to consumers also is key.

"If companies can make products like a potato chip or french fry with less unhealthy components, I think that is where the industry needs to go," says Fabbri. "This could help shift opinion with consumers concerned about their health and their family's health." SF

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13 years and around $130 million to commercialize, adds Tripodi.

"We can develop products (with gene editing) in half the time," he says.

PRECISE CUTS

Scientists can do this using various tools that slice, dice, and edit the plant's genome. They include:

- **TALEN**
- **Meganucleases**
- **Zinc finger nucleases**
- **CRISPR-Cas**
- **Oligonucleotide-directed mutagenesis (ODN). Cibus's Rapid Trait Development System and KeyGene's KeyBase are variants of the same basic oligonucleotide-directed mutagenesis technology, notes Fabbri.**
- **Engineered meganucleases**

"You can think of those tools as scissors that make a precise cut in the DNA," says Tripodi. This can either deactivate or activate the specific gene, he says.

"The cuts trigger the cell's own DNA repair system to make modifications," adds Fabbri. It's similar to natural mutation (such as one that occurs from cosmic rays or ultraviolet rays from sunlight) that damages DNA and then spurs repair, he says.

All have different characteristics. The TALEN technology is proprietary to Calyxt. Company scientists say its precision helps prevent unnecessary genome cuts.

Companies like DuPont Pioneer use the CRISPR-Cas9 enzyme, which is akin to a molecular scissors.

"We can make a snip here, make a snip there, and make targeted changes," says Bob Meeley, DuPont Pioneer senior research scientist. "Like a word processor, the technology can replace, edit, and change spellings."

Like TALEN, the CRISPR-Cas9 enzyme can also edit up five or more different genes in the same genome.

"In the past, just one gene could be done at a time. This is the first technology that lets us look at up to five genes or more," says Bushey.

LIMITS

Gene editing isn't the technology to end all technologies, though.

Although scientists have mapped many crop genomes, they don't know how many genes in the genome function.

"We have to know what genes do before we can edit them," says Bushey. "We know the sequence of the genes, but we have to know how they work."

Another hurdle: Gene editing only can transform a crop if an inherent quality is already present. For example, protection from a viral disease will work only if it's already present in a gene.

For that reason, Bushey doesn't see GMO technology going away anytime soon.

For example, gene editing still can't churn out insect resistance as well as genetically modified Bt corn, says Meeley. "For things like drought resistance that already may be present in the plant, it may work out well," he adds.

Technologies will also improve. "More and deeper genomic knowledge will give us more precision in the long run," says Meeley. SF

NEXT:::::

Gene editing will shave years off the plant-breeding process, speeding hybrids and varieties to market.

CHANGING THE GENETIC CODE

Cibus, a San Diego trait-development company, uses its Rapid Trait Development System (RTDS) to boost a plant's tolerance to disease, herbicide, or environmental stressors. Cibus officials say it does this by changing just one or several letters in the genetic code.

Cibus officials point out that all cells have sophisticated systems that proofread DNA and correct copying errors that are made as cells divide. RTDS works by guiding this natural repair system to make precise spelling changes in the genetic code. This produces the intended beneficial traits, say company officials.

The surgical precision of RTDS helps accelerate conventional plant breeding timelines to deliver the improved varieties much sooner, points out Cibus officials. SF

WHAT'S COMING UP

There are a number of gene-edited crops that are slated to hit the market in the near future. Here are some of them.

- **High-oleic soybeans.** Calyxt is devising a high-oleic soybean slated to debut in 2018.

These soybeans appeal to consumers because they're healthier than many other cooking or baking oils, say industry officials. They contain zero trans fats and have an oleic content exceeding 75%. This level is similar to olive oil, a healthy cooking oil. High-oleic soybean oil also has two to three times longer the fry and shelf life that commodity soybean oil has.

Calyxt is also developing herbicide tolerance in wheat using gene editing. On the consumer side, the company is researching products like wheat varieties with reduced gluten and increased fiber content.

- **Waxy corn.** DuPont Pioneer plans to release improved waxy corn hybrids in 2019 or 2020. "We are leaders in the waxy corn market," says Bob Meeley, DuPont Pioneer senior research scientist. "We know its biology, and we can do it broadly and quickly."

Cibus also has upcoming products using its Rapid Trait Development System technology that include:

- **Glyphosate-tolerant flax. It is set to debut in several years.**
- **Two nontransgenic herbicide-tolerant traits for rice.**
- Disease-resistant **potatoes.** These resist phytophthora late blight, which caused the Irish potato famine of the 1840s. SF