DuPont in CRISPR-Cas patent land grab

Seed giant DuPont Pioneer entered a strategic alliance with genome engineering pioneer Caribou Biosciences in October that sees the companies sharing intellectual property rights for CRISPR-Cas tool applications in plants. DuPont also made a minority stake investment in Caribou, founded in 2011 as a spin-out from the University of California, Berkeley, laboratory led by RNA scientist Jennifer Doudna. As one of the scientists who pioneered uses for CRISPR-Cas bacterial immune system genome editing, Doudna has filed several patent applications. With this cross-licensing agreement, DuPont and Caribou divvy up the use of the technology by crop type. The Johnston, Iowa-based DuPont will use the editing tools in major staple crops like corn and soybean, and Caribou in smaller market crops like fruits and vegetables.

This is DuPont's second CRISPR-Cas-related licensing deal. In June, DuPont licensed exclusive rights to editing technologies developed by Virginijus Siksnys, whose team at Vilnius University in Lithuania characterized how the Cas9 protein cuts DNA in bacteria (*Proc. Natl. Acad. Sci.* **109**, 2579–2586, 2012). "The basic purpose was to position ourselves well with both the intellectual property and the research," says Neal Gutterson, vice president of R&D at DuPont Pioneer. "Caribou and Vilnius are real leaders in the space."

For Dupont, which in December announced its intention to merge with Dow Chemical, forging an agreement with Caribou buttresses its position in the confused landscape of CRISPR-Cas9 patent ownership (*Nat. Biotechnol.* **32**, 599–601, 2014). The Broad Institute at the Massachusetts Institute of Technology is in a legal dispute with the University of California, Berkeley. Among other claimants is Seoul National University spin-out ToolGen, which has licensed its CRISPR-Cas9 intellectual property portfolio to Thermo Fischer Scientific for research applications including the sale of reagents, cell lines and animal models. ToolGen is focused on products for biomedicine and agriculture.

Beyond the legal disputes lies even greater uncertainty about how nations plan to regulate plants edited with these systems. Companies like DuPont hope regulators will view CRISPR no differently than conventional breeding as there is no foreign DNA involved. "We see it as a breeding technology. With CRISPR the outcomes are the same as you would get from

mutagenesis and conventional breeding," Gutterson says.

In at least eight cases in canola, maize, rice and potato, where plants edited with zinc fingers, transcription activator-like effector nucleases (TALENs), mega nucleases and oligo-mediated mutagenesis with no foreign DNA were submitted for review to the US Department of Agriculture, regulators deemed them outside the scope of regulation. The companies involved include: San Diego-based Cibus; Indianapolis-based Dow AgroSciences; New Brighton, Minnesota-based Collectis (now Calyxt); and Medford, Massachusetts-based Agrivida. In December, the Swedish Board of Agriculture declared that plants transformed with CRISPR technique do not fall under the EU definition for genetically modified organisms (GMOs) of the EU. This means that the plants can be cultivated for now without restriction, though the EU has yet to issue a decision on the matter.

So far, in the US, the regulatory prospects are encouraging. The Obama administration has called for a review of the US biotech regulatory system (*Nat. Biotechnol.* **33**, 1221–1222, 2015), a move that may foreshadow an overhaul of the way the US treats all biotech crops, not only those edited with CRISPR-Cas tools. "This is an area in the biotech industry where everyone is paying close attention," says Rachel Haurwitz, CEO of Caribou. "It's an evolving landscape."

In spite of the uncertainty, companies are pushing on. In October, DuPont published two papers using CRISPR-Cas9 to introduce chlor-sulfuron herbicide resistance into soybean and corn (*Plant Physiol.* **169**, 960–970, 2015; *Plant Physiol.* **169**, 931–945, 2015). Academic laboratories have also published studies on CRISPR-Cas-modified rice, tomatoes, barley and *Brassica* species.

"We're just ahead of the big wave," says Daniel Voytas, professor of genetics at the University of Minnesota and CSO at Calyxt. "Everyone is rallying around the CRISPR platform, but labs take time to grow those plants with new traits."

To date scientists have introduced phenotypic changes through knocking out genes—that is, introducing changes in a gene to render it nonoperational. Altering a trait by inserting new DNA, or knock-ins, with CRISPR is much more challenging.

"Knock-ins in plants are really difficult," says Nicola Patron, head of synthetic biology at the Sainsbury Laboratory in Norwich, UK. "Unless

Crops transformed with CRISPR-Cas could tolerate drought.

you get a lot of your DNA into the cells you can't really do it." Patron says that won't stop progress. Many attractive traits are amenable to knock-outs, ranging from drought tolerance, to disease resistance and nutritional benefits. "There are a lot of genes out there to be explored," she says.

One thing is certain: CRISPR gene editing will enable speedier results. "Conventional breeding takes about 7 to 10 years to bring a product to market. A GMO takes about 12 to 15 years. With genome editing, if you know [what to] edit, you can turn it around in as little as five years," Gutterson says.

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“Some people say ‘I can’t imagine it [people using CRISPR to augment themselves] happening’ And I say, ‘You have to imagine it happening.’” George Church, opining on the future of CRISPR research at NAS International Summit on Human Gene Editing, Washington, DC. (*Motherboard*, 3 December 2015)