A second chance for plant biotechnology in Europe

Europe tilts towards gene-edited plants, but progress could be derailed over who owns the patents.

By Cormac Sheridan

CRISPR editing can alter the plant genome precisely, without adding foreign DNA, to breed plants with useful traits.

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On 7 February the European Parliament voted in favor of a legislative proposal to markedly relax rules for certain gene-edited plants. But it also added several amendments to the draft legislation, originally proposed by the European Commission, that, if adopted, would also ban patents for all CRISPR–Cas9-edited plants, a stance likely to discourage companies from investing in new plant products.

The European Union has long history of opposition to genetically modified crops, but CRISPR and other genome editing technologies have prompted a rethink of the rules. A genetically modified plant or organism is obtained by inserting genetic material from another species using genetic engineering, in a way that does not occur in nature, whereas genome editing is a technology that can introduce desired traits — increased yield, improved resistance to pests, climate resilient, long shelf-life — by introducing modifications indistinguishable from those that could have happened naturally or by selective breeding. In the United States, such CRISPR-edited crops have been cultivated and sold with minimal oversight since 2016. Globally, only a small number of gene-edited plants are available at present, but that is set to change dramatically over the next decade.

The European Parliament's support for gene-edited plants, however qualified, is noteworthy. "Getting through this part of the legislative process was not necessarily expected by many," says Garlich von Essen, secretary general of Euroseeds, a Brussels-based lobby group for the seed sector. The vote reflects a consensus among public scientific institutions, industry and farmers on the need for reform, he says. The patent-related hurdles could be interpreted as a ploy on the part of those who remain staunchly opposed to commercial plant biotechnology to "split the pack," says von Essen

But patent revisions could complicate the picture considerably. They could result in "different patent rules for NGTs [new genomic technologies], for GMOs and for conventionally produced plants." says Mathijs Vleugel, scientific policy officer at Berlin-based All European Academies (ALLEA), an umbrella body for European academies of sciences and learned bodies. Another concern, von Essen says, is that adoption of gene-edited plants should not lead to market domination by a small number of large multinational firms, as was the case with transgenic crops. "Then the question is, how do you do this in practice?"

The push to revamp European Union plant rules follows a controversial judgment in 2018, which essentially ruled that all gene-edited plants are considered genetically modified organisms (GMOs). The European Union has been notoriously unfertile ground for transgenic crops, which have been widely adopted by the United States, Brazil, Argentina, Canada and India, among other countries, over the past 25 years. European countries import large volumes of genetically modified crops as food ingredients and animal feed, but their cultivation is limited. Just one, Leverkusen, Germany-based Bayer's insect-resistant maize strain MON 810, is authorized, but less than 70,000 hectares were planted in Spain and Portugal in 2022, which represents a tiny fraction of its global production.

Gene editing represents a second chance for plant biotechnology in Europe. Precise gene editing methods, such as CRISPR–Cas, zinc finger nucleases, transcription activator-like effector nucleases (TALENs) and oligonucleotide-directed mutagenesis — the European Union refers to them collectively as 'new genomic techniques' (NGTs) — can alter important traits such as nutritional profile, resistance to stress, and yield, without introducing foreign DNA.

Early examples of gene-edited plants include the Sicilian Rouge tomato (*Solanum lycopersicum*), from Tokyo-based Sanatech Life Science. It produces high levels of γ-aminobutyric acid (GABA), which the company claims can help lower blood pressure, by inserting a stop codon that interferes with expression of the autoinhibitory domain of the *SlGAD3* gene, which encodes the enzyme that catalyzes glutamate-to-GABA conversion in the plant. In the United States, where

Table 1 | Selected gene-edited plants undergoing experimental release in Europe

Country	Institution	Species	Edit	Purpose	First year of release or proposed release
Italy	University of Milan	*Oryza sativa* (rice)	CRISPR–Cas9-mediated deletions in three genes: *Pi21*, *HMA1* and *HMA2*	Resistance to rice blast (*Magnaporthe grisea*)	2024
Belgium	Flanders Institute of Biotechnology	*Zea mays* (maize)	CRISPR–Cas-mediated disruption of three genes involved in lignin biosynthesis	Improved digestibility of animal feed	2024
Spain	National Agri-Food Technology Centre (CTAEX), Badajoz	*Nicotiana tabacum* (tobacco)	CRISPR–Cas9 edits of *MPO* genes, encoding methyl putrescine oxidase, to lower nicotine production	Enhanced production of the anti-inflammatory anatabine	2024
Belgium	Inari Agriculture (Cambridge, Mass., USA)	*Zea mays* (maize)	CRISPR–Cas edits of undisclosed genes encoding a transcription factor and a transcriptional coactivator that influence plant height	Improved biomass productivity	2023
Denmark	KMC (Brande)	*Solanum tuberosum* (potato)	CRISPR–Cas disruption of the *StDMR6-1* gene, which is associated with susceptibility to blight infection	Improved blight resistance	2023
Denmark	KMC	*Solanum tuberosum* (potato)	CRISPR–Cas disruption of the *StGBSS1* gene, which encodes granule-bound starch synthase	Modified starch content	2023
Sweden	Swedish University of Agricultural Sciences (Umeå)	*Solanum tuberosum* (potato)	CRISPR–Cas-mediated mutations in three genes: *GBSS*, *SSS*, and *SBE*	Modified starch content	2023
Spain	Grupo Lucas (Murcia)	*Brassica oleracea* (broccoli)	CRISPR–Cas9-mediated disruption of *ABI1*, *HAB1*, and *GSTU17*, which regulate the abscisic acid signaling pathway	Improved drought and salinity tolerance	2022
Sweden	SweTree Technologies (Umeå)	*Populus* × *canescens* (gray poplar)	CRISPR–Cas9-mediated disruptions of the *CCR2* gene, to reduce production of cinnamoyl CoA reductase 2	Reduced lignin content and increased sugar yield for improved biomass-to-energy conversion	2022
Sweden	Swedish University of Agricultural Sciences (Alnarp)	*Solanum tuberosum* (potato)	Generation of three different edited strains, with deletions in either the *DMR6* + *CHL1*, *AsS1* or *PiS1* genes	Altered resistance to pathogens	2021
Spain	Institute of Molecular and Cellular Biology of Plants (Valencia)	*Nicotiana tabacum* (tobacco)	CRISPR–Cas9-based disruption of the *SPL* family of transcription factor genes	Delayed flowering	2020
Sweden	Lyckeby Starch (Kristianstad)	*Solanum tuberosum* (potato)	Crispr–Cas9-mediated deletions in the *GBSS*, *SSS3* and *SSS2* genes	Altered starch content	2019

Source: European Commission GMO Register Part B Notifications.

gene-edited plants that resemble conventionally bred counterparts do not require approval, Pairwise is ready to market its Conscious Greens mustard leaves (*Brassica juncea*), which carry CRISPR–Cas12a-induced knockouts of the type I myrosinase multigene family. Myrosinase enzymes normally hydrolyze sinigrin, and the resulting breakdown products give rise to the pungent 'mustard bomb' effect that occurs when the plant is eaten in large quantities. The company is now seeking partners to commercialize the milder-tasting product, which is more nutritious than many other types of salad leaves.

Even if only a few gene-edited plants are commercially available at present, the global development pipeline is large, as many countries have adopted liberal regulatory regimes with either no special rules or just minimal regulations for gene-edited plants that do not contain foreign DNA. The list of states embracing gene-edited plants extends well beyond the main adopters of GMOs.

"Latin America is clearly a leader here," says Dan Jenkins, vice president, regulatory and government affairs at Pairwise. Argentina was an early mover: it put a system in place in 2015, which, according to one analysis, has helped to foster a diverse group of innovators, led by small and medium-sized enterprises and public research institutes. Chile, Brazil, Colombia, Paraguay, Honduras, Guatemala and El Salvador all followed between 2017 and 2019. More recently, Costa Rica has also eased its regulatory requirements, and a gene-edited banana resistant to the fungal diseases sigatoka and fusarium wilt (caused by *Mycosphaerella fijiensis* and *Fusarium oxysporum*, respectively) may become available later this year.

In Africa, Nigeria, Kenya and Malawi acted early. China, a late adopter of GMO crops, has already approved a gene-edited soybean, which Shandong-based Shandong Shunfeng Biotechnology developed. The gene-edited soybean produces high levels of oleic acid, a monounsaturated fatty acid that may lower the risk of coronary heart disease. (Calyxt, now part of Cibus, introduced a TALEN-edited high-oleic-acid soybean to the United States in 2019.) The United Kingdom has also enacted new legislation to allow "precision-bred organisms" that do not contain foreign DNA.

In Europe, some plant biotechnologists are forging ahead with their development plans despite the regulatory uncertainty over patents (Table 1). But it is difficult to see how companies can build a viable commercial market without patent protection for the traits they have introduced to their target plants.

In the absence of patents, the European parliament has proposed that the existing Community Plant Variety Rights (CPVR) system, which has long been in place for conventionally bred varieties, would provide sufficient intellectual property (IP) protection. But this includes a 'breeder's rights' provision, which would allow any rival breeder free access to a given innovation once it became commercially available. "You lose the incentive to develop the trait because you cannot capture the value," says Mario Caccamo, CEO of NIAB, a Cambridge, UK-based not-for-profit crop science organization. Jenkins concurs: "I just don't know why somebody would invest in our company if, as soon as we go on the market, somebody else can take that trait."

What's more, the CPVR system requires breeders to demonstrate the "distinctness, uniformity, stability, and novelty" of a given variety. That is not easily done. "It takes a long time and quite a lot of money," says Heinz Müller, an IP expert and emeritus professor of biochemistry at the University of Basel, in Switzerland, who is co-chair of ALLEA's task force on IP and NGTs. That provision is more appropriate to a commercial variety to be planted at scale rather than a single trait that a developer would aim to distribute across multiple varieties.

In the absence of patent protection, gene-editing companies could instead opt for trade secrets, which would lead to less transparency, says Caccamo. Moreover, banning patents from certain forms of innovation would, says Müller, "go against some of the international agreements" on IP, such as the longstanding Paris Convention for the Protection of Industrial Property, administered by the World Intellectual Property Organization, and the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights, or TRIPS.

Ultimately, the legislation will be shaped by a three-way negotiation among the institutions that make up the European Union. This will take time, and new elections to the European Parliament in June will probably further delay the process. Even so, the parliamentary vote has added real momentum to the legislative initiative. The European Union's scientific credibility could suffer if it fails to pass legislation that gives its agbiotech sector an opportunity to embrace this innovation in the coming decades.

Climate change is another consideration. The extent to which gene editing — of plants or livestock — can help reduce the impact of agriculture on greenhouse gas emissions and deforestation and at the same time mitigate the effects of climate change on food production is an open question. But those considerations will loom large as the European Union's institutions hammer out a compromise in the coming months. "Not everybody will be happy. Not everybody will be equally happy," says von Essen. But for plant breeders grappling with the vagaries of climate change, legislative reform will buy them precious time, as it will accelerate their efforts to introduce useful traits to their germplasm.

The timetable leading to the final legislation is still unclear. The Commission's proposal had yet to receive an official response from the European Council, as *Nature Biotechnology* went to press.

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News in brief

Star-studded AI biotech launch

The latest biotech aiming to use AI to accelerate drug discovery emerged from stealth on 23 April flush with over $1 billion in venture capital. San Francisco–based Xaira Therapeutics envisions an end-to-end application of AI technologies, from applying fundamental computational methods for biological discovery, to de novo antibody generation, to managing human trials. The foundational technologies, AI-based models for protein and antibody design called RFdiffusion and RFantibody, were developed in the lab of co-founder David Baker at the University of Washington's Institute of Protein Design. Several Baker lab researchers have joined the company full time, as have teams from Illumina and Interline Therapeutics. Xaira's other co-founders include lead investors Bob Nelsen of Arch Venture Partners and Vik Bajaj at Foresite Labs, an incubator affiliated with Foresite Capital.

Marc Tessier-Lavigne, former CSO at Genentech and former president of Rockefeller and Stanford Universities, has been named CEO. "Witnessing how AI is impacting other industries and the considerable progress in applications of AI in biology, I believe we are poised for a revolution," said Tessier-Lavigne in a statement. "Xaira is in a strong position to both advance fundamental AI research and translate these advances into transformative new medicines, and I am excited to have the opportunity to lead the team." The company's high-powered board includes Nobel laureate Carolyn Bertozzi, former US Food and Drug Administration commissioner Scott Gottlieb and former Johnson & Johnson chairman and CEO Alex Gorsky.