Review Article

Europe's Dangerous "CRISPer" Volcano Ride

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Abstract

Mutations are essential for evolution and high biodiversity. Natural mutations occur spontaneously and are non-targeted. They have thus been very important for plant breeding since humans started domestication many thousand years ago. New genetic technologies such as genome editing with site-directed nucleases, e.g., CRISPR/Cas9 ("CRISPer"), allow mutations to be induced in a very fast and highly targeted manner. Genome editing will, therefore, drastically accelerate the traditional breeding process of already available crop plants, but also will produce new crop varieties. Genome editing is, similar to genetic engineering technology, a topic of high public controversy in terms of biosafety concerns. Although public debates to ensure the environmental safety of plants and animals derived from newly developed technologies are very important, such debates can also delay or even impede the practical use of novel innovative technologies. Europe must, in the next few years, make key decisions about the fate of such technologies, like genome editing. It is time to address the danger that the approval process of these technologies is getting tangled-up in the huge European bureaucratic net. CRISPR/Cas9 and other genome editing technologies could experience the same fate as genetic engineering, which has been the focus of endless public debates for at least 30 years. At the moment, the entire situation is like a ride on the rim of a volcano.

Keywords: CRISPR/Cas9; EU legislation; Genetic Engineering; Genome Editing; GMO directive

1. Genetic Engineering technology

Genetically modified plants (GMPs) have a long history. Since the first report on genetically modified tobacco in 1982 [1], numerous plant species have been genetically engineered until today, mostly either by applying the natural *Agrobacterium* transformation

system or by particle bombardment [2]. Commercialization of genetically modified (GM) crops began in 1992, and by 2018, the global area of these biotech crops had increased to 191.7 million hectares [3], compared to the 1.7 million hectares in 1996. GM crops are cultivated on four continents, with only Europe actually represented with a blank GM crop map.

In principle, GM crops in Europe could also be commercialized because different "Directives" have been published regulating the deliberate release and commercialization of GMPs as well as the labelling of food containing GMPs [4]. In March 2011, the European Policy Evaluation Consortium (EPEC) published a final report entitled "Evaluation of the EU legislative framework in the field of cultivation of GMOs under Directive 2001/18/EC and Regulation (EC) No 1829/2003, and the placing on the market of GMOs as or in products under Directive 2001/18/EC" [5]. The report concludes with remarks on the inadequacy of the current legislative framework to meet socio-economic needs and expectations, and its failure to meet the EU's own objectives. For more than ten years, the EU has not made a single decision, positive or negative, on any application for the commercial cultivation of a GMP.

The EU legislation on opt-out measures, published in January 2015, was a cowardly retreat. The measures allow EU member states to restrict or ban the cultivation of GMPs on their own territory, even if it is authorized at the EU level [6]. Crazy and incomprehensible is that it is not necessary to justify these measures due to conflicts with points established in the risk assessment carried out by EFSA. Rather, countries can opt out simply due to "different considerations". This official "compromise" of giving the authority back to the member states is a common response by European policy when long-term disagreements cannot be resolved.

2. Genome Editing

In Europe, the genome editing technologies applying site-directed nucleases (SDN) (also called 'molecular scissors'), like Oligonucleotide Directed Mutagenesis (ODM), Zinc Finger Nuclease Technology (ZFN), and others, now suffer a similar fate. The basic science behind genome editing has a long history. Zinc Finger enzymes were discovered in the early 1990s, and dominated as genome targeting technology for more than ten years. In 2009, the genome targeting abilities of transcription activator-like (TAL) effectors were described, and two years later, transcription activator-like effector nuclease (TALEN) was awarded the title "Method of the Year 2011". Just one year later, the CRISPR/Cas9-based defense mechanism was discovered. This mechanism inactivates viruses invading bacterial cells. The CRISPR/Cas9-system has proven to be the most efficient SDN as it uses a highly specific guide RNA to discover the target gene (gene editing). Today, worldwide, an immeasurable number of gene-edited microorganisms, plants and animals are stacked in the pipeline towards commercialization. Many gene-edited cultivars are ready for outdoor field testing, not only in the US and other countries, but also, at least theoretically, in Europe.

However, although the CRISPR/Cas9 technology has progressed very fast in the past five years, all predictions for its future development are virtually as uncertain as predictions about the weather. As a reminder, as early as in October 2007, the EU Commission had set up a working group to assess whether a number of new breeding techniques could or would fall within the scope of the GMO legislation [7]. In 2011, the New Techniques Working group published an "unofficial" final report [8] that is not available on

the EU Commission website. The report claims that "The views expressed … are those of an expert working group and do not necessarily represent those of the European Commission or the Competent Authorities. Only the European Court of Justice can give a binding opinion on EU law." The technologies selected for this report and the resulting products were assessed in accordance with the existing EU legislation on GMOs.

The expert evaluations clearly indicate that techniques like, e.g., CRISPR, ODM, and ZFN develop organisms that cannot be distinguished at the molecular level from those developed through "conventional" breeding techniques or through mutation selection in natural populations. Thus, it is concluded that the organisms derived from genome editing (including CRISPR) can be considered "as a technique of genetic modification yielding organisms to be excluded from the Directives" [8]. But, as is very often the case, things turn out very differently.

3. Case C-528/16

Just to recall, on July 25, 2018, the Grand Chamber of the European Court of Justice (ECJ) published its decision in Case C-528/16 on the regulative status of organisms derived from genome editing, but also those obtained by any kind of mutagenesis techniques [9]. The judgement stated clearly that all organisms obtained by any kind of mutagenesis are classified as genetically modified organisms (GMOs) and thus are subject to the obligations laid down by the GMO Directive 2001/18/EC (Press Release no 111/18 of the ECJ). However, the judgment exempted organisms from those obligations that were obtained by mutagenesis techniques which have conventionally been used in a number of applications and have a long safety record (Press Release no 111/18 of the ECJ). Since this judgement was handed down, an exploding number of discussion panels have been organized and statements have been published, ranging from both benevolent approval to scientific nonsense. One gains the impression that Europe is impeding itself by forming committees having endless discussions and is getting tangled up in the large bureaucratic net of the gene-editing regulation issue. Thus, recommendations that suggest researchers use the waiting period as a time for debates and public dialogues are a stab in the heart of European scientists.

It has already been shown in a myriad of publications that genome editing cannot per-se be compared with genetic engineering technology. The latter uses the naturally occurring plant pathogen Agrobacterium to transfer genes in the genome of a compatible organism. The integration of the foreign gene in the genome happens randomly and not specifically at a given position. Further, genomic rearrangements and sometimes trans-silencing effects may occur following integration. In contrast, genome editing uses precisely working SDNs (e.g., CRISPR/Cas9) which create precise breaks in the genome. The breaks are repaired by cell-specific DNA repair mechanisms. Mistakes can occasionally occur, such as when the wrong nucleotide is inserted, or one nucleotide is added or deleted. However, genome editing is highly precise, and no off-target modifications are observed when the system is correctly applied.

This is the reason why the United States and other countries have down-regulated many gene-edited plants. As a consequence, these plants are already grown in the field without any restrictions. These countries will clearly profit from the current genome editing equation with GM technology in Europe. Since the current GM regulations in Europe are complex, and applications for getting GM plants approved for commercialization are very costly and time-consuming, the future of genome editing had, similar to that of GM technology, ended

before it had really started in Europe. If "CRISPer" is to be further be considered as a GM technology, and derived plants NOT to be down-regulated in the near future, this blocking attitude in Europe is like a dangerous volcano ride. The scientific and economic damage for Europe, and particularly for Germany, cannot be calculated at present. In the U.S. and other countries, scientists and economists are ready to organize never-ending parties to celebrate the lack of European competition.

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References

1. Fraley RT, Rogers SG, Horsch RB, et al. Expression of bacterial genes in plant cells. Proceedings of the National Academy of Sciences 80 (1983): 4803-4807.
2. Mackelprang R, Lemaux PG. Genetic Engineering and Editing of Plants: An Analysis of New and Persisting Questions. Annual Review of Plant Biology 71 (2020): 659-687.
3. Brief 54: Global Status of Commercialized Biotech/GM Crops. ISAAA (2018).
4. Lynch D, Vogel D. The regulation of GMOs in Europe and the United States: a case-study of contemporary European regulatory politics. Apr 2001. Council on Foreign Relations (2016).
5. Evaluation Of The Eu Legislative Framework In The Field Of Cultivation Of Gmos Under Directive 2001/18/Ec And Regulation (Ec) No 1829/2003, And The Placing On The Market Of Gmos As Or In Products Under Directive 2001/18/Ec. EPEC (2011).
6. Parliament backs GMO opt-out for EU member states. News EP (2015).
7. Fladung M. Cibus' herbicide-resistant canola in European limbo. Nature Biotechnology 34 (2016): 473-474.
8. The views expressed in this report are those of an expert working group and do not necessarily represent those of the European Commission or the Competent Authorities. Only the European Court of Justice can give a binding opinion on EU law (2020).
9. Organisms obtained by mutagenesis are GMOs and are, in principle, subject to the obligations laid down by the GMO Directive. Court of Justice of the European Union PRESS RELEASE No 111/18 (2018).