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The European Court of Justice ruling on products derived from genome editing: a case for Brazil and Argentina?

Even from its beginning in the era of domestication of plants, plant breeding has been an activity in permanent change, evolution and in some cases sophistication. Since the middle of last century, however, this development acquired a significant acceleration as results of critical discoveries and developments in the genomic arena.

CRISPR, which stands for Clustered Regularly Interspaced Short Palindromic Repeats, is a family of DNA sequences found within the genomes of prokaryotic organisms such as bacteria and archaea that were discovered by the Spanish scientist Francisco Mojica around 2000. Cas (for "Crispr-Associated") is a group of genes that codify enzymes that uses CRISPR sequences as a guide to recognize and cleave specific strands of DNA that are complementary to the CRISPR sequence. CRISPR-Cas is a "search-and-destroy-method" used by bacteria and archaea to defend against invading viruses. Some years later after Mojica, several university research teams -mainly from universities of the United States-, redesign this bacterial immunity systems to invent an editing tool not preexisting in nature in which the CRISPR sequences and the Cas enzymes working together can be used to edit the genome in any type of organism. Plant breeders from public and private sectors has now the possibility to apply genome editing tools -ie. the process of making precise, targeted sequence changes in the DNA or RNA of organisms- to step up genetic progress.

One of the attributes that make genome editing so potentially impactful is that it can modify the plant genome without transferring new genes from one organism to another. There are several genome editing technologies available (meganucleases, zinc-finger nucleases -ZFN, and transcription activator-like effector nucleases -TALENs-), but CRISPR-Cas technology has the advantage to be also simpler, cheaper, and faster when compared to other genome editing methods or even GMO development, potentially saving years or even decades in bringing needed new varieties to farmers. CRISPR-Cas can edit DNA in a way like certain conventional breeding strategies that rely on mutations caused by chemicals or radiation. So, the modern genome editing achieves the same outcome – mutated plants – as techniques that plant breeders applied for decades, which never produced a single case of threat to the environment or animal or human health.

But there is another issue equally important; the regulation. If the genome editing products are considered conventional products

because they do not contain "foreign DNA", their development till reaching the commercial phase will be inexpensive when compared to GMO development. Such fact could open the door for public institutions and many smaller start-up firms to be deeply involved in this next great crop innovation.

To maintain their capacity to foster innovation and create new varieties of plants, plant breeders need to know now how to position the new breeding techniques and their resulting products of genomic edition with respect to the regulatory frame.

On this regard and around the globe, each country is in the process of evaluating whether, and to what extent, current biotech regulations are adequate for research conducted with, and products related to, genome editing. Although no internationally agreed-upon regulatory framework for genome editing exists, regulators of United States, Argentina, Brazil, Chile, Japan, Colombia and Canada have taken the position that, at least, SDN-1 and SDN-2 derived products (see box), do not contain foreign DNA and so, they must be regulated as conventional products.

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Despite the amount of scientific information available and the expert opinion all around the globe, on 25 July 2018, the European Court of Justice (ECJ) ruled that organisms obtained by genome editing techniques, such as CRISPR-Cas and any other genome editing method, are in principle subject to the same regulations as genetically modified organisms (GMOs).

This decision was a huge surprise, given the intrinsic contradiction with the opinion provided by the EJC advocate general in January 2018, who drew a clear line between mutagenesis, which changes an organism's DNA, and transgenics, which introduces the DNA from another species.

Due to this decision, the ECJ ruling will force European public institutions and private start-up firms to follow the same path GMOs in Europe take, which typically costs several millions just to go through the regulations. Because of this, only large companies will be able to afford the regulatory process to bring genome editing crop varieties to the public.

Rejections of the EJC ruling have come from everywhere, but from the European Union it self. For example, "by any sensible standard, this judgment is illogical and absurd"

Types of DNA Modifications Created with Site-Directed-Nucleases (SDNs) also called Sequence-Specific-Nucleases (SSNs)

SDN-1
This is the simplest targeted genome modification to achieve. It involves allowing the broken chromosome due to the action of the Cas enzyme at the precise site to be repaired by the natural cell process of non-homologous-end-joining (NHEJ), which rejoins the broken chro-mosomes precisely, thereby restoring the DNA sequence. On occasion small deletions or, more rarely, insertions (collectively called indels) are introduced at the break site, producing a single base mutation. The frequency at which such alterations occur varies, but indels are typically detected in the range of 5 to 75%.

SDN-2
If the chromosome breakdown is repaired by homology-directed-repair (HDR), the infor-mation is copied from a DNA template during the repair process. The template can be a ho-mologous chromosome, a sister chromatid, or an externally supplied DNA with a sequence similarity to the DNA flanking the site of disruption. SDN-2 generally refers to subtle modifi-cations, such as substitutions of a single nucleotide or small insertions or deletions that are made at the site of rupture.

SDN-3
It involves the site-specific integration of DNA. SDN-3 allows stacking of single or multiple genes into a single genomic locus, which simplifies the breeding process and avoids exces-sive linkage drag associated with trait introgression. Targeted insertion can be achieved by either NHEJ or HDR. Contrary to SDN-1 and SDN-2, SDN-3 is characterized by the insertion of naturally occurring or synthetic, large sequences of DNA such as those used in transgen-esis, cisgenesis, or intragenesis. Such sequences may range in content from multiple genes to a fragment of a gene.

Base Editing without Double Strand Breaks
It is also possible to edit genomes without requiring a double DNA strand break. Called "base editing," this development has attracted interest because double strand breaks are not repaired well in some organisms and cell types and because an alternative to HDR is needed for making specified changes in organisms and cell types in which HDR efficiencies are low. Base editing uses enzymes that convert one base in DNA without requiring or making a double strand break.

Adapted from "Genome Editing in Agriculture: Methods, Applications, and Governance", Council for Agricultural Science and Technology (CAST), July 2018.

Bioheuris is developing weed control systems for soybeans through gene editing

precise editing that can be implemented in DNA-free versions" (Rodolphe Bar-rangou, The CRISPR Journal); "it is the death blow for plant biotech in Europe" (Sarah Schmidt, Heinrich Heine University). From the United States the rejection was in the same direction: "the global regulatory treatment of genome-edited agricultural products has strategic innovation and trade implications for USA agriculture. For this reason, USDA has clear science and risk-based policies that enable needed innovation while continuing to ensure these products are safe. In light of the ECJ ruling, USDA will redouble its efforts to work with partners globally toward science and risk-based regulatory approaches" (Secretary of Agriculture Sonny Perdue),

(The Observer, UK); "is simply untrue that the highly precise technology of gene editing is somehow more risky than past, imprecise techniques" (The Times, UK); "by saying that genome-edited crops must be treated to expensive and uncertain regulation, the Court has ponderate to the views of a handful of misguided extremists" (Matt Ridley, British journalist); "it will be impossible to rationalize why archaic mutagenesis tools that randomly and heavily alter DNA supersede

This obscure ECJ ruling is also a reminder that in some cases the limiting factor for the development of promising technologies and scientific tools does not always is under the scope of science.

The EJC decision provides another reason to embrace the challenge of advancing the understanding of science and technology by the public. An understanding that must be start at the very early stages of education. On the other side, the academy and the industry must do much more efforts to work together with regulators and politicians in a collaboratively way.

In this regard, we must highlight the work done by the academy, the private sector and the regulators of Brazil and Argentina for the development of the regulatory analysis process for products derived from genome editing. Contrary to European decisions, this work considered that the key issues are basically both the relevant scientific information as well as the long history of security of products derived from conventional mutation techniques. A good and reasonable approach.

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"It will be impossible to rationalize why archaic mutagenesis tools that randomly and heavily alter DNA supersede precise editing that can be implemented in DNA-free versions"
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