Trends and future prospects of genome editing in human and plant health

International Centre for Genetic Engineering and Biotechnology

Genome editing technology

"Genome editing" is a recent technology that can be considered as an ultramodern microsurgery on genes. It is an innovative technology that is booming in molecular biology laboratories; in 2015 experts considered it the "breakthrough of the year" and, given its precision, low costs and ease of use, it has become the model of the "democratisation of science" [1].

Genome editing is a technology that generates DNA sequence variants at defined positions in a genome. This can happen either in the coding region for a protein, thus affecting its function, or in the promoter region to impact cell type specificity or timing of promoter activity. The best-known system in the genome editing toolbox is CRISPR/Cas9, for which Emmanuelle Charpentier and Jennifer Doudna, the inventors of the genetic scissors, received the Nobel Prize in 2020 [2]. Alternative systems are transcription activator-like effector nucleases (TALENs) or Zinc-finger nucleases (ZFNs). All these editing tools target a specific sequence in the genome and induce a DNA double strand break at the target site. Once the DNA is cut, the cell uses its own DNA repair machinery, consisting in two major mechanisms that occur in almost all cell types and organisms: homology-directed repair (HDR) and nonhomologous end-joining (NHEJ), resulting in targeted integration or gene disruption, respectively [3].

The ease of use, accuracy and efficiency of genome-editing tools has led to their broad adoption in research, as well as to proof of concept applications in gene therapies involving non-reproductive (somatic) cells. It is also possible to deploy genome editing in human germline cells (sperm and eggs) as well as in early embryos. Many stakeholder groups are debating this issue, which, for some, remains a line not to be crossed whereas for others it provides possibilities for improving the human condition through the repair of deleterious genetic mutations [4]. However, the promise that genome-editing offers in diverse areas of human health is immense – and will make SDG3, Health and Well Being, attainable for many diseases which hitherto could not have been cured or prevented. The use of this frontier technology in ICGEB and the capacity building towards its constituency, particularly developing countries is also perfectly aligned with SDG10 by reducing inequalities across the globe.

In plants, the situation with regard to genome editing appears similar to the issue of genetically modified organisms where certain techniques applied to living, replicating organisms may result in genetically modified products that are risk assessed on a case-by-case basis before they are released into the environment or placed on the market. However, there has been no universal consensus yet as to whether products resulting from genome editing should be treated in the same manner as GMOs or whether another regulatory framework is to be applied. Over the past years, different countries have taken different paths along these two possible regulations. Therefore, before the edited lines can be introduced into breeding programs and used as a product, the country has to develop a legal regulatory framework [5]. However, there is huge potential for the technology to make massive impacts across the world, both in addressing SDG2- Zero Hunger where such technology will rapidly overtake traditional means of crop improvement. In addition, many countries face incredible challenges as a result of climate change. This technology offers unique opportunities for mitigating the effects of climate change in various aspects of the agricultural sector, thereby addressing SDGs13 and 15.

Uses of genome edition in human health

Potential benefits of genome editing for human health include faster and more accurate diagnosis, more targeted treatments and prevention of genetic disorders. So far, ex vivo

genome editing has been the most widely used approach. This entails genetic engineering of cells in vitro and their re-engraftment back to patients. In recent years, teams in China and in the United States have performed a series of clinical trials of gene editing, aimed at producing more effective CAR T cells for cancer treatment and the knockout of the erythroid specific enhancer of BCL11A to upregulate gamma globulin in autologous hematopoietic erythroid progenitors as a therapy for sickle cell disease and β-thalassemia [6,7].

In addition to the many benefits of genome editing, there are some technical challenges in translating these treatments to clinical disease therapy, primarily in terms of accuracy, efficacy and delivery hurdles.

Being a novel and sophisticated technology, not ready to be deployed in all countries, human genome editing has the intrinsic risk of fueling more health inequity between countries. It will therefore be essential to promote systems-level improvements to build capacity in all countries and ensure that human genome editing is used safely, effectively, and ethically. Indeed, this can only be achieved through appropriate enhancement of capacity in such technologies, meeting SDG4 for quality scientific education and SDG9 to build industrial capability to make use of these technologies and foster appropriate innovation in the countries most in need.

Uses of genome editing in plants

A new agricultural transformation is underway which aims at improving crop yields while using reduced levels of agrochemicals; developing new abiotic and biotic resistant varieties and finding alternatives for plant disease control and plant growth promotion are very important targets [8]. With the global population projected to arrive at 10 billion by 2050, todays' agriculture will face enormous challenges, requiring crops with higher yields and of improved nutritional value, and needing fewer inputs being more sustainable. In addition, climate change is affecting crop yield due to the increase in temperatures as well as creating water shortages. At present, conventional breeding is the most widely used approach in crop improvement, however it is labor intensive and it takes a long time to go from the screens of the first crosses to arriving to commercial varieties.

Genetically modified (GMO) crops have been and are being created with beneficial traits via the transfer of genes (transgenes) or gene elements of known function into elite crop varieties. Despite the success in certain countries and usefulness that GMO crops have for global food security, their use is affected by largely unproven health and environmental safety concerns. Consequently, the tangible advantages of GMO traits have been few and these are restricted to a small number of crops.

Genome editing involves advanced molecular biology techniques that allows for precise, efficient, inexpensive and targeted modifications at the specific position in the plant genome. This technique can be used for gene knockout mutants as well as gene replacement (knockin) and insertion mutants which can be generated in a wide variety of plants, and many of these genome modifications can be useful for crop improvement. The potential and negligent risks involved in modifying genomes through genome editing technology are significantly lower than those of GMO crops because most changes consist of only a few nucleotides, producing changes similar to ones that routinely happen in naturally occurring populations. Therefore, the use of genome editing into modern breeding programs can revolutionize plant breeding via rapid, cheap and precise crop improvement.

In summary, genome editing is an advanced molecular biology technique that can produce precisely targeted modifications in any crop and promises to play a key role in speeding up crop breeding and in meeting the ever-increasing global demand for food. In addition, government regulations and consumer acceptance are likely to be more welcoming towards the use of this new breeding technology[8].

The ICGEB experience and lessons learnt/messages for policy makers

Regulatory issues. The regulation of genome editing might be particularly difficult, because it is a platform technology that can be employed across multiple fields. Multiple agencies may be charged with setting regulation standards, and levels of societal concern may vary across contexts. Constant communication between the industrial, research and regulators communities has the potential to improve clarity in the regulatory process and render the system more efficient and predictable. Guidance documents are welcome to help engagement as products come close to regulatory milestones. Discussion around regulatory cooperation needs to be continued, deepened, and made more inclusive in order to find avenues for facilitating commercialisation and diffusion of products and therapies across countries.

Policies. A peculiar feature of genome editing is the degree of public interest and concern. This likely stems from the potential use of the technology not only for somatic therapies, but also for germline modification, or in the context of gene drive, which exploits selfish genetic elements that are transmitted to progeny at super-Mendelian (>50%) frequencies [9]. As policies and institutional capacities develop around the use of genome editing, these should serve as a model for policies in other areas of advanced therapies and emerging technologies for health.

Public engagement. The degree of public interest and concern in genome editing underscores the need for public engagement at an early stage in the process of research and development. Engagement must be balanced, and stakeholders should avoid "overselling" the technology. A central lesson of systematic work on public engagement is that openness, transparency and participation are key. There is not a single public, but multiple "publics" that need to be engaged in different contexts, using different communication strategies.

Meeting all of the above requires Partnerships for Goals through SDG17, strong institutions for regulation and monitoring, thereby meeting SDG16. **In conclusion, genome editing will reduce the burden of disease, will mitigate the effects of climate change, will improve crop nutritional value, and provide crop resistance to various forms of biotic and abiotic stress. All of which goes directly towards addressing SDG1 – zero poverty.**

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