The CRISPR Journal
Volume 4, Number 1, 2021

DOI: 10.1089/crispr.2020.0098

The CRISPR Journal

PERSPECTIVE

(Broken) Promises of Sustainable Food and Agriculture through New Biotechnologies: The CRISPR Case

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Abstract

In recent years, the development of diverse CRISPR-based technologies has revolutionized genome manipulation and enabled a broad scientific community in industry, academia, and beyond to redefine research and development for biotechnology products encompassing food, agriculture, and medicine. CRISPR-based genome editing affords tremendous opportunities in agriculture for the breeding of crops and livestock across the food supply chain that could benefit larger portions of the population compared to CRISPR applications in medicine, for example by helping to feed a growing global population, reach sustainability goals, and possibly mitigate the effects of climate change. These promises come alongside concerns of risks and adverse impacts associated with CRISPR-based genome editing and concerns that governance systems that are ill equipped or not well suited to evaluate these risks. The international community will continue to gather, in multiple venues, in the coming years to discuss these concerns. At the same time, responsible research and innovation paradigms also promise to evaluate the risks and benefits better while incorporating broad stakeholder engagement across the research and development process. The CRISPR community therefore must actively engage with these international deliberations, society, and national governance systems that have promised to build better agricultural systems and provide better food products to achieve equitable outcomes while protecting the environment. Without this active engagement, the promises discussed in this paper are sure to be broken.

Introduction

Since the discovery of CRISPR loci in the 1980s, CRISPR-Cas systems have been repurposed as powerful molecular machines that enable genome editing in virtually all organisms across the tree of life.[1] In the last few years, the development of diverse CRISPR-based technologies has revolutionized genome manipulation and enabled a broad scientific community in industry, academia, and beyond to redefine research and development for biotechnology products encompassing food, agriculture, and medicine. Currently, the CRISPR community encompasses more than 40,000 authors at 20,000 institutions who have documented their research in 20,000 published and peer-reviewed studies.[2]

To date, the majority of CRISPR research literature has focused on the development of genome-editing technologies to address medical needs, notably gene therapies, disease models, and diagnostics.[1] For example, there are multiple companies actively involved in clinical trials that are underway, encouraged by promising results already obtained in sickle cell therapies,[3] as all three first-generation publicly traded CRISPR startup companies are already in the clinic. Editas Medicine, Intellia Therapeutics, and CRISPR Therapeutics have set the stage for second-generation gene therapy companies (e.g., Beam Therapeutics) and compelled others to join the fray (e.g., Bayer, Regeneron, Vertex, and Novartis). There appears to be broad interest in industry and academia and at the U.S. National Institutes of Health to exploit CRISPR-based technologies to develop next-generation gene therapies, cell therapies, antivirals, antimicrobials, diagnostics, and more. Despite the tremendous potential of

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CRISPR for medicine, only a relatively small portion of the population is afflicted by treatable genetic diseases, and whether they will have access to and can afford these therapies is an open question.

In contrast, CRISPR-based genome editing affords tremendous opportunities in agriculture for the breeding of crops and livestock across the food supply chain that could benefit larger portions of the population, including consumers. In fact, the biological role of CRISPR-Cas as an adaptive immune system was first demonstrated in food bacteria and dairy starter cultures. Further, CRISPR-enhanced dairy cultures for bacteriophage resistance have now been broadly commercialized for more than a decade in the global manufacturing of cheese and yoghurt,[4,5] and these molecular breeding techniques are readily available and more easily deployed in a wide range of agricultural and food systems and products. They are being used to develop next-generation products that constitute healthier and safer foods, more sustainable and environmentally friendly farming, and more humane livestock management.[6] However, like medicines, the question of who has access to and who can afford these next-generation food and agricultural products is not immediately clear, and will be determined in large part on how the patent, intellectual property, and governance landscapes develop in the coming years.

(Broken) Promises of CRISPR Governance

Along with the commercial and scientific promises of CRISPR applications are governance promises designed to maximize potential benefits while minimizing risk in order to realize its potential as a new biotechnology ultimately and fully. The first generation of genetically modified organisms (GMOs) was impacted by significant public backlash and international trade disagreements in some cases.[7] In fact, the acceptance shortcomings of agricultural GMOs have significantly hampered the field since the 1980s, with widespread skepticism about the safety of molecular technologies used for breeding.[7] One key question is whether coupling new food and agricultural biotechnology development with governance mechanisms will ensure its ultimate success.

Governance mechanisms are typically implemented as laws, regulations, guidance, and/or economic incentives that can span national and international levels. These mechanisms attempt to manage, shape, and control the impacts of these technologies in multi-actor contexts, while also making promises to evaluate risks, establish fair and equitable access to the technologies, align economic incentives across communities, and inform the decision frameworks for if/when these technologies can be used.

As of late 2020, governance promises for CRISPR are currently in flux, and most established mechanisms are trying to keep pace and adapt to the rapidly changing technology landscape. While some products developed with CRISPR will have a relatively straightforward review and approval process (i.e., medicines), others, such as CRISPR-enabled crops and foods, may challenge regulatory statutes, associated risk assessments, and potentially flex public trust in those products. Key questions include whether CRISPR-enabled applications in food and agriculture will fall under current GMO regulations, whether they will be exempt, or whether new regulatory regimes are needed.[8] Some countries have moved to answer this question, while others, including international treaties, protocols, and agreements, are struggling to keep pace.

In 2018, the European Court of Justice (Case C-528/16) ruled in part that plants produced using gene editing, which includes CRISPR, are in fact different from traditional breeding.[9] The ruling states that:

> the risks linked to the use of these new mutagenesis techniques might prove to be similar to those that result from the production and release of a GMO through transgenesis, since the direct modification of the genetic material of an organism through mutagenesis makes it possible to obtain the same effects as the introduction of a foreign gene into the organism (transgenesis) and those new techniques make it possible to produce genetically modified varieties at a rate out of all proportion to those resulting from the application of conventional methods of mutagenesis[9]

implying that gene editing in plants would need to go through its 2001/18 GMO directive's risk assessment prior to their release.

In the United States, any organism that has been altered or produced through genetic engineering is regulated if the donor organism, recipient organism, vector, or vector agent meets the definition of a plant pest. In 2018, the U.S. Secretary of Agriculture stated that:

> USDA does not regulate or have any plans to regulate plants that could otherwise have been developed through traditional breeding techniques as long as they are not plant pests or developed using plant pests. The newest of these methods, such as genome editing, expand traditional plant breeding tools because they can introduce new plant traits more quickly and precisely, potentially saving years or even decades in bringing needed new varieties to farmers.[10]

This sentiment appears to have been codified in the USDA's Sustainable, Ecological, Consistent, Uniform, Responsible, Efficient (SECURE) rule, which enables developers to seek exemptions for plants that contain a

single modification in one of three categories: (1) a change resulting from cellular repair of a targeted DNA break in the absence of an externally provided repair template, (2) a targeted single base-pair substitution, or (3) introduction of a gene known to occur in the plant's gene pool, or a change in a targeted sequence to correspond to a known allele of such a gene or to a known structural variation present in the gene pool.[11]

Most countries have ratified and incorporated the principles set forth under the Convention on Biological Diversity (CBD) into their local laws in relation to living modified organisms (LMOs; i.e., genetic engineering).[12] The CBD, which entered into force in 1993, has three main objectives: (1) the conservation of biological diversity, (2) the sustainable use of the components of biological diversity, and (3) the fair and equitable sharing of the benefits arising out of the utilization of genetic resources.

After entering into force, the CBD struggled to deal with genetic engineering until 2003, after which the Cartagena Protocol on Biosafety to the CBD was enacted.[13] The Cartagena Protocol aims to ensure the safe handling, transport, and use of LMOs resulting from modern biotechnology that may have adverse effects on biological diversity, also taking into account risks to human health.

Emerging genetic technologies, such as CRISPR, synthetic biology, and other forms of gene editing, challenge the CBD and its protocols, partially because of the definitions and/or terminologies that these agreements use. For example, since 2010, the CBD has been discussing ''synthetic biology,'' which it defines as a further development and new dimension of modern biotechnology that combines science, technology, and engineering to facilitate and accelerate the understanding, design, redesign, manufacture, and/or modification of genetic materials, living organisms, and biological systems.[14] The current definition of LMO is any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology.[13] Modern biotechnology means the application of *in vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.[14] Discussions have begun inside the CBD and Cartagena Protocol around genome editing and how, or if, these emerging tools fall within the current definitions of an LMO, and thus under the Cartagena Protocol, or whether the organisms, plants, and subsequent products resulting from these technologies require a new set of guidance all together. Similar conversations are occurring at the International Union for Conservation of Nature (IUCN)[15] to determine if/how these new tools/techniques should be governed or used at all in relation to conservation.

While national laws and international agreements all offer some promise in terms of their ability to oversee CRISPR applications in food and agriculture, it remains unclear whether they are designed to keep pace with new and novel technologies. While the metrics used in these deliberations may not be standardized, follow any one specific methodology, and can appear to hinder emerging technology adoption to some, they are debated and/ or negotiated on for many years, are based in science, and respect the sovereignty of individual countries. CRISPR scientists/developers will need to respect and abide by these agreements, but they should also be actively involved in the discussions/negotiations as they continue to evaluate gene edited products.

Inevitably, some regulatory authorities and/or countries will promise stricter regulations, some will promise a reduced regulatory burden, and others may take a long time to promise anything. The ultimate success of CRISPR applications in food and agriculture will be determined, in part, by where research and innovation take place, whether there are markets for such innovations, and whether the public trusts, approves, and has equitable access to them. Therefore, governance, and increasingly international governance, will play a critical role in the determination of CRISPR's success in food and agricultural markets. Synchronizing these governance systems will not be an easy task.

So, where does this leave us and our ability to oversee CRISPR applications in food and agriculture in a way that maximizes its benefits by offering more sustainable and equitable access to food, while also taking into account potential risks, along with strategies to incorporate diverse perspectives and needs? In other words, where do we go from here?

(Broken) Promises of Responsible Innovation for CRISPR

Many scholars have advocated for governance systems that are more forward thinking by anticipating impacts of technologies on society, particularly in terms of who has access to them and who can participate in decisions regarding their use. Within this context, some have suggested that technology oversight might benefit from coupling top-down governance mechanisms, as described earlier, with more bottom-up governance mechanisms, such as the practices of responsible research and innovation (RRI), through involving diverse stakeholder perspectives across innovation stages to guide technologies that can create a more sustainable and equitable world. Overall, by including environmental, health, and safety

assessments with societal needs and perspectives, practices of RRI propose not only to enhance informed decision making regarding the development and use of biotechnologies in food and agriculture, but also to build trust and confidence among diverse stakeholders, including industry, consumer and environmental groups, and regulatory agencies.

RRI is a framework to help innovate responsibly by incorporating societal considerations and needs iteratively within innovation processes, relying heavily on integrated public participatory processes. The European Commission's Horizon 2020 program defines responsible research and innovation as ''an approach that anticipates and assesses potential implications and societal expectations with regard to research and innovation, with the aim to foster the design of inclusive and sustainable research and innovation.''[16] RRI has four main principles—anticipation, reflexivity, inclusion, and responsiveness—all intended to guide technology development.[17]

In the case of gene editing of crops, RRI promises the attainment of safe, responsibly developed CRISPR food and agricultural applications while integrating societal views and needs, potentially ensuring acceptance from consumers by building public trust. RRI can serve as a focal point for technologies that are embedded in political struggles over the public value of research and innovation, especially at times when science policy is given a privileged role in driving economic growth,[18] resonating strongly with biotech and CRISPR debates as they pertain to food and agricultural applications. Further, pursuing RRI of CRISPR-based applications may avoid what was experienced with the first generation of GMO technologies.[18]

While the concepts of RRI are worthy of pursuit, challenges exist to put RRI theory into practice. RRI may be considered as external to one's own scope of activities, practices of RRI are perceived as merely additional imposed requirements, just a ''tick box'' or buzzword to use, or redundant with other existing practices such as life-cycle assessments or Memoranda of Understanding between universities and industry.[18] There are also tensions between the speed at which CRISPR in food and agricultural applications need to proceed, from research, investment (competitive), or immediate environmental reasons (i.e., fast), compared to the speed at which reflective, anticipatory, and participatory approaches of RRI occur (i.e., often slow), but necessary to understand fully the variety of environmental, health, and societal implications needed to adhere to RRI. These tensions can result in RRI's ineffectiveness in many instances.[19]

Other challenges within RRI processes, particularly as they pertain to new food and agricultural technologies, relate to integrating public participation. For example, Bogner and Torgersen[20] found that public participation in RRI processes applied to food and agricultural technologies may often be hampered by issues of: (1) obtaining a balanced mix of participants (e.g., ensuring diversity, gender balances, backgrounds, and forms of knowledge); (2) participants' ability (or lack thereof) to tolerate diverging perspectives and values from their own within participatory exercises; (3) issue framing as risk versus ethics, as risk-based issue framing will privilege expert knowledge over others; (4) participant willingness and availability to invest in time-intensive activities if they do not readily have a direct and immediate stake in the topic or technology; (5) tensions to involve participatory approaches early in innovation, with greater uncertainties in early stages of innovation compared to more mature stages; and relatedly (6) poor problem definition within public participation, leading to more abstract discussions of technology, typically leading to ethical discussions and challenges rather than more concrete or tangible input to help inform technological innovation.

While there are significant hurdles for putting well-intentioned theories of RRI into practice, the CRISPR community could help ensure technology promises are not broken by starting to incorporate the underlying principles of RRI (anticipation, reflexivity, inclusion and responsiveness) actively into new CRISPR applications in food and agriculture. In addition to ensuring CRISPR food/ag products are more responsible and responsive to public and stakeholder needs, it would also help train the next generations of biotech scientists and developers that are suited for science-for-society applications. In fact, this has been occurring, in part, within the International Genetically Engineered Machines competition, where students are judged on integrating societal concerns into their innovations both at the product level and design phases.[21] However, without broader and more dedicated buy-in from the CRISPR scientific community, it remains unclear whether the promises of RRI can be reached when applied to CRISPR applications in food and agriculture, or whether they may be broken. The point is that while there are potential benefits of CRISPR in agriculture, there are limitations to current systems that oversee and govern this emerging technology used in agriculture, and even suggestions of applying principles of RRI could be challenged due to obstacles presented in public participatory models (see Figure 1).

New Promises

Society is currently at a crossroads on how best to proceed with new and novel CRISPR applications with the promise to provide more sustainable and equitable

FIG. 1. The Ag stakeholder table. Engaging diverse stakeholders in CRISPR applications in food and agriculture is essential for responsible research and innovation. Stakeholder groups for inclusive engagement and dialogue include the CRISPR scientific community, regulatory authorities, industry, farmers, as well as consumer advocacy and indigenous populations. (Credit: Mon Oo Yee).

agricultural products for greater segments of our society. RRI promises to help guide technology development in a way that anticipates potential risks and benefits to health, the environment, and society, while also incorporating diverse perspectives. However, it remains unclear whether society (or governments and oversight agencies) will choose an inclusive RRI process to evaluate CRISPR applications or whether more rapid, but potentially less inclusive, evaluations on the environment, safety, and societal impacts will be chosen.

One solution to overcoming these challenges could be a complementary, tiered governance approach that works with current regulatory and oversight systems to couple CRISPR innovation with safe-by-design principles and broader RRI practices across innovation phases. Such complementary, tiered approaches could allow some CRISPR applications to proceed at a faster pace where there are decreased risks for adverse impacts on health, the environment, and society, while other applications that may pose greater risks to society would be subjected to more in-depth RRI practices, including the incorporation of public participatory models. This type of tiered approach would be separate from, but complementary to, existing regulatory oversight regimes to leverage existing frameworks and governance systems as much as possible. This tiered approach would start by incorporating safe-by-design principles in the early stages of CRISPR developments, using predefined criteria to screen out developments that could pose potential risks, such as adverse health and environmental effects that may lead to toxicity or ecotoxicity. This is similar to safe-by-design approaches that are being incorporated into the development of engineered nanomaterials[22,23] and which have recently been explored for CRISPR applications.[24]

The second tier would enable stakeholder engagement to vet CRISPR applications by evaluating the potential impacts on society and identifying how diverse stakeholders perceive a particular CRISPR application. This process could screen out potentially problematic CRISPR food/agriculture applications that may not be fully accepted or adopted by segments of society. While CRISPR developers may be able to carry out tier 1 assessments that utilize safe-by-design principles, a neutral third party may be best to review the results of tier 1 and oversee and conduct tier 2 activities that involve public participation and stakeholder engagement models.

Finally, applications that pass through the second tier would return to the CRISPR developers to evaluate the commercial viability. Applications chosen to move forward as market-based products would then follow the national and international governance regimes. Such a complementary, tiered approach could help address the current ''pacing problem'' between CRISPR technology development and oversight decisions and approvals by identifying issues earlier in the development process.

Keeping Promises

In 2021, the international community will gather in multiple venues to continue the discussion around CRISPR-based technologies. The UN CBD will continue its discussions on genome editing, under the auspices of synthetic biology and potentially the Cartagena Protocol, negotiating if/how these tools should be used and what the accompanying risk assessment requirements should be. Concurrently in 2021, the IUCN will vote on a set of guidelines that will lay the groundwork for its future

policy on how CRISPR-enabled applications (i.e., synthetic biology) might impact conservation goals,[25] whether as a tool to support conservation or whether it is something to protect against, or some variation of both.

It is also important to reflect on the fact that the first generation of GMOs were introduced without sufficiently encompassing or incorporating public deliberation, acceptance, or trust, which ultimately led to rejection from some populations and consumer groups, most notably in Europe. For this very reason, the concepts of RRI were born, in that it was realized that societal concerns along with environmental, health, and safety concerns need to be factored into technology innovation processes to help guarantee the ultimate success of new (bio)technologies. In fact, a recently published commentary in *Science* advocates for greater degrees of transparency and multi-stakeholder collaborations in the development of gene-edited crops to help avoid similar public backlash and loss of trust that characterized first-generation GMOs.[8] Further, the recent coronavirus disease 2019 (COVID-19) pandemic of 2020 has also highlighted how social factors, such as trust and communication, play large roles in how societies can respond to a new technology or innovation, in that only around half of the U.S. population recently indicated it would take a COVID-19 vaccine as of late October (2020),[26] since many do not yet trust that the vaccine will be safe and effective. This has highlighted the importance of including societal preferences within innovation cycles. These concepts have also been demonstrated in the field of sustainability, relying on the ''triple bottom line'' approach, by incorporating techno-economic, environmental and human health, and societal/ethical principles together to deem a product or process as ''sustainable.''

Understanding and evaluating CRISPR's societal and environmental effects takes time and will require broad societal and interdisciplinary convergence, including a dedicated and active participation from the CRISPR scientific community in general and perhaps this readership in particular. But time may be running out.[27] Arguably, society's reluctance or inability to meet the 2020 sustainability goals[27] is creating urgency and may require us to turn toward technological solutions such as CRISPR. In 2021, the UN will adopt a post-2020 global biodiversity framework, which will serve as a stepping-stone toward the 2050 vision of ''living in harmony with nature.'' How or whether CRISPR fits into these strategies is an open question.

Promises of CRISPR applications in food and agriculture; promises of equitable access and distribution; promises of sustainability; promises of governance and tools such as RRI; promises of safe development, deployment, and responsible use; promises to reduce risk; promises to build public trust; and promises to ensure equitable benefits. The CRISPR community must actively engage with international deliberations, society, and governance systems that have promised to both protect the environment and achieve equitable outcomes. Without this active engagement, promises are sure to be broken.

Acknowledgments

We would like to thank NC State's Genetic Engineering and Society Center for creating an ecosystem of collaboration across disciplines and departments that enabled the collective scholarship of this article.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

While no direct funding has been provided to produce this manuscript, NC State's Genetic Engineering and Society Center facilitated the ability for the manuscript to be conceived, written, and submitted.

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