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Genome Editing and the Future of Farming

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Genome editing in context

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ABSTRACT

Genome editing has created a new continuum between what might occur in nature and what can only occur in the laboratory. Remarkable though it is that we have developed the capacity to predictably and finely alter genetic codes it is perhaps as remarkable that a new technology enabling this has appeared, spread widely and become easily affordable and accessible within such a short timescale. The speed at which the CRISPR/Cas9 technology use has grown almost defies comparison. A factor contributing to this, and also to the complexity of the surrounding debates, is the sheer breadth of possible applications of the technology, in terms of target organisms and genetic constructs, and in terms of the processes it could be used to influence. These combined characteristics, while opening a world of possibilities for science and society, also present a pressing and complex set of questions about governance and regulation; it is difficult to have appropriately informed discussion let alone for regulation to keep pace.

There is good reason to anticipate that genome editing will continue to progress rapidly and to evolve more refined, and perhaps even more accessible, characteristics and capacities. Decisions about where and whether to apply the technology in controversial settings are already arising, and will continue to do so – the full range of contexts is difficult to anticipate. It is certainly the case that the pull on science and its applications from current

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big challenges in food security and sustainability; the interaction of nutrition and health; the regulatory environment and its adaptation; societal perception of genetic engineering and its drivers; will soon combine to create the context in which the application of genome editing to agriculture will play out. It is vital that scientists play an active, engaged and highly reflective role in this, both in technical communication with the sector and non-technical communication with public, business and policymakers.

Governments and business are wrestling with big challenges in food and nutritional security - predominantly the need to improve the available supply of nutritious food to expanding populations without increasing resource use in terms of land, water, energy, the application of chemicals (biocides and fertilisers), or contributing to greenhouse gas (GHG) emissions driving climate change. The search for knowledge of gene function to identify solutions to these challenges is generally encouraged at the research stage but often controversial in public and at the stage of application. Publicly and privately funded research has a role to play and therefore all scientist communities must be involved in responsible research and innovation as well as dialogue with stakeholder communities.

Existing legal and regulatory frameworks do not necessarily cover the possibilities emerging from genome editing, and new regulations will be needed in many jurisdictions. The very basic question of whether genome editing will, or will not, be regarded by regulators as genetic modification (GM) remains unresolved at the EU level, although some recent decisions in the USA have provided judgement on individual altered organisms.[5] The technical detail of whether a point substitution or deletion is involved, as opposed to CRISPR-mediated insertion of sizable sections of DNA, is often seen as a determining factor within the science community, but may not be so in the regulatory community, or in public.[6] Equally whether the absence of trans-genes exempts a modified organism from GMO status is also debated. However, continued delay and uncertainty in the EU, and elsewhere, will

[5] Anti-browning trait white button mushroom: https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_response_signed.pdf; Waxy corn hybrid: https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-352-01_air_response_signed.pdf

[6] VBIO (2016) *Genome Editing bei Pflanzen: Biologenverband für pragmatischen Umgang im geltenden Rechtsrahmen* http://www.vbio.de/vbio/content/e25/e15139/e15146/e36447/filetitle/160914_PM_Impuls_Genome_Editing_ger.pdf

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deter some innovation, while the creation of certainty around a legal environment would facilitate planning and development.

It is a genuinely challenging task to create a regulatory environment and mechanisms that recognise what should be permitted without closing off innovation or dissuading further development. However, this is essential in order to strike the right balance between having sufficient rigour to benefit the public, and introducing a hurdle (or series) that stifles innovation.

This challenge will require important decision-making among biologists, social scientists, the legal profession, ethicists, policy-makers and, importantly, the general public, to reach the best starting point for any regulatory framework. Ideally, this will enable continued exploration and innovation. Design of appropriate regulation must also build in capacity to adapt the mechanism and its framing based on the experience accumulated and the new questions that emerge. Early consideration of public and stakeholder issues is required to provide the strong foundation on which a regulatory framework can rest. Past experience in GMO debates and elsewhere indicates that mistrust can be difficult to address once it has emerged. Equally, it can be difficult to anticipate where the most obvious benefits of a new technology will accrue first. Early applications of new technologies often come to define the popular public view of a technology and can have undue influence on attitudes to subsequent applications regardless of any difference in character. In this context, regulation of genome editing must be tailored and adaptable as our understanding of the operation, potential and implications of these techniques improves.

As the possibility of release or use of genome edited organisms approaches, the characteristics and requirements of the regulatory system must be considered. The products of safe research, if recognised by the informed public as acceptable and sustainable, should not face a regulatory block. Any regulation must address a number of issues, only some of which can ever be answered by science. Technical and safety concerns are amongst those that can be approached objectively and potentially can be resolved, predominantly by science.

Nevertheless, regulation of genome edited organisms is complicated by the fact that certain applications, which do not introduce transgenes, may be effectively indistinguishable (in terms of sequencing) from those generated by traditional breeding techniques. Deletions, substitutions or small-scale insertions of genetic sequences can be introduced by either conventional breeding techniques or, more rapidly, using genome editing. It may be impossible to discern by sequence analysis which process produced the new organism, and yet the timelines for generating these products are likely to be dramatically different. Transparency and trustworthiness on the part of product developers is essential here, as in other areas of science. Ensuring that there are no perverse incentives in the regulatory system will be important in supporting this. Estimates vary, but it is not unreasonable to predict that editing techniques could more than halve the time required to develop crops carrying a novel trait. The clear advantage afforded by this speed is a more rapid route to addressing any urgent challenge from disease, or to get a product to market to meet a need. However, it is not inconceivable that a slow and cumbersome regulatory system could erode the time advantage in development. It is increasingly likely that combinations of technologies will be used to generate novel varieties – a capacity to assess and accommodate the combination of a range of technologies is therefore desirable but not straightforward.

Moral and ethical considerations must be addressed by society, and for each society this will be informed by inherent moral frameworks in operation. Increasingly, fairness and equity in the beneficial outcomes of research and innovation are key concerns for citizens assessing the acceptability of applied science.

Agriculture and food production carry particular cultural and ethical contexts as well as the very essential function of nutrition and provision of sustenance. Genome editing, as with other technological developments, has the capacity to alter the socioeconomic structures affecting farmers and food producers, life-course and welfare of farm animals, and the impact of farm animals and crops on surrounding biodiversity. The speed of progress and breadth of application alone are reasons for special attention. Scientists involved in development programmes have a role to explain their motivation and aspiration on generating new products and how these can address existing challenges.

Previous technological developments have become intimately bound to a range of issues unrelated to the science behind their development. To many, GMOs are intrinsically linked with the operation of large corporations, an issue compounded by the fact that few, other than those large corporations, can afford to take new products through the regulatory approval system. In particular, concerns surrounding GM crops focus on the progressive concentration of land and resources in the hands of a few (and to the detriment of local small-holders and small-scale farmers) and a potential burden of litigation on farmers planting GM crops if neighbouring crops are shown to have acquired GM material.[7,8]

Animal welfare implications of genome editing are complex. On the one hand the technology has already been shown to have particular promise in disease resistance breeding, potentially removing a significant burden of illness and early death,[9] or removing characteristics unsuited to a farm setting (e.g. hornless cattle). There are some objectors to livestock farming in principle who cannot be convinced of the merits of genome editing, but there is clear scope for engagement with others on a case-by-case basis. Agricultural impact on the environment and biodiversity is particularly relevant in relation to disease control and is likely to be complex, with the need to carefully assess all potential risks before proceeding. Genome editing of insect disease vectors for example, involving release (and potentially incorporation of gene drive features, see below) requires careful analysis in relation to ecosystem function.

Alongside the possibilities afforded by utilising genome editing techniques on domesticated species of crop or livestock, it is possible that CRISPR/Cas9 could be used to design gene drives designed to spread in wild populations. A gene drive is a genetically determined characteristic that can spread through a population, over multiple generations, at a rate faster than would be possible through Mendelian inheritance. In theory, gene drives could be used to spread a desired characteristic through an entire wild species. The potential applications for such a technology are evident, from reducing the ability of disease vectors

[7] IAASTD (2009) *Agriculture at a Crossroads* http://www.unep.org/dewa/agassessment/reports/IAASTD/EN/Agriculture%20at%20a%20Crossroads_Synthesis%20Report%20%28English%29.pdf;
[8] Encyclical Letter *Laudato Si* (2015) http://w2.vatican.va/content/francesco/en/encyclicals/documents/papa-francesco_20150524_enciclica-laudato-si.html#_ftnref113.
[9]Lillico, S.G., et al. (2013) *Live pigs produced from genome edited zygotes.* Scientific Reports **3**: 2847 http://www.nature.com/articles/srep02847

to carry a pathogen, to supressing the population of a given species by disrupting their reproductive efficiency. Whilst targeting vectors of human disease in this manner has received most attention, it is technically feasible to apply gene drive technologies in other settings, including the introduction of chosen traits to agriculturally important insect pests or other wild species.

No gene drive organisms have been released to date and gene drives targeting agricultural pests remain theoretical. Nevertheless research into gene drives requires particular consideration and early engagement with stakeholders, because in theory at any rate, a single gene drive organism released into the wild could pass on its engineered trait to (eventually, for example in the absence of negative natural selection pressure) all progeny of the species. That means that a decision to release gene drive organisms in one jurisdiction, under the local regulations, should take into account all other habitats of the species; ie the release of a gene drive should be considered globally. In all probability the number of species for which this approach might be appropriate is very low.

A proposed nuance arises through so-called "daisy-chain" gene drives[10], which are designed to persist for only a defined number of generations before disappearing again. Daisy-chain drives could be used to target invasive species only in their non-native range therefore, or suppress pest populations in a local area; this might offer a more applicable and perhaps more widely acceptable technology. However, careful, gradual and monitored moves towards testing are essential.

The checks and controls required to police this kind of research are varied and should include molecular containment (separating drive elements) physical containment (the laboratory containment) and ecological (eco-system containment, whereby research on a particular species should not occur in areas where wild individuals of that species are present)[11]. Alongside this and of absolute necessity will be the training in practice and communication of responsible research at all levels of involvement[12].

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[10] Noble et al., (2016) *Daisy-chain gene drives for the alteration of local populations*, bioRXiv, posted 2016
[11] Oye et al., (2014) *Regulating gene drives*. Science 345: 626-628
[12] Akbari et al., (2015) *Safeguarding gene drive experiments in the laboratory*. Science, 349: 927-929

The targeting of pest species or vectors of animal disease may offer realistic alternatives solutions to problems currently addressed by the use of pesticides - leading some to label them as "sustainable" agriculture options.[13] Care should be taken when using terms such as this, given the complexity of the issues involved, and absolute transparency around any application of the technology and how this achieves its aims is essential, including justification of how this might achieve well-understood objectives of sustainability. Nevertheless, new technologies offer alternatives to current practice and should receive open analysis of benefit. Criticism of the current regulation of GM technologies in Europe often focuses on their failure to take into account risks associated with existing, non-GM solutions[14].

The potential for deliberate misuse of genome editing technologies to inflict damage on agricultural systems, and thereby on businesses, populations or nations, cannot be ignored. In this context the recent report of the Nuffield Council for Bioethics noted that "*New possibilities raised by convergence of genome editing and gene drive technologies may become a matter of increasing concern as the technologies develop.*" Robust detection and counter-measures as well as strong normative values within the science community will be important[15].

Despite the novelty of genome editing, the bedrock issues that will be pivotal are familiar – being trustworthy and listening communicators will be vital for scientists if they want to be supported to continue good work in this area. The life sciences community has not just a role but a duty to raise awareness. Having governance capacity to truly minimise risks would bring real benefits. Active dialogue between researchers, research leaders, funders, authorities and civil society should underpin this. The UK is a good environment in which to

[13] Montenegro, M. (2016) *CRISPR is coming to agriculture — with big implications for food, farmers, consumers and nature*. http://ensia.com/voices/crispr-is-coming-to-agriculture-with-big-implications-for-food-farmers-consumers-and-nature/

[14] House of Lords Science and Technology Select Committee (2015) *Genetically Modified Insects*. 1st Report of Session 2015–16.

[15] RSB statement on responsible research and dual use research of concern https://www.rsb.org.uk/policy/policy-issues/dual-use-of-research

approach this. We need to be very aware of public preferences and priority topics because all forms of public support will be needed – funding, regulatory and popular.

Openness and transparency can be effective in winning support. But scientists must show themselves to be independent and trustworthy – with the highest standards of reporting and self-criticism. Science must be absolutely honest in the presentation of facts and assessment of risks and benefits. The temptation to over-simplify the pros and cons has real risk if it over-sells the specificity for techniques for example; CRISPR/Cas9 was presented as exquisitely precise in early discussion so when reports of improved techniques with higher efficiency and fewer off-target effects appear the implication is not lost on the listening public. Additionally, clear communication that genetic assessment of edited organisms must be accompanied by phenotypic assessment should be stressed

Genuine public engagement that can inform policy development is not easy to achieve. Encouraging and empowering life scientists to join in development and delivery of any engagement is crucial. And again this is not easy. It is essential that all scientists utilising gene editing techniques consider and try to fully understand the ethical and societal implications of their work, as well as the legal ones. Scientists are not necessarily trained, or experienced in communicating in these areas however. A greater attention to this challenge would benefit the profession overall, as well as future applications of genome editing. Provision of skills and training to engage with these issues will be essential to creating an informed scientific workforce. There are distinct training needs in relation to each aspect of this. Recognition is needed that while not everyone has the capacity or resource to engage publicly, all should understand the context and issues.

Presentations at Genome Editing and the Future of Farming[16] amply demonstrated awareness and thoughtfulness in the science community in the motivation and means employed in using genome editing to address challenges in agriculture. We need more and wider discussion of the issues and possibilities of genome editing to truly advance practice and its beneficial applications. We must not wait for a public controversy or crisis before

[16] Genome Editing and the Future of Farming (2016) http://www.nib.ac.uk/event/genome-editing-and-the-future-of-farming/

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beginning to engage and communicate. We need to think and talk about the combined possibilities from genome editing, gene drive, current GM, marker assisted and conventional breeding technologies. Overall we must be ready to disaggregate the issues as much as possible and communicate about products and purpose, risks and benefits, as well as processes.

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