DEPARTMENT OF
SCIENCE AND TECHNOLOGY STUDIES

RESPONSIBLE RESEARCH AND INNOVATION IN GENE EDITING

A briefing note

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Introduction

Gene editing technologies have existed for almost 20 years. However, the latest innovation in genome editing, the CRISPR/Cas9 system, has resulted in increased enthusiasm among the research community and a hastening of research. For this reason, the profile and impacts of genome editing may increase in prominence and demand greater attention. This briefing examines recent developments in genome editing techniques, highlights issues relevant to Responsible Research and Innovation (RRI) and provides recommendations for implementing RRI governance of the development of genome editing.

The technology

Gene editing involves making precise 'cuts' in DNA in order to remove unwanted genes or insert new genes, for example to create beneficial traits. Several techniques exist. Older systems, known as ZFNs and TALENs, are slow and expensive due to their use of proteins in locating the area of DNA to be cut. The newer CRISPR/Cas9 system, which uses an RNA molecule instead of a protein guide, is cheaper and quicker,[1] although less tried and tested[2] than these earlier techniques. CRISPR/Cas9 is also able to make multiple edits at once, for example to treat diseases caused by multiple genetic mutations.[3] These qualities indicate the potential of CRISPR/Cas9 to spur significant progress in research into genome editing and its application. So far, genome editing has been performed in the cells of many different organisms, including humans, mice, fruit flies and wheat.

The latest technique promises research and therapeutic benefits for diseases such as sickle-cell anaemia, haemophilia, cystic fibrosis and HIV. More distant possibilities include the treatment of arthritis, Huntington's disease and even infectious diseases. In the field of agriculture, applications include research into plant gene function, manipulation or adding of DNA to create new traits, promising crop improvement, nutrition and feeding the world. These promises are based partly on the advantages of high precision that genome editing (especially CRISPR/Cas9) has over traditional genetic modification. However, there are also huge uncertainties. Despite the high degree of precision, the technique will present unanticipated consequences. Harmful, off-target mutations are possible and the successful application of genome editing rests on further research into related complexities and challenges.[4]

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[1] Colin Barras, 'Right on Target: New Era of Fast Genetic Engineering,' *New Scientist*, January 27, 2014.
[2] Monya Baker, 'Gene Editing at CRISPR Speed,' *Nature Biotechnology* 32, no. 4 (April 2014): 312.
[3] Feng Zhang, Yan Wen and Xiong Guo, 'CRISPR/Cas9 for Genome Editing: Progress, Implications and Challenges,' *Human Molecular Genetics*, March 20, 2014, 6.
[4] Ibid., 9–11.

Issues arising from research and innovation

Speed

The recent discovery of CRISPR/Cas9 has generated a lot of interest, activity and promises. Research is speeding ahead without wider public scrutiny of its purposes or trajectories. For example, in early 2014, two monkeys with edited genomes were born.[5] In 2015, news that scientists in China had genetically modified human embryos using CRISPR prompted calls for strong scientific self-governance.

While some scientists appear to have adopted a fairly cautious approach to the technology and its potential, the speed of development and stiff competition, creates a tension in a new and potentially lightly-regulated field. Despite this caution, the speed of research and innovation processes and their potential outstripping of ethical and regulatory oversight is likely to be a public concern.[6]

Commercialisation

The excitement over CRISPR/Cas9 has prompted the rapid creation of several private start-ups. For example, in 2013, Editas Medicine, backed by venture capital, was incorporated in order to exploit both CRISPR/Cas and TALENs (another genome editing technique) for human therapeutic purposes. A number of other companies offering tools for genome engineering have also sprung up.[7]

While the research landscape appears to be highly commercial, competitive, expert-driven and insulated from external engagement, non-profit organisations such as Addgene do exist to promote scientific sharing.

Intellectual property

One facet of swift commercialisation has been dubbed the 'CRISPR IP land-grab'.[8] Patents can encourage but also hinder research and innovation, for example through patent thickets. Some patent holders are committed to broad licensing.[9] At the same time however, two research tools companies have chosen not to work with TALENs for IP reasons.

While RRI would encourage open discussion and responsiveness in the governance of genome editing, the IPR regime creates a system of *de facto* governance which places limits on responsiveness and the effectiveness of an RRI approach to the field. Both the land-grabbing and swift commercialisation are likely to raise concerns about the distribution of financial (and other) benefits[10] and whether the research will reflect public, as opposed to just commercial, interests. Mistrust of government and industry is also likely to be a factor, especially with respect to agricultural biotechnology.[11] These, and perennial concerns over patenting life, require scrutiny.

[5] Helen Shen, 'First Monkeys with Customized Mutations Born' *Nature*, January 30, 2014.
[6] Phil Macnaghten and Jason Chilvers, 'The Future of Science Governance: Publics, Policies, Practices,' *Environment and Planning C: Government and Policy* 32, no. 3 (2014): 536.
[7] Baker, 'Gene Editing at CRISPR Speed,' 311.
[8] Ibid.
[9] For example, see the Two Blades Foundation: http://2blades.org/tal-effector-code.php.
[10] Luigi Pellizzoni, 'Responsibility and Environmental Governance,' *Environmental Politics* 13, no. 3 (September 2004): 544.
[11] Macnaghten and Chilvers, 'The Future of Science Governance,' 535.

Gene drives, dialogue and IP

'Gene drive' describes an increased likelihood that certain genes are inherited, eventually leading to wide diffusion of genetic traits throughout a population. Engineering gene drive uses biotechnology to harness this phenomenon to distribute desired, engineered traits throughout wild populations. The advent of CRISPR/Cas9 brings closer the possibility of using engineered gene drives to target ecological and health problems, such as malaria or agricultural pests. While the potential benefits are great, this would involve unprecedented, intentional altering of entire ecosystems, with the potential for extinctions or other dangerous impacts. The technology would be essentially uncontainable. Acknowledging some of these issues, researchers have called for open and inclusive public discussions. However, if the fruits of research are immediately patented,[12] thereby imposing on the technology a specific governance structure, there may be limits to what even earnest and early public dialogue can achieve.[13]

Recommendations

Genome editing research is nascent but progressing at pace. Institutions are encouraged to open up their research to scrutiny and to involve stakeholders. Agricultural biotechnology is often viewed by publics as offering fewer benefits than, for example, health care technologies.[14] Therefore, particularly where research relates to agriculture and food, attempts to engage with public concerns, the purposes of genome editing, the motivations of scientists and research institutions, uncertainties and the trajectory of research, would be of value.[15] Early public and stakeholder dialogue, especially focussing on patenting, is recommended in order to anticipate concerns and engender reflexivity in the development of genome editing.

Such activities should be neither final, nor one-off. Findings from these exercises should be fed back to researchers and institutions to enable reflection of the purposes and directions of their research, challenging assumptions and commitments and allowing such activities to provide a degree of oversight. Research institutions are encouraged really to listen to the concerns and values expressed and to respond (rather than refusing to acknowledge their legitimacy)[16] if necessary by adapting research purposes and directions accordingly, before research becomes locked into a particular course of action.

Perhaps understandably, scientists looking to use and develop genome editing are concerned with the question of whether it counts as a form of genetic modification as understood by current regulatory regimes. Some scientists argue that it does not, and that it therefore should not be encumbered by GM regulations. Rather than attempting to evade what has clearly been a controversial technology, scientists, companies and others should reflect on the novelty of what is being imagined for this technology and consider that new possibilities will inevitably invite new scrutiny from outsiders, which should not be ignored. Difficulties and risks are currently narrowly construed and technical. Given the speed of development and the force of the promises, anticipation may help open up consideration of likely, plausible and possible consequences of the research[17] and focus on realistic future impacts before paths and purposes are fixed.

[12] http://elifesciences.org/content/early/2014/07/17/eLife.03401/article-info.
[13] K. M. Esvelt et al., 'Concerning RNA-Guided Gene Drives for the Alteration of Wild Populations,' *eLife* 3, no. 0 (August 1, 2014).
[14] Macnaghten and Chilvers, 'The Future of Science Governance,' 538.
[15] J. Stilgoe, R. Owen and I. Macnaghten, 'Developing a Framework for Responsible Innovation,' *Research Policy* 42, no. 9 (2013): 3.
[16] Pellizzoni, 'Responsibility and Environmental Governance,' 558.
[17] Ibid.