Section 2

Science in context

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Overview

This section offers an account of the external conditions that bear on the production of knowledge and the development of technologies using genome editing. This is intended to complement the discussion in the previous section, which considered the nature of the techniques and emergence of the concept of genome editing within the context of the biological sciences. The present section therefore explores the interaction and interpenetration of science, and particular developments within science, and the wider society in which it takes place.

The vaunted advantages of genome editing, especially the CRISPR-Cas9 system, in terms of relative speed, accuracy, efficiency, low cost and ease of use are put into context, in relation to some of the current applications in basic research, such as the generation of gene-targeted mice. Current limitations in cases where new genetic elements or multiple edits are to be introduced, and where use is dependent on allied skills such as animal breeding, are described. Consequently, claims about the advantages of genome editing have to be considered carefully and in a broad context. Advances in genome editing may therefore reveal bottlenecks elsewhere that will impede the development of practical applications. External constraints on research, in terms of how research is encouraged and resourced, and the cultural responses of researchers to these factors have also influenced the attention given to genome editing.

The relationship between research and innovation is discussed. Although scientific research is thought to be socially beneficial, the relationship is complex and non-linear. Despite this, the idea of research impact is still considered by some to be an important rationale and justification for research funding. Another important expectation is that scientific knowledge should be available as a public good; this ethos is occasionally in tension with the reliance of innovation systems on private enterprise and has given rise to intellectual property rights (IPR) that secure the producer's income while allowing their know-how to be made publicly available. The commercial value of companies with IPR makes market speculation a factor capable of shaping innovation and concentrating power in the hands of certain firms, complicating the relationship between supporting research and securing societal benefits.

Consideration is given to the sense in which genome editing is transformative (capable of significantly changing practice and reorganising concepts). The implications that this transformative potential has for the broader public interest in the technology are discussed and the question is raised about the extent to which this interest reaches through into basic or underpinning research, and how that interest might be given effect through governance and regulation.

The significance of the 'editing' metaphor is examined and the need is noted for a coherent relationship between systems of concepts within science and within normative discourses by which they are governed, such as those of law and morality. The disruption of this relationship and the need to re-establish it in the case of transformative biotechnology is noted.

The conclusion identifies two main sources of public interest in genome editing, concerning societal investment in research and innovation and the potential impact of genome editing on the wellbeing and moral fabric of societies.

Introduction

2.1 Genome editing is primarily used in scientific research at present, where specialist knowledge and skill are brought to bear on the design and execution of experiments to produce, confirm or challenge ideas. The rapid adoption and diffusion of genome editing in the biological sciences, particularly the CRISPR-Cas9 system, has been due largely to its perceived superiority, in ways that are valued by users, to existing techniques, and to the fact that it enables experiments to be accomplished that were not previously achievable. Genome editing has, however, potentially many wider uses than as a scientific research technique.

2.2 In the Nuffield Council's 2012 report, *Emerging Biotechnologies: technology, choice and the public good*, biotechnologies were characterised as 'conjunctions of knowledge, practices, products and applications'.[24] This characterisation emphasises the way in which science and its practices, objects, conditions and aims correspond with and influence each other as biotechnologies emerge and become established in different fields of application. It offers a useful way of thinking about the prospects and possible pathways for genome editing. Having looked at the techniques of genome editing themselves in section 1, this section considers how these techniques might come

[24] Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good* (London: Nuffield Council on Bioethics), available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/.

to comprise new treatments and technologies, and how such developments may be influenced by (and influence) a range of contextual conditions. These conditions include institutional, economic, social, legal and moral conditions that determine how quickly or slowly genome editing emerges, the objectives to which it is directed, the geography of its use, and the technological forms it takes.

Research and innovation

Basic research

2.3 Why has genome editing, particularly the CRISPR-Cas9 system, spread so rapidly through the biological sciences? The main advantage of CRISPR-Cas9 in comparison to previous methods is its versatility and ease of use. The availability of proprietary CRISPR-Cas9 kits requiring less technical skill (compared to ZFNs and TALENs) make genome editing, in effect, an off-the-shelf technology. This is made possible by the ease of production of both the CRISPR component, which is a short guide RNA (sgRNA), and Cas9, which is a one-size-fits-all protein that can be used to cut perhaps any DNA sequence. The use of synthetic guide RNA led to a widespread uptake in laboratories around the world as guide RNA is made to order and delivered by post.[25] Successful genome editing by CRISPR-Cas9 requires skills that can readily be acquired by those with standard degree level skills in molecular biology, which both potentially lowers the cost of deploying it (if it is no longer necessary to have expensively trained specialists) and increases the potential pool of users.[26] (This pool might potentially extend to include non-specialists and even amateur enthusiasts.)

2.4 The CRISPR-Cas9 system makes experiments that involve editing stem cell genomes *in vitro* quick to design and execute, allowing very rapid progress without expensive equipment and reagents. A final year undergraduate, for example, might feasibly design some sgRNAs and make a mutated cell line in a 10-week project. Furthermore, the *in vivo* use of CRISPR-Cas9 can imply significant time and cost savings in the generation of animal models through the direct injection of Cas9 and transcribed sgRNA into early embryos (zygotes). This is a more efficient way of producing the desired mutation, allowing the ES cell targeting phase to be bypassed, meaning that the generation time for rodent models can be reduced from over a year to just a few weeks, while the precision of editing is improving.[27] Moreover, mutant mice used for the study of disease can be produced in just one generation rather than after multiple generations of breeding, as was the case using previous methods that involved backcrossing modified mice through several generations to ensure the desired variation appeared in the desired inbred genetic background.

2.5 While the CRISPR-Cas9 system has enabled one-step generation of knockout mice by microinjection of zygotes, low success rates of introducing new functional DNA elements (cassette knock-in) in the same fashion currently limit its range of application, at least without recourse to embryonic stem cell approaches.[28] In fact, the efficiency of CRISPR-Cas9 varies considerably depending on the repair pathway (NHEJ or HDR, with HDR hitherto less efficient or not available in certain cases) and among cell types and organisms.[29] Furthermore, multiple edits may prove challenging in some circumstances owing not to the ineffectiveness of the editing system but to

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[25] See: Petherick A (2015) Outlook: genome editing *Nature* **528**(7580): S1.

[26] The ease of use of CRISPR-Cas9 has contributed significantly to the rising number of orders for genome-editing kits (for example from producer Addgene) for different genome editing applications from ca.2.500 in 2012 when CRISPR was introduced to more than 20.000 in 2014 and a growing number of research tool companies are launching CRISPR-related products. See: Baker M (2014) Gene editing at CRISPR speed *Nature Biotechnology* **32**(4): 309-12; Corbyn Z (2015) Biology's big hit *Nature* **528**(7580): S4-S5.

[27] Hsu PD, Lander ES, and Zhang F (2014) Development and applications of CRISPR-Cas9 for genome engineering *Cell* **157**(6): 1262-78.

[28] See, however, Aida T, Chiyo K, Usami T, *et al*. (2015) Cloning-free CRISPR/Cas system facilitates functional cassette knock-in in mice *Genome Biology* **16**: 87.

[29] Golic KG (2013) RNA-guided nucleases: a new era for engineering the genomes of model and non-model organisms *Genetics* **195**(2): 303-08; Hsu PD, Lander ES, and Zhang F (2014) Development and applications of CRISPR-Cas9 for genome engineering *Cell* **157**(6): 1262-78.

natural cellular repair mechanisms, which mean that if multiple double-stranded breaks are introduced into a single genome they may recombine with each other, in effect scrambling the genome. It may be possible, however, to circumvent such an outcome: as an alternative to introducing DNA breaks to effect editing, enzymatically modified forms of Cas9 have been produced to allow the targeted, direct conversion of one DNA base into another – so-called 'base editing'.[30] Moreover, performing multiple edits in a cell line context should permit selection of the appropriate cell genotype prior to further use. Culture of cells and micromanipulation of embryos, and their reintroduction to living animals, also require, variously, controlled laboratory conditions, precision equipment and advanced embryology and surgical skills.

2.6 Thus, while it is commonly and frequently claimed that genome editing has become significantly (perhaps radically) quicker, cheaper, more efficient, easier to use and therefore more accessible, care is needed when interpreting these claims.[31] The extent to which genome editing displays these features varies considerably, depending on many factors, including the field of application, the precise technique used, how it is applied and who is using it. Furthermore, although it greatly facilitates some research procedures, this will often reveal other bottlenecks and challenges confronting researchers. Nevertheless, the efficiency of genome editing, particularly CRISPR-based systems, is continually being improved.[32] We should therefore, at least for the purposes of this ethical discussion, take seriously the reality that it is already possible to make affordable and efficient edits to any genome with seemingly very low risk of unintended, direct molecular effects.

2.7 In addition to the intrinsic features of the technique, the rapid development and diffusion of genome editing techniques to date has been driven by both demand from researchers and high-profile advocacy by the developers and early adopters, and enabled by the conditions and culture of research in the biological sciences.[33] Biological research is international in scope, shares a domain of problems that transcend national interests, and communicates in a *lingua franca* (English), including through open access publication that allows universal diffusion and the formation of consensus. That culture, however, itself develops in response to a number of extrinsic influences and constraints.[34]

2.8 One of the main constraints on research is resources. In recent years, the direction of applied research has been significantly shaped by the interaction of several factors, often driven by the need to secure adequate funding. State funding is increasingly dependent on the demonstration of past success by research teams and on the articulation of a promise of future value.[35] Contemporary funding streams, such as those of the UK Research Councils and the European Union's Horizon 2020 programme, are orientated by 'societal challenges'.[36] In practice, while this may mean that research questions are addressed under different rubrics from the point of view of funding ('stem cell research' rather than 'developmental biology', for example) it may also mean

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30 Komor AC, Kim YB, Packer MS, *et al*. (2016) Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage *Nature* **533**(7603): 420-4.

31 This claim, particularly in respect of the CRISPR-Cas9 system, was found in many of the responses to our *Call for Evidence*, for example: PHG Foundation; Christian Medical Fellowship; MRC Harwell; Vlaams Instituut voor Biotechnologie (VIB); Carolyn Riley Chapman; Royal Society; Association of Medical Research Charities (AMRC); Biotechnology and Biological Sciences Research Council (BBSRC) and Medical Research Council (MRC); Angel Petropanagos, Dalhousie University and Carlos Mariscal, Dalhousie University & University of Nevada; Wellcome Trust.

32 Kleinstiver BP, Pattanayak V, Prew MS, *et al*. (2016) High-fidelity CRISPR-Cas9 nucleases with no detectable genome-wide off-target effects *Nature* **529**(7587): 490-95; Slaymaker IM, Gao L, Zetsche B, et al. (2016) Rationally engineered Cas9 nucleases with improved specificity *Science* **351**(6268): 84-8.

33 The promotion of CC9 has arguably transcended conventionally measured forms of communication of incremental scientific advance. It has been supported by charismatic and high-profile advocates (e.g. Jennifer Doudna, George Church), with the encouragement of commentators (e.g. Steven Pinker), vested interests (research funders and patent holders) and both the scientific and popular press. It appeals to scientists trying to stretch their exiguous grant money.

34 The unintended consequences of such constraints for scientific culture were discussed in *Emerging Biotechnologies* (see: http://nuffieldbioethics.org/project/emerging-biotechnologies/) and explored further in the Council's *Research Culture* engagement project (see: http://nuffieldbioethics.org/project/research-culture/).

35 The 'impact agenda' is one of a broader set of conditions that influence the phenomena of contemporary scientific research culture as their (sometimes unintended) effects. See *ibid*.

36 For Horizon 2020, see: https://ec.europa.eu/programmes/horizon2020/en/h2020-section/societal-challenges. There is inevitably some uncertainty associated with this given the result of the 2016 referendum on the UK withdrawing from the European Union.

a change in the kinds of research question that are addressed, as well as how researchers interact with those outside the laboratory, and how they explain, locate and portray their work in the world. Whereas scientific knowledge is international, science funding is often national, and researchers are constantly embroiled in direct competition for resources, jobs and recognition.[37]

2.9 Researchers who are not funded by the state may also need to account for the value of their work. For example, those employed in the commercial sector are likely to emphasise the value of their research in terms of enhanced shareholder value, while researchers funded by charitable foundations may be more inclined to emphasise the contribution of their research to the charity's strategic mission. Very little contemporary research is funded purely on the evaluation of past performance; most is funded on the basis of *projects*, that fall within particular strategic programme areas, in the expectation that transferable or commercially valuable knowledge will be produced.

Emerging technology and innovation

2.10 How the relationship between research and technological innovation is understood informs the formulation of research funding policy, and reveals or obscures opportunities for the ethical governance of science. A commonplace but now largely discredited perspective viewed science as a resource from which innovators draw, leading to new technological innovations that provide social or commercial benefits, such as increased wellbeing and productivity.[38] The flaws in this 'linear model' are generally thought to stem from its failure to give due attention to the complexity of innovation processes, the importance of feedbacks, the role of markets and other actors, and the effects of uncertainty and serendipity. Science now tends to be seen less the wellspring of technological innovation than a 'co-producer' along with these other forces and actors. Nevertheless, future applications of scientific research continue to have a justificatory role with regard to research in general and – increasingly, even – in particular, through the contemporary 'impact agenda' that pervades academic research evaluation and funding.[39] In private companies, future applications justify expenditure on research and development (although expenditure on *basic* research is left largely to the academic sector).[40]

2.11 Sociologists of science have long observed the dependence of science on particular types of social and institutional structures.[41] Writing in the early 1940s, the sociologist Robert Merton identified 'common ownership' as an integral element of the modern scientific ethos, in which the substantive findings of science are understood as a product of social collaboration and thus assigned to the community "as common heritage, in which the equity of the individual producer is severely limited."[42] The scientific ethos of common ownership also coheres with the nature of information and technological knowledge or know-how as a 'public good'. From an economic

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[37] On the perceived role of individuals, see George Church's counterblast to the lionisation of Jennifer Doudna (The Scientist (29 December 2015) *Credit for CRISPR: a conversation with George Church*, available at: http://www.the-scientist.com/?articles.view/articleNo/44919/title/Credit-for-CRISPR--A-Conversation-with-George-Church/) and the furore over Eric Lander's alternative hagiography in *Cell* (Lander ES The heroes of CRISPR *Cell* **164**(1): 18-28; The Scientist (19 January 2016) *"Heroes of CRISPR" disputed*, available at: http://www.the-scientist.com/?articles.view/articleNo/45119/title/-Heroes-of-CRISPR--Disputed/).

[38] The 'linear model' is conventionally traced to Vannevar Bush's influential 1945 report *Science, the endless frontier* (United States Government Printing Office, Washington), available at: https://www.nsf.gov/od/lpa/nsf50/vbush1945.htm. See also Godin B (2006) The linear model of innovation: the historical construction of an analytical framework *Science, Technology & Human Values* **31**(6): 639-67 and Edgerton D (2004) The linear model' did not exist: reflections on the history and historiography of science and research in industry in the twentieth century, in *The science-industry nexus: history, policy, implications*, Grandin K, Wormbs N and Widmalm S (Editors) (Sagamore Beach, MA: Science History Publications), pp31-57.

[39] The different ways in which 'impact' figures in funding among the Higher Education Funding Councils and Research Councils are often poorly understood, at least outside academia. For RCs see: http://www.rcuk.ac.uk/innovation/impacts/.

[40] For a comparative assessment of UK gross domestic expenditure on research and development see, for example: http://www.publications.parliament.uk/pa/cm201516/cmselect/cmsctech/340/34006.htm.

[41] The canonical work is Merton R K (1973 [1942]) The normative structure of science, in *The sociology of science: theoretical and empirical investigations*, Storer NW (Editor) (Chicago and London: The University of Chicago Press), pp 267-78.

[42] Merton, op.cit., 273.

perspective, information (including the knowledge generated from scientific research) has two important characteristics: the consumption of information is both non-rivalrous (one person's use of information does not diminish any other person's ability to use the same information) and non-exclusive (once produced, information can be made available to all others at negligible additional cost).[43] The fact that it is easy to share information and difficult to exclude others from access to information once it is in circulation means that it is likely to be under-produced if provision is left to the interplay of the forces of demand and supply in the market (since 'free riders' who consume a good they have not shared in meeting the cost of producing, will undermine the producer's investment), yet there is no value-free mechanism for determining the appropriate level of provision.

2.12 The development of intellectual property regimes can be understood as a response to the problem of incentivising the provision of 'informational goods' such as scientific knowledge. In particular, the patent system essentially creates artificial property rights in order to spur innovation by creating a monopoly in favour of the patent-holder for a limited period of time and requiring the publication of know-how in return.[44] Hence the communal character of modern science was, even at the time when Merton was writing, fundamentally in tension with understandings of technological know-how as private property, which is given legal recognition within capitalist economic systems in the form of legally enforceable intellectual property rights.[45] Since the 1970s, the quest to secure patent rights has been influential in shaping the dynamics of research in the biosciences, spurred by the passage in the USA of the Bayh-Dole Act, which took effect in 1981, allowing US universities and small businesses to own patents in the inventions that they had developed with US federal government research funding.[46]

2.13 In the contemporary context, the need to secure funding and commercial investment through the promise of market exclusivity secured by intellectual property rights and stock market speculation on the value of biotechnology firms are likely to play a significant part in shaping the dynamics of scientific research and technological innovation. The reporting of the CRISPR-Cas9 system in the scientific press was attended by an increasingly high profile patent dispute between the two main claimants to intellectual property in the underlying invention.[47] Since then the prospects of biotechnology firms using genome editing are regularly analysed in the business press.[48] All of these factors may exert influence on the orientation of research and may, in turn, generate ethical concerns.

2.14 Critics of the patent law regime question the extent to which it strikes a balance between the private interest of patent owners and the overall social gains of the patent system,[49] with a growing consensus shared by economic historians and industrial organisation scholars that the importance of IP rights varies significantly across industries and fields of innovation, and that the link between

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[43] Stiglitz JE (1999) Knowledge as a global public good, in *Global public goods. International cooperation in the 21st century*, Kaul I, Grunberg I and Stern MA (Editors) (New York: Oxford University Press), pp308-25.

[44] Hettinger EC (1989) Justifying intellectual property *Philosophy and Public Affairs* **18**(1): 31-52.

[45] Merton, op.cit, 275. These protections have certain relevant (although potentially difficult to interpret) limitations: for example, the EU Biotechnology Directive (Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998L0044:EN:HTML) prohibits patenting of "processes for modifying the germ line genetic identity of human beings."

[46] Drahos and Braithwaite comment that prior to the Bayh-Dole Act, "patents in such inventions ended up with the relevant federal funding agency, or the inventions were put straight into the public domain by means of publication. The enactment of Bayh-Dole resulted in "US universities and hospitals hurrying to the patent office. In the 5 years following Bayh-Dole these organizations increased their patent applications in the human biological area by 300 per cent." Drahos P and Braithwaite J (2002) *Information feudalism* (London and Sterling, VA: Earthscan Publications), at page 163.

[47] Smith-Willis H and San Martín B (2015) Revolutionizing genome editing with CRISPR/Cas9: patent battles and human embryos *Cell and Gene Therapy Insights* **1**(2): 253-62.

[48] See, for example: Forbes (31 May 2016) *Riding the gene editing wave: reflections on CRISPR/Cas 9's impressive trajectory*, available at: http://www.forbes.com/sites/brucebooth/2016/05/31/riding-the-gene-editing-wave-reflections-on-crisprs-impressive-trajectory/#2f1959fd141c.

[49] See, for example, Picciotto S (2003) Private rights vs. public interests in the TRIPS agreement *Proceedings of the Annual Meeting (American Society of International Law)* **97**: 167-72.

IP rights and social welfare improvement is extraordinarily complex.[50] The existence of what appears to be a highly competitive market for biotechnology patents and the licensing regime that it has spawned suggests that IP rights do not, at present, constitute a major obstacle to the discovery phase of scientific research. However, the costs associated with the development, distribution and marketing of products that utilise these discoveries can, in practice, only be borne by the major corporate firms that operate in the biotechnology sector, with potential consequences for global development, access and distribution, and distributive justice.[51] (We will return to this in relation to particular fields of application in sections 4 to 7.)

Box 2.1: CRISPR-Cas9 patenting

The origins of the CRISPR-Cas9 system are a matter of controversy. Like almost all modern scientific discoveries, a large and interacting cast of characters is involved.[52] The patenting system nevertheless militates against the collaborative ethos by assigning rewards on the basis of priority, and is compounded by other rewards and accolades, including international science prizes (a Nobel prize is assumed to be at stake).

One US academic group (Feng Zhang at The Broad Institute at Harvard University and MIT) has been granted a US patent on CRISPR as a gene editing tool but another US academic group (Jennifer Doudna and Emanuelle Charpentier at the University of California, Berkeley) has a pending patent submission that predates the one already granted.[53] This has raised concerns that the IP will deter researchers from using CRISPR, and that the uncertainty of ownership will deter commercial companies. Through our interviews, and from the number of publications we found no evidence that either of these two concerns was justified.

It is likely that the patent landscape will become complex, and it may take years before the ownership of any particular claim becomes clear, probably only through litigation. Getting clarity could take 10-15 years, and the outcomes may be different in different jurisdictions, notably in the US compared to Europe. How, therefore, could this not become a major issue?

- It is generally accepted, at least outside the USA, that pre-commercial research is exempt from IP, in that it is not necessary to have a licence to explore the usefulness of the claims, and the IP owner is not expected to act to prevent such exploration in practice. It may also be in the IP holder's interest to have ongoing research that may expand the utility of their claims.
- CRISPR-Cas9 falls into the category of 'enabling technology', i.e. its use does not directly provide a product but it enables a product to be made using other knowledge and probably technology. Historically, this type of IP has been licensed through a 'fully paid-up licence', i.e. the IP holder does not share a royalty on any product resulting from its use, just one or a series of payments, which may be tiered depending on the scale or number of products. Only in rare cases does the IP holder refuse to licence, where they have their own applications to advance and where they use the IP to keep others out. Given the breadth of potential application and the fact that the main contenders for ownership are universities this is unlikely. It is usually in the interests of the IP owner to allow the widest use, to increase the chance that someone will find a valuable application, so that they can set the price higher than if it were set before any solid uses had been identified. A similar situation prevailed with IP covering the polymerase chain reaction (PCR) technology that underpins genetic research and genome sequencing: progress was not hindered and, when a kit is sold by a laboratory supplier, it includes a small payment for the right to use the IP, which is invisible to the user.
- Many commercial companies have already taken a licence from one or both of the patent contenders, either because they have a view on who will ultimately win, or because they believe the licence will be less expensive while uncertainty remains.
- In addition to the broad claims, the specific Cas9 claims and, potentially, claims on modified CRISPR components, two other pieces of IP are likely. The first is a claim that identifies how to address a specific application (e.g. editing such and such allele would control such and such disease) and, very likely, a narrower claim for a specific method that efficiently and effectively results in a product that delivers the potential benefit. There could therefore be at least four levels of IP that would need to be assembled to gain freedom-to-operate on any specific invention. This has raised concerns about the potential for 'evergreening' patents (to extend exclusivity)[54]; past experience, however, suggests

[50] Mennell PS (2000) Intellectual property: general theories, in *Encyclopedia of Law & Economics: Volume II*, Bouckaert B and de Geest G (Editors) (Cheltenham: Edward Elgar), pp129-88.

[51] Drahos P and Braithwaite J (2002) *Information feudalism* (London and Sterling, VA: Earthscan Publications), at page 166.

[52] Lander ES (2016) The heroes of CRISPR *Cell* **164**(1): 18-28; Ledford H (2016) The unsung heroes of CRISPR *Nature* **535**(7612): 342-4.

[53] Smith-Willis H and San Martín B (2015) Revolutionizing genome editing with CRISPR/Cas9: patent battles and human embryos *Cell and Gene Therapy Insights* **1**(2): 253-62.

[54] Jasanoff S, Hurlbut JB and Saha K (2015) CRISPR democracy: gene editing and the need for inclusive deliberation *Issues in Science and Technology* **32**(1), available at: http://issues.org/32-1/crispr-democracy-gene-editing-and-the-need-for-inclusive-deliberation/.

> that although this process can extend patent life, it does so only on an increasingly narrow base, as the initial, broader patents expire.

2.15 The factors that act to attract, secure and consolidate investment may also have the effect of confirming a course for innovation, creating both 'lock in' of contingent technological forms and forward momentum along a particular technological pathway.[55] The reasons for this include factors such as sunk costs, learning effects, increasing returns to scale, high transaction costs associated with any change of direction and the mutual adaptation between technologies and associated conditions of use, including the structure, governance and practice of institutions, and not excluding social conditions, normative rules and standards,[56] and public acceptance.[57] This is not to deny that commitment to a particular course may have associated benefits (for example, efficiency, economies of scale) but it is important to recognise that different bundles of benefits and costs (including unforeseen and unintended consequences, both deleterious and serendipitous) may be defined and valued differently from different societal perspectives.

Is CRISPR-Cas9 a transformative biotechnology?

2.16 Questions of how the technologies emerge and are adopted may lack much broader public significance so long as genome editing, or particular systems such as CRISPR-Cas9, remain merely techniques among others, at the disposal of scientists for the execution of particular tasks. They become significant, however, if the technologies that they underpin become so dominant that they overtake and potentially transform an area of practice.[58] Economic analysts refer to such technologies as radical innovations or 'disruptive technologies', although the 'disruption' may extend to social, institutional and moral domains as well.[59] Such technologies may have the capacity "to transform or displace existing social relations, practices and modes of production, or create new capabilities and opportunities that did not previously exist, or may not even have been imagined [in ways that] might be entirely unexpected or unsought."[60] An example of such a technology outside biology is semiconductor-based technologies, which replaced vacuum tubes and paved the way for the miniaturisation and commensurately increasing power of electronic computing. In biomedicine we might recall here that, in the 1950s, it was projected that the cost of treatment for those affected by poliovirus would absorb a huge percentage of the US healthcare budget; by the early 1960s, with effective polio vaccination, the cost of polio healthcare had

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55 On 'technological momentum' see: Hughes TP (1969) Technological momentum in history: hydrogenation in Germany 1898-1933 *Past and Present* **44**(1): 106-32; on 'lock in' see: Boas TC (2007) Conceptualizing continuity and change: the composite-standard model of path dependence *Journal of Theoretical Politics* **19**(1): 33-54.

56 In some cases, early market entrants can establish industry standard practice, which may become adopted into regulatory measures which then act as barriers to entry to the market for new firms, and consolidating the market dominance of the established firms. There is a stark disjunction in the so-called 'politics of regulation' between two perspectives: so-called 'public interest perspectives' understand regulation as created to serve the public interest (primarily in safeguarding society against various forms of harm, including market failure and other kinds of non-market risks); 'private interest' theorists (including public choice theorists), in contrast, emphasise the play of power involved in the establishment of regulatory standards and regimes, arguing that the most powerful players in the industry lobby politicians in order to secure regulatory norms that operate to further the interests of the industry (at the expense of the general public), often creating barriers to new entry and shoring up existing monopolies. In this way innovation trajectories may be shaped by political-economic forces that may not best serve the public interest, which is a source of ethical concern.

57 See: Winner L (1978) *Autonomous technology: technics-out-of-control as a theme in political thought* (Cambridge, MA and London: MIT Press). See also: Hughes TP (1994) Technological momentum, in *Does technology drive history? The dilemma of technological determinism*, Smith MR and Marx L (Editors) (Cambridge, MA and London: MIT Press) for the claim that the larger and more complex technological systems become, the more they tend to shape society and the less amenable they are to being shaped by it.

58 See Nuffield Council on Bioethics (2012) *Emerging biotechnologies*: *technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/.

59 See: Christensen CM (1997) *The innovator's dilemma*: *when new technologies cause great firms to fail* (Boston MA: Harvard Business School Press) where a dichotomy is established between sustaining and disruptive technologies. It is of note that disruptive innovations often perform poorly at the outset, but survive and flourish due to adoption by a user group who find value in a feature that is not shared by incumbent technologies and may not be what is generally thought most valuable about that technology.

60 See Nuffield Council on Bioethics (2012) *Emerging biotechnologies*: *technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/, at page 40.

dropped precipitately.[61] Given the rapid diffusion of genome editing across biological research and its displacement of incumbent approaches, the impact of the CRISPR-Cas9 system and its analogues is potentially of this order and has already been compared to the invention of the PCR (polymerase chain reaction) method of DNA amplification that supports modern genetic testing, molecular cloning and genome sequencing.[62]

2.17 Nevertheless emerging technologies, which are promissory by nature, are characteristically subject to 'hype' and over-claiming.[63] Whether unintentional or deliberate, the structuring of expectations through the way in which the prospects of the technology are presented may help to create the conditions in which they are realised (for example by attracting funding or investment, identifying demand or stimulating prospective policy debates). It may, equally, crowd out alternative approaches, starving them of attention, favour or resources. Possibly adverse consequences of over-claiming in areas in which science encounters politics are increasingly recognised by the scientific community, and have led to renewed injunctions to present developments in research candidly and soberly, despite the competitive environment in academia as well as business.[64] Nevertheless, the formation of expectations and the interrogation, comparison or – in some cases – confrontation of different visions of desirable and scientifically attainable futures ('imaginaries') is vital to innovation.[65] It is not necessary (or possible) that this should take place in neutral language or against a background of acknowledged priorities and values; what is dangerous is where there are asymmetries of power, information or representation in the public sphere that mean that certain visions and values go unappreciated and others go unchallenged.[66]

Interpretation and governance

The metaphor of genome editing

2.18 Whether intentionally or not, the 'editing' metaphor distinguishes the approach from less 'precise' forms of genetic 'engineering' and, simultaneously, distances it from their associated connotations, including the range of public responses that these terms typically excite.[67] The editing metaphor also plays on characterisations of the genome as the 'book of life' containing 'sentences' (genes) made up of a 'genetic alphabet' of four 'letters' (A, C, G and T, the initial letters of the four chemical bases comprising DNA) that were common around the time of the Human Genome Project. [68] The editing metaphor transfers easily to the more contemporary image of

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[61] Thompson KM and Duintjer Tebbens RJ (2006) Retrospective cost-effectiveness analyses for polio vaccination in the United States *Risk Analysis* **26**(6): 1423-40.

[62] See Ledford H (2015) CRISPR, the disruptor *Nature* **522**(7554): 20-4.

[63] "Emerging biotechnologies are promissory by nature. Belief in the beneficial prospects of a particular biotechnological initiative is necessary, but not sufficient, to bring that technology about; on the other hand, scepticism about those prospects may be sufficient, but not necessary, to cause it to fail." Nuffield Council on Bioethics (2012) *Emerging biotechnologies*: *technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/, at page 33.

[64] See, for example, a recent update to guidelines from the International Society for Stem Cell Research, available at: http://www.isscr.org/docs/default-source/guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=2; see also: Caulfield T, Sipp D, Murry CE, Daley GQ and Kimmelman J (2016) Confronting stem cell hype: against hyperbole, distortion, and overselling *Science* **352**(6287):776-7.

[65] See for example, Harvard Kennedy School of Government's 'Sociotechnical Imaginaries Project' (http://sts.hks.harvard.edu/research/platforms/imaginaries/) which explains the role of imagined future states as both aims and justifications for government policy initiatives.

[66] See Nuffield Council on Bioethics (2012) *Emerging biotechnologies*: *technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/, Chapter 4 ('Public ethics and the governance of emerging biotechnologies').

[67] References to genome editing's alleged 'precision' is challenged by some, pointing to the use of 'precision' as a 'thick' concept, connoting approbation (one that surfaces in a number of contemporary tropes, such as 'precision medicine' or 'precision warfare') or dissembling the actual capacities of the technology (confusing the ability to manipulate nucleotide sequence with precision with the level of control over the consequences of doing so in terms of gene function).

[68] See, for example, a series of blogs by Brigitte Nerlich of Nottingham University, e.g.: *The book of life: reading, writing and editing* (22 November 2015): http://blogs.nottingham.ac.uk/makingsciencepublic/2015/11/22/the-book-of-life-reading-writing-and-editing/.

modifying computer code.[69] The metaphor suggests not only the type but also the significance of the intervention: it is technical, is not dependent on scale (as it applies equally to changes large or small) and is seen as corrective or improving (at least in relation to the editor's vision). In this way, the concept of editing has a certain thickness, whereby, while apparently descriptive, it implies a tacit evaluative judgement.[70] It also implies an editor (the one who does the editing) and, by deeper implication, may distinguish the editor, who merely corrects and improves, from a putative, creative 'author'. But whether authorship is assigned to a divinity or not, the implication is that the work of editing is trivial in comparison. (Genome 'rewriting', another trope in the extended metaphor that has been used, although less frequently, for this practice, suggests a more substantial intervention.[71])

2.19 Other metaphors have been used less commonly to describe the practice of genome editing. These include 'genome surgery' (which evokes the cutting and removal of sections of DNA as well as the typically medical aims of the practice) or genome editing as a 'magic bullet' (that eliminates undesirable genetic features without collateral damage or adverse consequences). It appears, however, that the metaphor of the genome-as-text has taken an unshakeable hold. This may owe something to its familiarity, its fertility and the apparent ease with which the metaphor may be extended. The danger of the metaphor lies not in the fact that it is a metaphor, and therefore a non-reducible way of referring to complex realities; it lies in the possibility that the metaphor might either dissemble significant ethical questions through the use of euphemism, or lead reasoning astray by overstretching the power of analogy.

Genome editing in law, regulation and morality

2.20 The existence of regulatory regimes and standards that are specifically concerned with biotechnology suggests that, rightly or wrongly, they are framed in legal and regulatory terms as having special societal significance. Such measures rely on decisions about what features of a biotechnology or product are to be treated as relevant and on the possibility of distinguishing (often using specific criteria) between different classes in order to subject them to different kinds of response. Thus, the regulatory regime for assisted human reproduction in the UK uses a variety of criteria (the kinds of activities carried out, the purposes at which they aim, the type of cells involved, etc.) to distinguish what is impermissible, generally permissible, or to be permitted only under licence.[72] In notable cases, such as that of somatic cell nuclear transfer (or, more thickly, 'cloning') the correspondence between, on the one hand, how these terms are constructed and interrelated as concepts employed within legal and moral systems, and, on the other, what contemporary genomics and embryology afford in practice can come to be tested.[73] In another example, genome editing is currently testing the approach to the legal regulation of genetically modified organisms in the European Union, not only with regard to whether genome edited organisms fall under the GMO legislation, but by precipitating a more fundamental reflection on the legislative approach and its moral and political foundations (to be discussed in section 5 below).[74]

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[69] See also: Merriman B (2015) "Editing": a productive metaphor for regulating CRISPR *The American Journal of Bioethics* **15**(12): 62-4.

[70] For 'thick concepts', see Bernard Williams (2006 [1985]) *Ethics and the limits of philosophy* (London and New York: Routledge).

[71] The notion of genome 'writing' has recently become associated with a project in synthetic biology to engineer whole human genomes, known as 'HGP-write' (see http://engineeringbiologycenter.org/), which has re-envisioned the original Human Genome Project, substantially completed in 2003, as 'HGP-read'.

[72] Leather S and Mills P (2005) Regulation of assisted reproductive technology: the UK experience – themes and trends, in *Textbook of in vitro fertilization and assisted reproduction*, 3rd Edition, Brinsden PR (Editor) (London: Taylor and Francis), pp623-31.

[73] In a judicial review that concerned whether embryos created by somatic cell nuclear transfer should fall under the regulatory regime of the UK's Human Fertilisation and Embryology Act 1990, the court was obliged to adopt a 'purposive' construction with regard to the meaning of 'embryo' in the 1990 Act (*R. v. Secretary of State for Health ex p. Quintavalle (on behalf of Pro-Life Alliance)* [2003] UKHL 13. A similar anxiety resurfaced in the case of 'human admixed embryos' which was settled by the Human Fertilisation and Embryology Act 2008.

[74] See, for example: Ammann K (2014) Genomic misconception: a fresh look at the biosafety of transgenic and conventional crops. A plea for a process agnostic regulation *New Biotechnology* **31**(1): 1-17; Kokotovich A and Kuzma J (2014) Conflicting

Conclusion: the public interest in genome editing

2.21 There is a public interest in research for at least two main reasons. The first is to the extent that a great deal of research in the academic sector is publicly funded, from money collected through general taxation. This implies a public interest in the fact that this money is spent in a way that reflects public priorities and pursues them with the greatest possible efficiency.[75] The second, more profound, reason is that products and practices, processes and tools produced by the application of knowledge gained through research may have a direct or indirect impact on the wellbeing and welfare of the public (including their moral and social welfare). The public have an *interest* in science, in terms of its expectation of net social benefits, and *invests* in science both financially and through the trust placed in scientists to contribute to the delivery of these benefits. But more profoundly than this, the public have an underlying public interest in the overall moral and ethical texture of the society in which they live. How technologies like genome editing are taken up and regulated both reflects and influences the broader moral values on which common social life is based and the social meaning of the practices in question.

2.22 Research and innovation in biotechnology and biomedicine are now contested intensely in political arenas, demanding both democratic engagement and attention to broader questions of justice and value:

> "technology, once seen as the preserve of dispassionate engineers committed to the unambiguous betterment of life, now has become a feverishly contested space in which human societies are waging bitter political battles over competing visions of the good and the authority to define it. In the process, the virtually automatic coupling of technology with progress, a legacy of the Enlightenment, has come undone. Uncertainty prevails, both about who governs technology and for whose benefit. No matter which way one looks, the frontiers of technology are seen to be at one and the same time, frontiers of politics."[76]

2.23 It is important but open to question whether, and the extent to which, this second reason – that research is not separate from but a part of social behaviour – reaches through into so-called 'basic' or 'underpinning' research, which is concerned with the production of knowledge without an immediate practical application in view. That is, regardless of the entitlement that funding secures, the extent to which basic research is bound up with the flux of social transformation or is itself part of the set of wider social practices. To the extent that it is part of the set of wider social practices, there is a public interest in the conduct (that it should proceed according to principles of moral behaviour, for example) and aims of research (for example, that it should endeavour to conform and contribute to the overall public good).

2.24 A difficulty in securing the optimum mix of public benefits and the avoidance of societal harm arising from research (alongside whatever private benefits are appropriate to the developers) arises from complexity and indeterminacy in the relationship between research and innovation. This makes the processes of biomedical and biotechnological innovation highly uncertain.[77] Whereas it is a reliable inference that the pursuit of scientific knowledge *in general* will contribute to more powerful technologies that can, in turn, give rise to productivity and welfare benefits (but may also have a greater capacity for harms if misused) it is not possible to conclude from this that the pursuit of any *particular* knowledge will do so. Nor is it possible to conclude that any given

futures: environmental regulation of plant targeted genetic modification *Bulletin of Science, Technology & Society* **34**(3/4): 108-20; Araki M and Ishii T (2015) Towards social acceptance of plant breeding by genome editing *Trends in Plant Science* **20**(3): 145-9; Conko G, Kershen DL, Miller H and Parrott WA (2016) A risk-based approach to the regulation of genetically engineered organisms *Nature Biotechnology* **34**(5): 493-503.

[75] This is particularly the case given the withdrawal of commercial firms from basic research owing to the financial risk involved, which they leave to be borne by the academic sector; on the other hand, in more recent years, there has been an increasing expectation that the academic sector will operate more like a business and secure IPR so it can commercialise its discoveries.

[76] Jasanoff S (2006) Technology as a site and object of politics, in *The Oxford handbook of contextual political analysis*, Goodin RE and Tilley C (Editors) (Oxford: Oxford University Press), pp745-63.

[77] For a discussion of uncertainty in relation to emerging biotechnologies, see Nuffield Council on Bioethics (2012) *op.cit.*

innovation will benefit all equally, or that it will not benefit some only at the expense of others, in ways that, regardless of net overall benefit, may be offensive to principles of justice. How the production of knowledge and innovation is managed, controlled and directed can therefore have potentially profound implications for the public interest.

2.25 In the second part of our programme of work on genome editing we intend to start with a domain of problems rather than with a particular technical development, in order to evaluate what impact genome editing may and should have, in order to consider both the value and opportunity costs of particular solutions, and to avoid hypothecating a particular set of societal challenges to a given technology. For the time being, however, having now considered the 'instances' of genome editing and the external circumstances of its emergence, we will continue to examine the moral perspectives from which it can be viewed and the chief questions to which it gives rise; that is, not genome editing itself but its moral, legal and social, and scientific and technological ramifications.