Cambridge Public Policy

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Planning for the Future of Gene Editing

UNIVERSITY OF CAMBRIDGE

Planning for the Future of Gene Editing

A Joint Stem Cells and Public Policy Strategic Research Initiative Seminar

A report of a workshop held in Cambridge in January 2016 to discuss current and future applications of gene editing technology along with ethical and regulatory issues and policy considerations.

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Executive Summary

The science of gene editing

- A tool whereby DNA sequence can be altered in cells
- DNA is inserted into the genome of an organism (such as embryonic stem cells) using engineered nucleases
- Breaks in the genome result, which can be repaired or 'edited'
- Faulty DNA can be repaired, offering the potential to cure certain genetic diseases such as cystic fibrosis
- CRISPR/cas9 makes the process of gene editing fast, efficient and low cost

Applications of gene editing

- Basic research into biology including modelling human disease
- Offering healthy gene transplantation and xenotransplantation (animal to human)
- Using genetically-engineered mosquitoes to prevent disease outbreaks such as malaria, Zika
- Improving genetically modified crops and eradicating animal disease

Ethics of gene editing in human stem cells

- Altering DNA via gene editing includes germ-line modification, which will affect future generations
- Germ-line modification effects for future generations are uncertain and could be harmful
- Developments are blurring the important ethical distinction between treatment and enhancement in relation to gene therapy
- Clear distinctions between ethical and unethical practices are challenged when acceptable boundaries are more likely to sit on a continuum

Key Issues for Policy and Regulation

- New scientific advances challenge established ethical and legal regulatory structures around research using human stem cells
- The boundaries between somatic and germ-line editing, which affects future generations, requires careful definition within legal, regulatory structures
- International regulations in gene editing that establish principles and agreed sanctions for research and clinical use are desirable as this is an international endeavour
- International conventions such as the Oviedo Convention establish such principles but the UK is not currently a signatory

Contents

Policy Development

It is important that agreement is reached, which consists of a set of guiding principles for policy development around gene editing. These principles should be responsive to the developing science but they should also reflect prevailing social values and ethical concerns raised in response to this important area of scientific discovery. These principles are:

Open and consultative

Policy development in this fast moving field should be open and consultative. It is important that information is communicated to the public, that discussions bring together people from a variety of backgrounds, and that the public is involved in the decision making process in an informed and meaningful way.

Balance in risk and opportunities

It is important to ensure balance in discussions of gene editing, to show the public where the key scientific advances will be made, and to ensure appropriate open discussion of risks and ethical concerns. Despite the enormous potential of scientific developments in gene editing, there is still uncertainty around which applications will have the biggest impact. Currently, the greatest opportunity for CRISPR technology is that it makes for an extremely powerful research tool. Gene function can be assessed with unprecedented speed and ease for innumerable biological questions. Most of this research is largely non-controversial, and only a very small fraction involves human embryos. Ethical and regulatory considerations should distinguish clearly between *clinical* and *research* applications, and *appreciate the particular set of ethical challenges surrounding research involving human embryos.*

CRISPR policy development

Involve the public in open policy development process around gene editing potential.

Ensure appropriate balance between opportunities and associated risks in gene editing.

Consider the potential clinical applications and public health implications of CRISPR for particular conditions and purposes.

Support inclusive, responsive international regulation of gene editing.

Inclusive, responsive regulatory environment

Policy discussions around the legal and ethical implications of new technologies such as gene editing should be inclusive rather than separate from, and conducted as a response to, scientific development. Science and technology scholars have emphasised that in contrast to science moving ahead followed by legal, ethical and policy issues having to 'catch up', these are all value-laden social practices that are 'co-produced'. Policy makers have to set thresholds for acceptable developments in science that include a range of expert views including leading scholars, patient and advocacy groups and other stakeholders.

The assessment of an evidentiary threshold or of 'risks' inherent in a technology cannot be done only by scientists but must include an assessment not only of science but also of social, ethical, and legal issues, on which input from a range of expert views is required. As the contributions from bioethics experts to debates about gene editing show, the consideration of the new technologies such as gene editing require input and contribution from a range of perspectives, asking questions such as why this technology, why now, and to what effect? (Camporesi, 2015; Lewens, 2015)

The science of gene editing

The technique of gene editing is a type of genetic engineering, whereby DNA is inserted into the genome of an organism, such as embryonic stem cells, using engineered nucleases, that create breaks in the genome, which are repaired, resulting in targeted mutations or 'edits' (Dance 2015). Research using gene editing has been conducted in laboratories since the mid-1980s.

The CRISPR/Cas9 system is a new technique for gene editing. It consists of two components: Cas9 and an application specific guide RNA. Cas9 is a nuclease enzyme that can cut strands of DNA. The guide RNA is a short stretch of RNA that is complementary to the DNA region of interest. Its role is to target the Cas9 nuclease to a specific location in the genome. With the combination of nuclease and guide RNA researchers can introduce cuts into DNA at defined places.

The cellular DNA repair machinery will recognise these cuts and depending on the number of cuts and their position will either introduce mutations or delete DNA sequence. Researchers also have the option of providing a DNA template for repair, which the machinery will use to insert new sequence into the cut region. The introduced alteration into the repaired DNA sequence can range from a single base to thousands of bases.

CRISPR technology's advantage over alternative methods, which make use of different enzymes to edit genomes or different techniques to insert DNA into stem cells, lie in its speed, efficiency, and low cost (Ledford 2015, Xiao-Jie et al. 2015). This means that while not qualitatively different in outcome to previous methods, the improvement in technology for gene editing is so substantial that applications previously prohibited by time and technological challenges are now feasible or at least conceivably feasible within the next few years (Doudna and Charpentier 2014).

CRISPR has the potential to cure both monogenic diseases, caused by a single gene (for example, Huntington's disease, cystic fibrosis) and multi-genic diseases caused by mutations in different genes and their interplay with the environment (for example, diabetes, Alzheimer's disease). CRISPR technology can be used to model different diseases and also has significant potential for editing plant DNA to create improved species, and to eradicate pathogens (Shan et al. 2013, Yoshimi et al. 2014).

Cutting of the DNA is precise in the region of interest, but it has been shown that there is a risk of 'off target' effects, meaning that in addition to the intended cut, unintended ones are being made in the genome with the potential for negative consequences (Ledford, 2015). Development of the technology focuses on addressing these unwanted effects and it is anticipated that the method will continue to improve (Kleinstiver et al 2016).

CRISPR technology

The CRISPR/Cas9 system is a new tool with which DNA sequence can be altered in cells.

While gene editing has been used for many years and is not a new concept, CRISPR technology makes the process fast, efficient and cheap.

CRISPR technology is widely used in basic research to study the function of genes.

Above and beyond the use of CRISPR as a research tool, medical and bioengineering applications can be envisaged.

Current and future applications

CRISPR technology is the state of the art tool for gene editing and is currently used widely in laboratories around the world to answer questions that further our understanding of mammalian biology. Because of its speed and relative ease of use the technology has already had a significant impact on basic research (Doudna and Charpentier 2014). However, CRISPR technology also holds great potential for medical or bioengineering applications. For example, correcting a mutated copy of a gene is an attractive route for the treatment of genetic diseases affecting a single gene only, such as cystic fibrosis, Duchenne muscular dystrophy, or Alpha-1-antitrypsin deficiency (Colemeadow et al 2016; Xue et al 2016). Such inherited diseases can have devastating consequences for the individual, and while the conditions are individually rare, in sum they are a substantial public health issue.

Researchers are working towards a scenario in which a patient's cells could be biopsied, either converted into induced pluripotent stem (iPS) cells or directly grown to organoids of the biopsied tissue and their DNA edited to replace the mutated copy of the affected gene with a functional one.[1] The modified iPS cells could then be re-differentiated into the target cell type and modified organoid can serve directly (Orqueda et al 2016). These modified cells and organoids can be thoroughly tested for safety and functionality, and then be used to reconstitute mature organ function after transplantation back into the patient (Yin et al 2016). Upon successful treatment, a proportion of the cells in the most affected tissue type would contain a functional gene copy thereby alleviating the symptoms of the disease. This type of gene therapy on patient's own cells provides a healthy source of transplantation with a minimum chance of immune rejection. However, this would likely only cure the individual and not future generations.

In adult stem cells there is potential to use gene editing in a variety of applications, for example, in modifying blood cells and blood stem cells so that they are diseases-resistant, for example, current trials on HIV-resistance (Kaminski et al 2016) and also using the technology to genetically modify pig tissues and organs for transplantation into humans, known as 'xenotransplantation' (Feng et al 2015).

In addition to CRISPR's potential for improvements in human health, it could also be used to tackle diseases through genetically engineered mosquitoes, which could help prevent outbreaks of diseases spread by mosquitoes such as Dengue fever, malaria and Zika virus (Kistler et al 2015; Deong et al 2015).

The application of CRISPR in plants and livestock, particularly in food production, is intended to be the subject of future discussions of this type, such is the huge potential for application in this area; for example, in improving genetically modified crops and eradicating disease in animals (Shan et al, 2013). Given the specific ethical, legal and policy issues challenges resulting from the different applications of gene editing technology, the discussions detailed in this report focused on gene editing in human stem cells.

1. For a detailed description see: *insights.bio/cell-and-gene-therapy-insights/?bio_journals=stem-cell-derived-organoid-cultures-and-genome-editing-tools*

Ethics

Scientific development is moving at a fast pace and it is therefore particularly important to consider whether boundaries are being crossed in the drive to support new scientific developments. It is recognised that scientists need to actively engage with the public in order to ensure that policy makers and the international scientific community establish rules and regulations around the technology that are supported by informed public opinion (Jasanoff et al 2015).

Discussions at the Cambridge workshop followed a series of international meetings and discussions about gene editing including an international summit held in Washington DC involving the US National Academy Medicines, the UK Royal Academy of Sciences, and the Chinese Academy of Sciences[2] and also a recent public call for evidence on the implications of gene editing from the Nuffield Council for Bioethics[3]. The Cambridge discussions focused on exploring what new ethical and regulatory concerns were being raised by current and likely future scientific developments in gene editing and how to achieve policy decisions that support the development and regulation of gene editing as well as supporting public discourse around gene editing.

Gene editing is already being used in the majority of molecular laboratories in the UK for a variety of purposes. Studies that focus on gene function usually involve knock-out or mutation of the gene of interest in cell lines or model organisms. These genetic modifications are now routinely done with CRISPR. The scale of the research endeavour using gene editing is relevant when considering its regulation (Evitt et al 2015). It is an extremely powerful research tool that has a wide range of potential applications. It is important to consider how and why different applications may raise different ethical and regulatory challenges and also how best to support gene editing as a research tool now and in the future.

CRISPR Ethical Issues

New scientific advances in CRISPR technology challenge established ethical and legal regulatory structures.

The societal impact of non-human uses of gene editing is potentially far greater than in human stem cells.

The boundaries between somatic and germ-line editing, which affects future generations are unclear and require careful definition within legal and regulatory structures.

International regulations on gene editing technology that set out principles for research and clinical use are desirable.

2. December 1-3 2015, *nationalacademies.org/gene-editing/Gene-Edit-Summit/*
3. *nuffieldbioethics.org/wp-content/uploads/NCOB_GenomeEditing-CallForEvidence1.pdf*

We consider here the significant issues that were raised at the Cambridge workshop with respect to gene editing in human stem cells.

The somatic/germ-line distinction has played a significant role in bioethics and policy making in the last thirty years both in the UK and in the US (Anderson 1985; Anderson 1989; Ishi 2015; Addison 2016). In somatic editing, altered DNA sequence would only affect the treated individual. In germ-line editing, the individual's gametes (reproductive cells) would carry the modified sequence as well, which would therefore be propagated to future generations (Lunshof 2016).

It is widely felt that different ethical considerations apply to the two cases. However, our discussions showed that this strict differentiation is now open to challenge. First, it is no longer universal that information can only flow from germ-line to soma: somatic cells can be used for the derivation of iPS cells, which, in turn can be differentiated into germ cells (Kurimoto and Saitou, 2015). Secondly - while still under debate - some evidence suggests the inheritance of epigenetic information (van Otterdijk and Michels, 2016). This would mean that any treatment of an individual could, if it changes the human genome, affect future generations. Thirdly, recent legislation in the UK has already called into question the restrictions on genetic modification of the germ-line in some jurisdictions by allowing mitochondrial DNA replacement therapy (Vogel et al 2015) raising the question of whether a special status for nuclear DNA is merited.

Crossing the germ-line, or germ-line modification, particularly for clinical purposes, in order to affect future generations has been viewed as a line that cannot be crossed (Lewens 2015). One of the main objections is that it could lead to non-therapeutic genetic enhancement. Broader objections refer to the long-lasting effects of changes, the fact that changes could be harmful and are uncertain, and that future generations cannot provide consent for changes made today, which will affect them in the future. Such objections may be true of other scientific and broader societal changes that take place – Lewens (2015) makes the comparison with town planning – and it may be that case that future developments are agreed if broader tests for the responsible management of risk are satisfied (Lewens 2015).

The distinction between therapy and enhancement is an important one in debates about gene editing. Most people would consider correction of a faulty gene as treatment, whereas they would consider increasing physical prowess as enhancement. The position of altering a gene to a variant that confers a lower cancer risk is less clear. This example illustrates that most of the boundaries are set on a continuum and the boundaries can shift over time. Discussion at the workshop focused on whether the media representation of enhancement application of genome editing technologies is the appropriate one, and if we should not instead work towards different kinds of 'more realistic' media representations of gene editing technology, such as prevention of cancer or other traits that confer a susceptibility to a disease.

Regulation

The Human Fertilisation and Embryology Authority regulates assisted reproduction and research on human embryonic stem cells in the UK[4]. According to the Human Embryology Act (1999), research can be performed 'in vitro' up to fourteen days, but each research group still needs to apply for a research license to the HFEA, which grants licenses on a case-by-case basis[5].

Discussion at the workshop focused on the need for international regulation and agreement, given that scientific research in this area is an international, often collaborative activity. At present there is no international treaty on the human genome and international consensus has not been reached on how gene editing in humans should be regulated and how breech of regulations should be sanctioned (Ledford 2015). The legal playing field is uneven, ranging from essentially unrestricted to a complete ban (Araki et al 2014). Workshop participants discussed the desirability of international agreement on gene editing technology that sets out legal, regulatory principles for research and clinical use (Evitt et al 2015). It was not clear what model of regulation would be most suitable; different models were discussed and new proposals were put forward such as the licencing of individual laboratories conducting gene-editing research but there was no overall consensus on the model of regulation.

At European level, the 'Oviedo' Convention on Protection of Human Rights and Biomedicine represents a legally binding series of principles and prohibitions, which protects human rights against the misuse of biological and medical advances[6]. However, the UK is not a signatory to the 1997 UNESCO Declaration on the Human Genome or the Council of Europe's 'Oviedo' Convention (Hitchcock, 2016).

The Convention's starting point is that the interests of human beings must come before the interests of science or society and as such, it lays down a series of principles and prohibitions concerning bioethics, medical research, consent, rights to private life and information, organ transplantation and public debate. The treaty allows genetic engineering only for preventive, diagnostic or therapeutic reasons and only where it does not aim to change the genetic make-up of a person's descendants. It prohibits the use of techniques of medically assisted procreation to help choose the sex of a child, except where it would avoid a serious hereditary condition. The Convention also requires protection of embryos where countries allow in-vitro research. In considering European and other international regulation, 'interventions that would change the germ-line genetic identity of human beings' has been offered as a possible agreed frontier for research (Hitchcock, 2016).

4. *www.hfea.gov.uk/1319.html*
5. For example, licence recently granted to Kathy Niakan and her team at the Francis Crick Institute to use CRISPR–Cas9 technology in embryos for early-development research *www.nature.com/news/uk-scientists-gain-licence-to-edit-genes-in-human-embryos-1.19270*
6. *www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164 (Oviedo Convention)*

Therapeutic and public health potential

Participants at the Cambridge workshop spent time considering possible future scenarios where gene editing technology was routinely applied in therapeutic and public health settings; for example, in which embryo screening with CRISPR technologies could lead to a society free of certain traits, disabilities or disorders. Participants felt that given historical developments in this area, including, for example, the association with eugenics, this was regarded as an area that would require very careful consideration regarding the ethics of any future scenarios envisaged. At the same time, participants felt that public discussion of the clinical and public health implications of CRISPR technology applied to the germ-line should now be started.

The therapeutic potential of CRISPR should be distinguished; between the therapeutic potential of *somatic* applications of CRISPR technologies in humans, and the therapeutic potential of *embryo* applications of CRISPR technologies. The latter would currently require a change of law in the UK, which participants felt was unlikely at this stage but could perhaps be worth considering in a proactive way. Somatic applications fall under the remit of 'gene therapy' and some scientists argue that it is there that most of the therapeutic potential of CRISPR lies, for example Lundberg, Ante and Novak (2015).

There are many questions to be addressed when considering any future clinical or public health application of CRISPR – and these questions were raised at the workshop; for example, what treatment for which patients? what are the potential risks? What costs and benefits do gene editing techniques have over existing alternative techniques?

There was support at the workshop for further policy development work to be conducted in relation to these significant questions around gene editing; for example, conducting scenario planning, which could consider the range of societal, ethical, and economic implications of applying gene editing technology in clinical and public health settings, for particular conditions and purposes.

Researchers, policy makers and practitioners represented at the workshop highlighted the importance of discussing future scenarios in an inclusive way, involving scientists, social scientists, ethicists, policy makers, and legal specialists so that rather than being discussed separately, and understanding the potential of gene editing should be 'co-produced' and necessarily include the views, including the social values, of the population who might be affected by new scientific developments.

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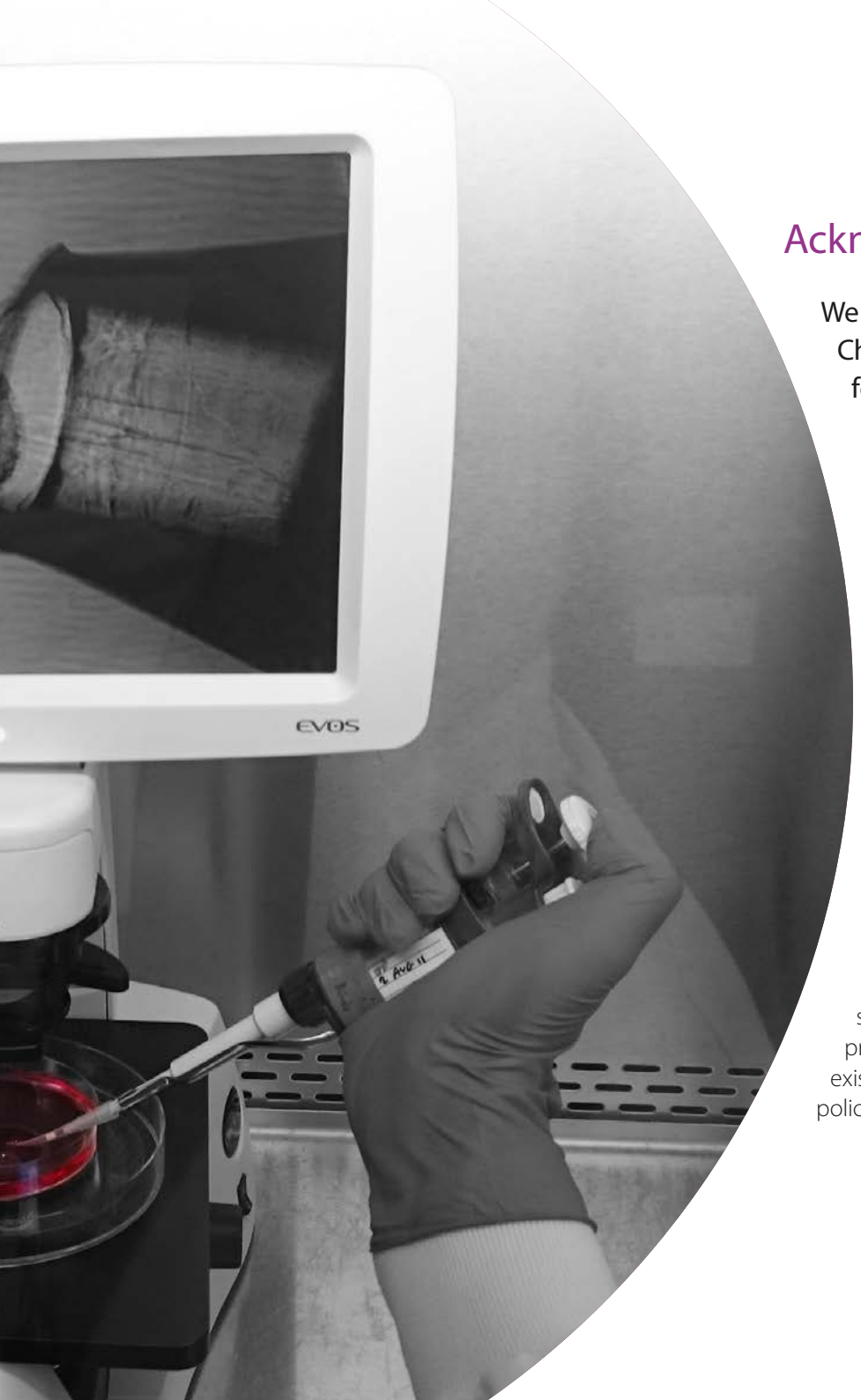

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About the Strategic Research Initiatives

Stem Cells

The Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute is an international centre of excellence for research into stem cell biology and medicine. Scientists in the Institute collaborate to generate new knowledge and understanding of the biology of stem cells and provide the foundation for new medical treatments. The Institute is supported by a strategic funding partnership between the Wellcome Trust and the Medical Research Council.

Public Policy

We aim to support public policy research across Cambridge University, working with colleagues in science, social science, the arts and humanities, to apply new thinking to public policy problems and promote research and analysis into the public policy process. We hope to connect and raise the profile of existing public policy related work across the University and support collaborative research that includes policy development in a range of subject areas.

The Cambridge Public Policy Strategic Research Initiative (SRI) aims to support public policy research across Cambridge University, working with colleagues in science, social science, the arts and humanities, to apply new thinking to public policy problems and promote research and analysis into the public policy process.

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