Brief for GSDR – 2016 Update

CRISPR/Cas9 - gene-editing technology takes off

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Introduction

Recent years have seen rapid progress in the area of biotechnology and the life sciences, driven by factors such as the sharply falling cost of DNA sequencing and the wider application of computational approaches. In particular, it is a very new gene-editing technology called CRISPR[1] that has caused excitement among researchers with its potential applications in biotechnology and medicine. The development of a rapid, reliable, and cost-effective technology for editing the genomes of living plants, animals and humans holds out great promise. However, the new technology – especially the possibility of editing the genome so that changes are passed down, so-called germline editing – raises ethical and safety concerns (Ledford, 2015a). Reports that scientists had used CRISPR to engineer human embryos (albeit ones unable to result in live births) have added urgency to the ethical debate about the use of the technology (Cyranoski & Reardon, 2015). Safety concerns include the risk that the technique may cause unintended and potentially risky edits, or that lack of adequate controls may lead to the escape of edited organisms capable of disrupting ecosystems and harming biodiversity (Ledford, 2015a).

The very rapid adoption of the technology, and its relative simplicity, adds urgency to discussions around how and when it should be used, as well as the need for monitoring and oversight.

Issues for scientific debate

The CRISPR technology involves the application of a defence mechanism developed by bacterial; cells against viral invaders. In very simplified terms, what makes it useful is that it allows researchers to precisely target a location on the DNA of a cell, make a "cut", and then insert a custom-designed DNA sequence. Or, alternatively, "cut" and thus delete the targeted genetic sequence, say a gene encoding an undesirable trait associated with an illness. Unlike previous gene editing technologies, it is easy to use, in that the various elements can be quickly and reliably assembled, without a process of tinkering and trial and error. The process of gene-editing has essentially moved from being a very specialized, custom-designed approach, to a powerful, reliable tool at the disposal of a wide range of scientists.

Like any new technology, there are different views about its application. Among the applications that have been raised is the use of CRISPR to propagate so-called gene drives to eliminate diseases such as malaria, by influencing the capacity of the mosquito vector to transmit the disease, or improving crops varieties (Je Wook Woo et al, 2015). In human medicine, the CRISP could be used for a range of purposes, including improving the function of genes, carrying out screening for new targets for therapeutics, and direct therapeutics, i.e. gene therapy (Charpentier, 2015).

Outside the realm of human medicine, CRISPR is poised to accelerate efforts to use biotechnology to create plants and animals

[1] CRISPR stands for "clustered, regularly inter-spaced palindromic repeats". It often referred to as CRISPR/Cas9, with Cas9 being the enzyme that cleaves (cuts) the DNA strand.

with desirable traits. CRISPR has also made possible the realization of a "gene drives", which works by installing the gene-editing machinery in a living thing so that it will spread specific DNA every time an organism reproduces (Gantz & Bier, 2015). This has it possible, for instance, to engineer in the laboratory mosquitoes that resist malaria and spread this trait to their progeny (James et al, 2015). A recent overview paper by leading authorities in the field states that gene drives have the potential to prevent the spread of disease, improve agriculture by addressing pesticide and herbicide resistance in insects and weeds, and help manage invasive species (Esvelt et al, 2014). The authors caution, however, that "the possibility of unwanted ecological effects and near-certainty of spread across political borders demand careful assessment of each potential application."

It is important to distinguish the kinds of human gene therapy that can be carried out with CRISPR. One involves targeting the therapy to body cells such as bone marrow or blood cells, so-called somatic cells. Importantly, any changes made using this kind of gene therapy cannot be passed on to a person's children. A second form of gene therapy can targets egg and sperm cells, so-called germline cells. Changes made to germline cells – deletions or insertions – would be passed on to future generations (NHI, 2016). While such as therapy could, for instance potentially free future generations in a family from a particular genetic disorder, there is also the risk of long-term side effects that are not yet known. Thus it ought to be considered that the human genome reflects our evolution, and that there may be as yet unknown reasons why favourable, protective genes are not more common (Lander, 2015). Related to this, is the question of pleiotropy – a single gene may have multiple effects. Thus in deleting a gene a gene on grounds of its deleterious effects, one would also need to consider other, protective effects (Lander, 2015).

In addition, from an ethical standpoint, there is the consideration that the since the people who would be affected by germline gene therapy are not yet born, they are not in a position to decide whether to have the treatment (NHI, 2016). Considerations such as this, together with appeal to some of genetic enhancement ("designer babies"), underpin the call to secure through the United Nations a complete ban on germline editing for reproductive purposes (Haker, 2015).

The argument has been made that there is no pressing need for making heritable modifications to the human germline (Lander, 2015). First, diseases caused by a single errant gene are actually rare, and germline gene editing is not applicable to common diseases like cancer or diabetes where the hereditary component is caused by many different genes, in conjunction with environmental factors. Second, in most cases pre-implantation genetic testing can be used during IVF to detect the egg cells carrying the disease-related gene. An opposing view disputes the safety concerns related to "off-target" edits, pointing out that CRISPR is very accurate (Church, 2015) and becoming more so (Ledford, 2015b). It is also argued that genetic diseases where prenatal diagnosis would be of no assistance – e.g. where one parent has two dominant copies of a disease-related gene – are more common than otherwise thought (Church, 2015).

A statement released by the Organizing Committee of the International Summit on Human Genome Editing, held in December 2015, stated that germline editing in a clinical setting should not proceed unless concerns regarding safety and effectiveness have been resolved, and there is broad social consensus about the appropriateness of the use in this

setting (NAS, 2015). The scientists concluded that: "At present, these criteria have not been met for any proposed clinical use: the safety issues have not yet been adequately explored; the cases of most compelling benefit are limited; and many nations have legislative or regulatory bans on germline modification" (NAS, 2015). However, they added the clinical use of germline editing ought to be revisited at regular intervals, recognizing that scientific knowledge advances and as societal views evolved.

The Summit was notable in being organized by the U.S. National Academy of Sciences, the U.K. Royal Academy, and the Chinese Academy of Sciences, thus spanning key domains of activity in the life sciences. In addition, the gathering consciously featured participants outside the natural sciences, in order to address ethical, institutional and regulatory dimensions of the issue.

The statement recognized that basic and clinical research will continue, including with human germline cells, but that where in the "process of research, early human embryos or germline cells undergo gene editing, the modified cells should not be used to establish a pregnancy" (NAS, 2015). The statement is an attempt to establish a consensus among scientists and researchers –modelled on earlier initiatives from the 1970s relating to genetically modified organisms – and thus possesses persuasive, not legal significance. In a 2014 article, of 39 countries surveyed, 29 had what were termed bans on clinical germline editing, but in several cases such "bans" were more akin to non-binding guidelines that legal prohibitions (Araki & Ishii, 2014). At the international level, the 1997 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, adopted under the umbrella of the Council of Europe, provides in Article 13 that: "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants"**.** The Convention, which has been ratified by 29 European countries (Council of Europe, 2016), effectively prohibits germline interventions and limits the use of somatic gene therapy (Adorno, 2005).

Among the applications that have been suggested somatic cells - where changes are not transmitted to following generations – are sickle cell disease, haemophilia, and cystic fibrosis (Porteus, 2015). While risks and benefits need to be weighed, such clinical applications can be evaluated within existing and evolving regulatory frameworks for gene therapy (NAS, 2015). It also needs to be recognized that many of the most important consequences of CRISPR are not the ones grabbing the headlines, but rather fact that the technology makes many experiments easier to carry out, thus facilitating basic research on diseases such as cancer and autism (Regalado, 2015). Another promising area of development is the production of non-human organ donors. Scientists reported that they were able to use CRISPR to modify a record number of genes in a pig embryo, opening the possibility of growing donor organs that would not be rejected by the human immune system (Reardon, 2015).

Issues for policy consideration

For policymakers, it is worth bearing in mind the conclusion expressed at the International Summit on Human Gene Editing that: "The international community should strive to establish norms concerning acceptable uses of human germline editing and to harmonize regulations, in order to discourage unacceptable activities while advancing human health and welfare" (NAS, 2015). In this regard,

Statement recommended that the three national academies that co-hosted the summit take the lead in establishing an international forum to discuss potential clinical uses of gene editing, as well as inform policy-makers, and draw up recommendation and guidelines.

Consideration could be given to what other action may be needed at the international level, whether in regional forums or at the United Nations.

While the application of CRISPR with respect to human germline cells raises the most burning issues, the technology also has implications for policy in relation to the plants and animals. Appropriate containment and control of gene drive technology are an issue. CRISPR may also require reconsideration of regulations governing genetically modified organisms (GMOs). For example, changes can be made to organisms not by inserting foreign DNA, but simply by deleting undesirable genes, as was done experimentally in the case of potatoes to remove genes that repress defences against the mildew. Arguably, such a modified crop would not be transgenic.

Finally, there is a need to raise awareness among policy-makers and the public about the implications, benefits, and potential ethical problems posed by gene-editing technologies.

References

Adorno, Roberto. The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law, Journal of International Biotechnology Law 2005; 2(4):133-143.

Araki, M., and Ishii, T. Reproductive Biology and Endocrinology. 12, 108 (2014)

Charpentier, Emmanuelle. The transformative CRISPR-Cas9 technology: A bacterial mechanism. Presentation, International Summit on Gene Editing, 1-3 December 2015, Washington, D.C.

Church, George. (2015). Perspective: Encourage the innovators. Nature 528 S 7.

Council of Europe: Chart of signatures and ratifications of Treaty 164. Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164/signatures?p_auth=04uN8E2G

Cyranoski, David, and Reardon, Sara. (2015). Embryo editing sparks epic debate. Nature 520, 593-595.

Esvelt, K.M., Smidler, A.L., Catteruccia, F., and Church, G.M. Concerning RNA-guided gene drives for the alteration of wild populations. eLife (2014).

Gantz, Valentino M., and Bier, Ethan. The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. Science 348 6233 442-444 (2015).

Haker, Hillie. Societal Implications of Emerging Technologies. Presentation, International Summit on Gene Editing, 1-3 December 2015, Washington, D.C.

James, Anthony A., Gantz, Valentino, A., Jasinskieneb, Nijole, Tatarenkova, Olga, Fazekas, Aniko Macias, Vanessa M., and Bier, Ethan. Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi. Proceedings of the National Academies of Sciences 112 49 E6736–E6743 (2015).

Je Wook Woo, Jungeun Kim, Soon Il Kwon, Claudia Corvalán, Seung Woo Cho, Hyeran Kim, Sang-Gyu Kim, Sang-Tae Kim, Sunghwa Choe & Jin-Soo Kim. DNA-free genome editing in plants with preassembled CRISPR-Cas9

ribonucleoproteins. Nature Biotechnology 33, 1162–1164 (2015)

Lander, Eric. Genetic Basis of Human Disease and Implications for Germline Editing. Presentation, International Summit on Gene Editing, 1-3 December 2015, Washington, D.C.

Ledford, Heidi. (2015a). CRISPR, the disruptor. A powerful gene-editing technology is the biggest game changer to hit biology since PCR. But with its huge potential come pressing concerns. Nature, News Feature. 3 June 2015. http://www.nature.com/news/crispr-the-disruptor-1.17673

Ledford, Heidi. (2015b). Biologists create more precise molecular scissors for genome editing: Engineered Cas9 enzyme makes fewer mistakes. Nature, News, 1 December 2015. http://www.nature.com/news/biologists-create-more-precise-molecular-scissors-for-genome-editing-1.18932

National Institutes of Health. Handbook: Help me understand genetics (2016) http://ghr.nlm.nih.gov/handbook

Reardon, Sara. Gene-editing record smashed in pigs: Researchers modify more than 60 genes in effort to enable organ transplants into humans. Nature, News, 5 October 2015 http://www.nature.com/news/gene-editing-record-smashed-in-pigs-1.18525

Porteus, Matthew. Therapeutic Genome Editing of Primary Human Somatic Stem Cells (Personalized Definitive and Curative Cell Based Therapies). Presentation, International Summit on Gene Editing, 1-3 December 2015, Washington, D.C.

Regalado, Antonio. Everything You Need to Know About CRISPR Gene Editing's Monster Year. MIT Technology Review, 1 December (2015). http://www.technologyreview.com/news/543941/everything-you-need-to-know-about-crispr-gene-editings-monster-year/