Gene Technology Ethics and Community Consultative Committee

March 2018

Are there new social and ethical issues posed by new gene technologies?

1. CONTEXT

Recent advances in genome-editing technologies are likely to enable genetic changes in ways that are rapid, scalable, accessible and much more cost effective. This is predicted to result in a rapid uptake in many areas of biomedical, biological and conservation research[1] [2]. Anticipated uses of genome editing, including gene drives, in areas of, for example, agricultural productivity, human and veterinary medicine, conservation of natural ecosystems, as well as experimentation by laypersons, have given rise to discussions about whether current ethical and social issues ought to be reappraised[3].

This paper is written as advice from GTECCC about key social and ethical issues and/or questions that are raised by new gene technologies. It does not necessarily reflect the views of the Minister, the Department of Health, the OGTR or the Gene Technology Regulator.

2. ETHICAL PRINCIPLES

Decisions about uses of gene technologies, whether established or new, require researchers and end users to reflect on the ethical consequences of their decisions and actions. Prior to investigating whether an action is scientifically or technically achievable, it behoves researchers to consider whether its practice and outcomes are ethically acceptable.

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[1] Nuffield Council on Bioethics (2016) *Genome Editing: An Ethical Review.* http://nuffieldbioethics.org/project/genome-editing/ethical-review-published-september-2016

[2] Appendix 1 provides a brief description of the new technologies considered in the Gene Technology Regulator's Technical Review of the Gene Technology Regulations, including two genome-editing techniques (oligo-directed mutagenesis and site-directed nuclease techniques) and gene drives.

[3] Mulvihill, J.J., Capps, B., Joly, Y., Lysaght, T. Zwart, H.A.E. and Chadwick, R. (2017) Ethical issues of CRISPR technology and gene editing through the lens of solidarity. *British Medical Bulletin* 122(1): 17-29. https://doi.org/10.1093/bmb/ldx002

The OGTR operates with 10 ethical principles[4] in mind:

1. Acting with integrity
2. Avoiding conflicts of interest
3. Maintenance of scientific records
4. Caring for the environment and sustainability
5. Avoiding harm to humans and other animals
6. Assessing long-term impacts
7. Sharing knowledge and benefits
8. Promoting benevolent purposes
9. Ensuring transparency
10. Considering responsibility beyond national borders

3. APPROACH TO THE DISCUSSION

At its meeting on 30 August 2017, GTECCC recognised that in approaching social and ethical issues relating to genome-editing technologies, the committee needed to be mindful of:

- a cautious approach that ensures risks to human health and the environment are properly assessed and minimised (Ethical Principles (EP) 1, 4-6)
- any potential public good/benefit associated with the technologies including in relation to medical, agricultural and industrial applications (EP 7-10)[5]
- the use of the new technologies in Australia with a desire to ensure that there is (EP 1-3, 10):
    - a commitment to the adoption of best practice in relation to the ethical, legal and social implications of new technologies
    - continued compliance with international agreements, for example the UN Convention on Biological Diversity[6] and World Trade Organisation[7] agreements

4 GTECCC National Framework of Ethical Principles, 2012. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/gtecccethicalprinciples2012-toc

5 Consideration of public good/benefit associated with the technologies is explicitly excluded from decision making under the GT Act. This is discussed in Section 5 (iv).

6 https://www.cbd.int/

7 https://www.wto.org/index.htm

- maintenance of capacity and competitiveness in relation to research, and that research into these techniques is not unnecessarily restricted[8].

4. SOCIAL AND ETHICAL ISSUES POSED BY CURRENT TECHNOLOGIES

Social and ethical issues relating to current technologies are well known and include concerns about:

- risks of unintended effects on the health and safety of people, and on the environment (Section 56, *Gene Technology Act 2000* (the GT Act))
- a lack of consensus on community attitudes towards gene technologies, their uses and equitable access. For example, when considering:
  - genetic selection of embryos on the grounds of health, gender, or enhancement
  - research-animal and production-animal welfare (e.g., unintended phenotypic expression)
  - genetic modification of animals for xenotransplantation
  - the technology being put to harmful uses
  - moral disagreement about issues such as 'playing God'.

5. ADDRESSING SOCIAL AND ETHICAL ISSUES POSED BY NEW TECHNOLOGIES

While advances in genome editing raise many of the same social and ethical concerns as noted above, the prospect of rapid uptake of the technology, and its expanded use, raises new aspects that require careful reconsideration about:

(i) Consumer and researcher awareness

(ii) Are existing regulations keeping pace with new technologies?

(iii) The use of gene drives in environmental management

(iv) Weighing moral 'goods': Is there a need for new decision-making approaches?

[8] Noting that any research must occur in accordance with existing ethical frameworks, animal welfare legislation and in accordance with the requirements of the OGTR.

Access and scalability of genome-editing technology, given the low cost and relatively low technology requirements, gives rise to a more rapid expansion in new areas of genetic research and application. This may risk a gap developing between new research and application and the regulatory framework.

In Australia, some social and ethical issues posed by access and new uptake of the technology are addressed through existing legislation, codes and guidelines pertaining to:

- gene technology (including through the gene technology regulator's consideration of risk to human health, and the environment)
- food standards legislation
- animal health and welfare
- human assisted reproductive technology
- research involving human embryos
- human cloning
- xenotransplantation
- privacy, discrimination and consumer protection and common law actions.

However, some components of these regulatory frameworks were introduced before the emergence of new technological innovations, particularly the improvements to genome-editing technology brought about by CRISPR/Cas9. Social perceptions of safety and risk relating to new technological innovations may also have shifted in the intervening period.

(i) Consumer and researcher awareness

For the above reason, GTECCC believes that it is important that:

- researcher and consumer awareness and understanding of the technology and the ways in which it is currently regulated[9] be built.
    - It is only through such awareness and understanding that consumer confidence in the regulatory scheme can be sustained, and consumers can be engaged in legitimate debate.

[9] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/newtechnologies-htm

(ii) Are existing regulations keeping pace with new technologies?

GTECCC believes that it is important that OGTR, IBCs and other regulatory bodies seek to build public confidence in the regulatory scheme by continuing to be vigilant (through education and monitoring):

- to ensure that researchers and others are aware of, and comply with, the regulatory requirements relating to the use of the technology.
- to propose timely adjustments to the regulatory scheme in line with new developments, thereby minimising the risk of the technology being used inappropriately or outside of regulatory constraints.

(iii) The use of gene drives in environmental management

The application of new gene technologies to wildlife conservation and pest population control through the use of gene drives may create new ethical and social concerns.

Recently, gene drives have enabled a technique with the potential to completely eradicate targeted mosquito species. The rationale for a deliberately targeted extinction is to reduce human suffering and deaths from mosquito-borne diseases[10]. This is seen as a moral 'good'.

However, mosquitos are integral to many ecosystems for nutrient recycling, as prey for bird and bat species, and as pollinators of plants. The removal of mosquito species may upset ecological balances in natural systems and harm the environment[11]. Healthy functioning ecosystems are also seen as a moral 'good'. How, then, ought we to proceed when we are weighing competing moral 'goods'? (see section (iv), below.)

(iv) Weighing moral 'goods': Is there a need for new decision-making approaches?

GTECCC believes there is a need for agreed decision-making approaches when risk is inherent in the need to choose one moral 'good' over another.

[10] Proposals for the deliberate extinction of introduced mammals in New Zealand and amphibians in Australia show that many taxa may be controlled by gene drives.

[11] Pugh, J. (2016). Driven to extinction? The ethics of eradicating mosquitoes with gene-drive technologies. Journal of Medical Ethics doi:10.1136/medethics-2016-103462. http://jme.bmj.com/content/early/2016/04/26/medethics-2016-103462.short

The GT Act excludes consideration of benefits from decision making. Section 56 of the GT Act provides:

> "The Regulator must not issue the licence unless the Regulator is satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in such a way as to protect:
>
> (a) the health and safety of people; and
>
> (b) the environment."

This does not preclude GTECCC and others from discussing these issues as part of the broader conversation and for consideration by policy makers.

In the example of targeted extinction of mosquito species, above, the use of gene drives to improve human health (a moral 'good') must be balanced against the requirement to protect the environment (also a moral 'good'). Can both be achieved? Or does one have precedence?

GTECCC has produced a discussion paper on environmental ethics and gene technology[12]. In weighing one moral 'good' against another, the principal question relates to how environmental values are to be approached. From an ecocentric perspective, environmental ethics opposes the use of gene technologies beyond the human biomedical sphere; ecocentric ethics argues for equitable consideration of protection of the environment in comparison with human-based needs. However, the values underlying the GT Act are generally anthropocentric and the moral 'good' of human health can be argued to outweigh risk to the environment in practical terms.

Is this as it should be with the advent of technologies that are potentially capable of deliberate extinctions of particular species? How might decisions about which species to render extinct be made? Under which statutes can such decisions be authorised? These are multifaceted and challenging questions that should engage key sectors of the community and involve a whole-of-government approach to establish guidance.

12 GTECCC Discussion Paper: Environmental Ethics as it Relates to Gene Technology in Australia (2011). http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/gteccc-envir-ethics-toc

6. SUMMARY

This paper has explored some complex questions which GTECCC recognises do not necessarily have simple answers. GTECCC also recognises that there may be a diversity of public viewpoints on these questions and that any public discourse about those questions will occur within a broader regulatory context.

GTECCC recognises that some of the social and ethical issues posed by new gene technologies are addressed through existing legislation including the GT Act, animal welfare legislation and legislation pertaining to human ethics, particularly relating to germline genome editing and research involving embryos. However, GTECCC notes that some adjustments may be needed to the regulatory scheme to ensure that it accommodates new technological developments.

GTECCC continues to support the exclusion of ethical and other considerations, such as any benefits of the technology, from decisions made by the Regulator, and as required by the current GT Act. However, GTECCC also recognises that in some circumstances these considerations are brought into such sharp relief by new gene technologies (such as the impact of the technology on competing moral 'goods'), that they require further scrutiny. If they did arise, GTECCC considers they may be best dealt with by utilising policy principles made under the existing legislation under clearly defined circumstances when risk is inherent in choosing between competing benefits. GTECCC acknowledges that any such policy principles would need to be consistent with the provisions of the GT Act.

Appendix 1

New technologies considered in the Regulator's Technical Review of the Gene Technology Regulations

The Gene Technology Regulator has initiated a technical review of the Gene Technology Regulations 2001 to provide clarity about whether organisms developed using several new technologies are subject to regulation as genetically modified organisms and ensure that new technologies are regulated in a manner commensurate with the risks they pose. The background information below about the new technologies under consideration in the Technical Review is extracted from OGTR's 2016 Discussion Paper[1]

Oligo-directed mutagenesis

Oligo-directed mutagenesis (ODM) is a process for making small, precise changes to a genomic DNA sequence using a short piece of single stranded synthetic nucleic acid (DNA or RNA) called an oligonucleotide (oligo) as a template. The oligo is designed so that the majority of the sequence is identical to the target gene sequence. However, the middle of the oligo contains the desired sequence change. Oligos typically range from around 20 nucleotides to 100 nucleotides in length, and the longer the oligo, the more changes it can contain.

For organisms with large genomes, e.g. plants, the oligo is introduced into a cell and binds to the matching sequence in the target gene[2]. The cell's proof-reading enzymes then recognise that the two sequences are not a perfect match and changes one of them so that they match. If the oligo is changed to match the original strand then the cell's DNA is not changed. However, if the cell's DNA is changed to match the oligo then the cell's DNA will contain the new sequence.

For plants, ODM is carried out on cells in tissue culture, and whole plants are grown from these cells. For organisms with small genomes, such as viruses and bacteriophages, the reaction can take place in a tube with a mixture of oligos, nucleotides and enzymes rather than in a cell.

The small change(s) made via ODM can switch off a gene, change how much of the gene product is made, or change the function of a protein by changing the amino acid sequence produced from a gene.

Site-directed nuclease techniques

Site-directed nucleases (SDNs) such as zinc finger nucleases, TALENs (transcriptional activator-like effector nucleases), CRISPR/Cas9 (clustered regularly-interspaced short palindromic repeats/CRISPR-associated protein 9) and meganucleases are becoming widely used in biological research. These are specially designed proteins, or protein/nucleic acid combinations, that are capable of cutting DNA at a specific nucleotide sequence.

[1] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/reviewdiscussionpaper-htm

[2] DNA is most stable as a double stranded molecule and therefore single strands of DNA will naturally seek out and bind to the best match available.

Once the DNA has been cut, there are two main pathways by which the cut can be repaired, both of which involve natural repair mechanisms:

1. Non-homologous end-joining, which joins the two ends back together. This can be an error prone process with the potential for nucleotides to be added, lost or changed at the cut site. If the cut is repaired correctly, then there is no sequence change and the sequence may be cut again by the SDN. However, if a mistake is made during non-homologous end-joining, a small random sequence change may alter how the gene functions. Additionally, repair of two nearby cuts can delete the sequence between them, creating substantial deletions. This technique is known as SDN-1.

2. Homology-directed repair can be used to deliver predetermined sequence changes. The cellular process for homology-directed repair is very similar to ODM, where an oligo acts as a template to direct modifications. Without human intervention, homology-directed repair can occur using sequences available naturally within the cell. The process can be directed by providing a piece of DNA with ends matching the sequence surrounding the DNA cut site to achieve a predetermined sequence change. This piece of DNA can be an oligo to guide a specific small modification of one or several nucleotides (SDN-2) or a large DNA cassette which includes new sequences such as additional genes, regulatory sequences or selectable markers (SDN-3).

One of the earliest uses of the SDN-1/2/3 terminology was by Lusser *et al* in their 2011 report for the European Commission's Joint Research Centre, New Plant Breeding Techniques; state-of-the-art and prospects for commercial development[3]. Lusser *et al.* described the outcomes of modification using zinc finger nucleases as ZFN-1, ZFN-2 and ZFN-3.

SDN techniques can be used on animal embryos so that germline tissues carry the resulting sequence changes and offspring of that animal will uniformly carry the sequence change. SDN techniques can be used on plant cells in tissue culture, from which whole plants can be grown.

Successive rounds of modification using SDNs can be used to accumulate sequence changes to a genome. Alternatively, multiple sequences can be targeted at once by using a variety of SDNs (with or without different repair templates) at the same time.

Gene drives

Gene drives are genetic elements that are favoured for inheritance. This results in gene drives spreading through populations at a greater rate than genes with standard Mendelian inheritance. Genetically modified gene drives can only spread from sexually reproducing parents to their offspring, and not by transmission between organisms. Research into gene drives began over 50 years ago after the discovery of natural gene drives.

Internationally, there is rapidly growing research interest in using site-directed nucleases to create gene drives for a variety of purposes. Potential applications include:

- Reducing or eliminating populations of invasive animals, for example exotic rodents, to protect natural environments
- Reducing transmission of diseases from insects to humans, for example malaria from mosquitoes, by modifying the ability of insects to carry the disease or by reducing insect populations
- Controlling weeds of natural or agricultural environment

[3] http://ftp.jrc.es/EURdoc/JRC63971.pdf