ROYAL SOCIETY TE APĀRANGI

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REFLECTIONS FROM THE PANEL CO-CHAIRS

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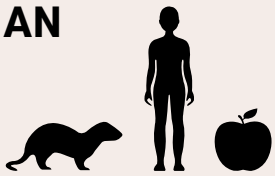

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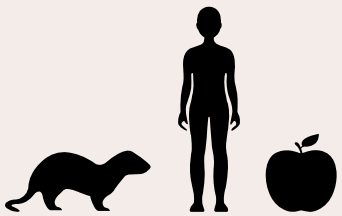
Nā te iahia kia titiro, ā,
ka kite ai tātou te mutunga.

You must understand the beginning
if you wish to see the end.



GENE EDITING: REFLECTIONS FROM THE PANEL CO-CHAIRS

BARRY SCOTT AND DAVID PENMAN

Random mutagenesis and selection in nature has underpinned evolution and diversity of all life and the resulting domestication of plants and animals. In modern times, advances in science and technology have allowed humankind to augment this natural process in increasingly sophisticated ways through selective breeding programmes and the use of techniques such as irradiation and chemical mutagenesis to enhance the rate of gene mutation.

The development of a number of DNA technologies, and our ability to sequence entire genomes, has opened the door to modifying specific genes to generate new traits and characteristics. The publication by Doudna, Charpentier and colleagues in 2012, demonstrating how a bacterial system for adaptive immunity called CRISPR-Cas9 could be engineered to precisely edit genomes, has set in motion a revolution in biology. It has been quite astounding how quickly laboratories around the world have adopted this new tool for applications across biology, from modifying plants, to altering insect development and potential treatment of some human diseases. The relative ease with which genomes can now be sequenced and edited has generated considerable excitement within the scientific community. However, it has also raised significant concerns about the social, legal and ethical issues raised by the use of the technology, none more so than the potential to edit genes in human embryos.

In response to these advances, many reports have been released and summits organised by academies and research organisations around the world to explain the technology, the context in which it is being used, the issues that arise for society, and the impact of these scientific advances on current regulatory frameworks. Prominent among these was the *"International Summit on Human Gene Editing"* organised by the US National Academies of Sciences and Medicine, the Royal Society (London) and the Chinese Academy of Sciences in late 2015 to discuss guidelines for the use of gene editing in humans.

These international reviews and summits have been immensely helpful in informing the public, researchers and regulatory bodies around the world, including New Zealand, and providing a framework for engaging internationally. However, New Zealand needs to have its own perspective given our unique cultural heritage and environment, the special challenges we face in maintaining our biodiversity and a viable and productive primary industry, and our unique regulatory environment. Furthermore, there has been no review of gene technologies in New Zealand since the Royal Commission on Genetic Modification held in 2001 and the subsequent amendments to the Hazardous Substances and New Organisms Act (1996). The field of genome science has advanced dramatically since then, especially the ability to sequence organism genomes and to manipulate those genomes in a very precise way.

ROYAL SOCIETY TE APĀRANGI GENE EDITING PANEL AND MĀORI REFERENCE GROUP

Royal Society Te Apārangi, as an independent science body, has a function under its Act to provide expert advice on important public issues to the Government and the community. In 2016, the Society initiated a programme of work to explore the implications of gene editing technology for New Zealand, motivated by the importance of this rapidly advancing science, the need to raise awareness of its potential applications, and to support informed discussion and debate about its implications for New Zealanders.

The first output of this programme was a short document entitled *"Gene editing. Evidence update"*, released in November 2016. This provided background on gene modification technologies and their evolution for the media, educators, policy makers and the public. Royal Society Te Apārangi then convened a multidisciplinary panel of experts, supported by a Māori reference group, to consider the social, cultural, legal and economic implications of gene-editing technologies for New Zealand. This paper outlines the approach of the panel and makes some concluding observations.

The panel was not asked to come to a view about the merits or otherwise of any particular application of gene editing. Rather, its role has been to provide information and resources that will allow others to have well informed discussions and debates. Indeed, one of the panel's main observations is that there is an urgent need for wide discussion and debate about gene editing within and across all New Zealand communities, as global research and development in applications of gene editing is continuing apace. Some countries are reviewing, or have already reviewed, their regulations in response to these developments.

The panel chose to consider the implications of the technology in parallel work streams using a range of scenarios in three areas: healthcare, environmental pest management and primary industries. The scenarios are illustrative – they are not panel recommendations for priorities for New Zealand application. They are presented in a stepped approach of increasing potential risk averseness and near and long-term benefits, to challenge and promote public engagement, and test the current regulatory regime. Each set of scenarios aimed to consider potential ethical, cultural and legal issues alongside the opportunities and potential risks and benefits. This approach proved to be a productive one for initiating a conversation with the New Zealand public.

Sitting behind the scenarios are technical papers that provide a more comprehensive overview of the research evidence base and implications for each of the three areas. These are fully referenced for readers to access the primary literature relevant to each area considered, and have been peer reviewed nationally and internationally.

New territory for Royal Society Te Apārangi was to enlist the support of a Māori Reference Group to assist the panel in capturing Māori views and approaches to assessing this technology. While the papers reflect particular ways in which some Māori would assess their use of gene editing technology, the panel observed wide diversity in views across both Māori and non-Māori communities.

PUBLIC FEEDBACK

Other innovations for Royal Society Te Apārangi in this process were the publication of material in a series of discrete work pieces over time rather than one large report, and initially publishing the scenarios in draft form to allow feedback. This enabled the panel to undertake a series of engagement workshops around the country to seek feedback and identify additional information that could be covered in the final technical papers. Senior school students attended some of these sessions and the panel invited informal comment via the Society's website. Two hui were specifically aimed at Māori communities.

This feedback process targeted testing the information in the documents for completeness and usefulness – undertaking a comprehensive national consultation was beyond the resources and mandate of Royal Society Te Apārangi and the panel. A number of themes were apparent from these interactions:

- For all three themes, there were views for and against the use of gene editing.
- In healthcare, there was an appetite to consider certain therapeutic gene-editing applications as long as it was safe enough to rule out negative side effects, and that it would enhance human health.
- In pest control, there was some appetite to consider gene drives for pest management if the benefits outweighed the risks. However, there were concerns over unintended consequences of removing species and around the risks of gene-edited pests finding their way back to their native countries.
- In the primary industries, comments on the benefits of using gene-editing technology included that it could provide a useful tool for supporting competitive advantage, and for protecting New Zealand's flora and fauna. There were concerns about unintended consequences, a need for better understanding of the relevant genetics, and that use of gene-editing technology would compromise the New Zealand brand and any "GM free" competitive advantage.
- Across all scenarios, feedback from Māori participants highlighted the importance of whakapapa and mauri, involving tangata whenua around indigenous species, protection of data, and intellectual property implications of gene editing taonga species.
- Royal Society Te Apārangi was criticised on occasions for appearing to take an advocacy position on gene editing through its publication of scenarios.
- The Society also received considerable positive feedback on undertaking the work and its use of scenarios. The society was often encouraged to lead a much wider engagement with communities given its independence and scientific standing.
- The panel has considered all the comments and incorporated additional information where possible into the final papers published.

CONCLUDING COMMENTS

The following are some closing thoughts on gene editing having explored a range of potential applications and their implications, and heard from a diverse range of interested communities.

Healthcare

Although the genetic changes proposed to achieve the outcomes in the scenarios are relatively 'simple' single-gene edits, gene editing potentially allows for multiple edits and much more complex scenarios than proposed in this discussion paper. However, the panel did not develop such scenarios, as our understanding of how multiple genes interact to determine a given trait is still rather poorly understood. Furthermore, the single gene editing scenarios developed proved to be a satisfactory approach to identifying the medical, legal and ethical considerations that need to be taken into account for implementation of gene editing approaches in healthcare.

While germline editing of embryos for research purposes is permitted in some countries, most, including New Zealand, have a ban on clinical uses of germline editing – that is changing heritable DNA. Despite these international guidelines, during the course of our work the reported editing of embryos to create two HIV-resistant babies by biophysicist He Jiankui in China this year has brought this issue into very sharp international focus. Furthermore, the fact that scientists aware of the work did not speak up highlights the need for a global framework under which human gene editing is carried out. Meanwhile, there has been a call for a global moratorium on clinical germline editing.

Pest control

This work piece provided an overview of the current state of gene drive technologies as potential solutions to the pest problems in New Zealand. Gene drives are a process that occurs naturally in some organisms, but which is greatly facilitated by deploying CRISPR-Cas.

Gene drives are a potentially useful technology for the eradication of pests given the need to widen the range of approaches if we are to achieve the goals of Predator Free 2050. However, they will not be a 'silver bullet' for pest control in New Zealand; controlling and containing pests in complex ecosystems is very challenging and will require deployment of a combination of technologies and management systems.

A number of risks and barriers, both biological and social, need to be addressed before such systems can be deployed in New Zealand. There is also growing international concern, such as expressed through the Convention on Biological Diversity and by the release of a report by the Sustainability Council in 2018 of potential negative consequences demanding that research must embrace public acceptance, cultural concerns, and legal issues before gene drives for pest control can be implemented. Furthermore, our relatively poor understanding of the reproductive biology and genetic systems of major New Zealand insect and mammalian pests, including wasps, possums, stoats and rats, precludes any rapid deployment of this technology.

Even with greater knowledge and technical ability to modify the genomes of these pest organisms, it was clear from the conversations held around these scenarios that there is a high level of risk averseness to using gene drives in the field. The challenge for New Zealand, given the significant potential for extinction of native species, is how we can achieve environmentally and socially acceptable solutions. The lack of scientific knowledge should not deter a focus on ongoing investment in long-term research in containment, to allow better understanding of the biology of New Zealand's pest organisms. This is a prerequisite for scientific breakthroughs needed to support development of acceptable solutions.

Primary industries

This paper was anticipated to be the most contentious given the history of the GM debate around crops and foods in New Zealand in the late nineties/early 2000s. The primary industries are a major part of New Zealand's economy and there are inevitable sensitivities to the impact of gene editing on offshore market perceptions in parts of the export sector. However, there is little publicly available independent evidence to inform conclusions about niche market impacts and their scope and complexity was beyond the remit and resources of the panel. Suffice to note that there are some strong views, as there have been in the past.

Although the single-gene edit scenarios proved useful for identifying issues around gene editing in the primary industries, most agriculturally important traits are determined by multiple genes rather than single genes. While gene-editing technology is sufficiently well developed to enable multiple gene edits, identifying which alleles (genotypes) to select and how they interact with one another to contribute to a particular trait (phenotype) remains a major technical challenge.

Legal and regulatory framework

Part of the panel's work was to assess the scenarios in the context of the New Zealand legal and regulatory framework. This resulted in a further paper on the regulatory system, which identifies a number of potential issues with the current framework, not the least of which is that it is becoming increasingly out of date given the advances in gene-editing technology.

The Panel would like to see a legal and regulatory system that is more future-focused and 'fit-for-purpose' by being easier to navigate, having clear and consistent definitions, and providing a better basis for assessing the risks and opportunities of particular applications of gene editing rather than focusing on the gene editing process itself. There is also an urgent need for a wide and well-informed discussion across New Zealand's diverse communities about preferences for the application of gene editing, in order to inform regulatory change.

The future

While publication of this panel's work has initiated the conversation on gene editing and identified many of the issues that arise, it is important that those conversations continue, as there are very significant social, legal and ethical issues associated with this technology. In particular, there needs to be meaningful engagement with Maori communities on the risks and potential benefits of these new DNA technologies, consistent with the principles of partnership, participation and protection enshrined in te Tiriti o Waitangi.

Many future valuable targets of gene editing will be traits, including common disease susceptibilities, which are influenced by many genes. Indeed, for some traits, thousands of independent genes have been implicated as having an impact. As single genes can also have effects on multiple different traits, there will be a fundamental need to deal with and understand the trade-offs inherent in modifying the genes for polygenic traits, with likely impacts on many other non-target traits, regardless of the precision and accuracy of the gene editing technology itself.

Genomic data is being increasingly used to study the genetic basis for human social and behavioural traits, including measures related to intelligence and educational attainment. In a future world where gene editing is routine, the potential risks in the misuse of the technology are high, and the ethical and moral challenges are manifold. Although these risks are currently remote, they will become more practically relevant as our tools for genomic manipulation become routine and precise, and cheaper to use.

Having said that, humankind has a history of successful adoption of new technologies that have the potential to enhance our health and sustain our wellbeing. Heart transplants and the introduction of IVF are two examples that were highly controversial when first proposed and which are now routinely available. Plant and animal breeding through genetic selection has made a major contribution to human wellbeing, and such innovations are never completely risk free. However, risks can be minimised and managed with well-designed, thorough, safe and transparent research programmes supported by the public. In the case of gene editing, there still needs to be a huge advance in the science and understanding of genetic architecture and the interconnectedness of different genes, if we are to realise its full potential.

Finally, our sincere thanks to the members of the panel, the Māori reference Group, our legal advisers and all those that helped us develop and articulate the scenarios and their implications. Our hope is that the panel's work will be widely distributed and provide a useful resource for informing others' views on the implications and acceptable applications of gene editing technologies.

Ngā mihi maioha.