THE ROYAL SOCIETY

Submission to the Nuffield Council on Bioethics on Genome Editing

Summary

1. Genome editing is a valuable technique for biological research to improve our understanding of biological processes and genetic conditions, and possibly it will be used in the future in the treatment and prevention of disease.

2. The speed, ease of use and accuracy of the new gene editing techniques may raise new issues as it becomes feasible to use them for a wider range of applications.

3. Public views should inform how gene editing techniques are used in practice, and how these applications are regulated to earn and maintain public trust.

4. The ethical questions raised by genome editing should be considered on a case-by-case basis, depending on the genes being modified and the context in which they are applied.

Introduction

The Royal Society is the national academy of science for the UK. It is a self-governing Fellowship of many of the world's most distinguished scientists working across a broad range of disciplines in academia, industry, charities and the public sector. The Society draws on the expertise of the Fellowship to provide independent and authoritative scientific advice to UK, European and international decision makers.

This response draws on recent work of the Royal Society including the International Gene Editing Summit, that was co-hosted by the Royal Society with the Chinese Academy of Sciences and U.S. National Academy of Sciences and the InterAcademy Partnership report on 'Assessing the implications of science and technology development for the Biological and Toxin Weapons Convention'.

Perspectives on genome modification

Genome editing techniques are valuable research tools that are already widely used. CRISPR/Cas9 is a significant development in biological research and is likely to have a wide-ranging use, like previous techniques which have become ubiquitous research tools e.g. restriction enzymes, reverse transcriptase and PCR. It is quicker, cheaper and easier to use than previous techniques, allowing a wider range of researchers to employ them in their work and making them a standard technique in academic and bioindustry research worldwide.

Genetic engineering techniques are focussed on altering the genetic sequence in single genes or groups of genes in order to understand how they operate or change how they work. These techniques can be applied so that they affect the whole organism but may also be applied to parts of the organism. They can introduce gene variations that may not be present in the population and can be used to transfer genes between species. They can also be applied to "repair" damaged genes.

Newer genetic engineering techniques, like CRISPR/Cas9, are more precisely targeted than previous techniques. This increased precision decreases the likelihood of changes being introduced in locations not intended that have similar DNA sequences ('off-targets'). Although it will depend on the precise sequences to be targeted, the smaller the genome the less likely are near-identical sequences, so off-targets are of less concern in bacteria than in humans and other species, especially where there have been genome duplication events during their evolution. However computational design can minimise the risk of off-targets in organisms, including human, where the full genome sequence is known. The time of exposure to active genome editing components will also affect the number of off-targets. This influences the appropriateness of the different methodologies for different purposes. Greater understanding of the precise mechanism of action of the genome editing components on DNA are leading to modifications of, for example, both the CAS9 enzyme and guide RNAs that significantly reduce the likelihood of having off-target events.

Recent developments have also led to modifications in the Cas9 enzymes so that they do not cut the DNA and can be used to label genes (through the addition of green fluorescent protein) and to switch genes on or off, modifying when or in which cell type the gene functions without altering the genetic sequence.

Genome modification creates the possibility that the resulting changes will be inherited. The possibility of changes being passed on to future generations is, however, not unique to the latest gene editing techniques. For example, selective breeding also modifies the genome so that only certain traits are passed on to future generations. Genome editing techniques do not raise new and unique moral considerations but are a continuation of those raised by all techniques which modify the genome, including deliberate (or accidental) exposure to ionising radiation or chemical mutagens. However, these modifications can now be generated more quickly, cheaply and easily than before, as well as in ways that are considerably more efficient and accurate, and with potentially fewer damaging side-effects.

The difference between genetic engineering, including genome editing techniques, and selective breeding is that selective breeding generally (and certainly as practiced over millennia) selects for the characteristics of an organism exhibited in a particular environment, the phenotype, and looks to optimise them (e.g. the yield of crops). The phenotype is often contributed to by more than one gene, sometimes hundreds of genes, or it can also be the result of epigenetic differences. The specific contribution of individual genes or the epigenome to the phenotype may be unknown. By contrast, in genetic engineering specific genes are modified with the objective of obtaining organisms with a particular phenotype. Unlike the process of selective breeding in which only genes in the initial organisms can be exchanged, in genetic engineering novel genes can be introduced, even from another species, to obtain the required phenotype.

Currently genome editing techniques are being used extensively in research using loss of function experiments where changes are introduced to genes which prevent them functioning so the role of the gene can be studied. The direction of travel is to make specific changes to the genetic sequence to see how these alter the function, rather than delete the gene function completely. This approach also allows the 'repair' of broken genes or the creation of new variants of the genes. As the understanding of how genes contribute to phenotypes grows, the use of genome editing techniques to influence phenotypes is likely to increase. However this use is currently limited to those areas where the genetic basis of phenotypes is well characterised.

All scientists, including those using genome editing techniques, should be open to others reviewing and challenging their data, ideas and hypotheses and applications. The Royal Society supports a responsible approach to research and innovation and considers that public views and the latest science should inform how research is conducted and regulated to ensure that the public can have confidence in the research and its applications.

Scientists should work with regulators, such as the Health and Safety Executive and Human Fertilisation and Embryology Authority, and policymakers to ensure that the laws and legal frameworks governing their work are informed by the latest science, as well as public opinion, to ensure that the public can have trust in the regulatory process and that the process does not inhibit research and applications that have public support.

Gene drives

Gene drive techniques allow the inheritance of specific genes in successive generations ('drive') to alter entire populations of organisms. Applications of gene drives include attempts to eradicate insects (e.g. mosquitoes in the control of malaria), the control of invasive species in agriculture and ecological restoration of threatened habitats. Gene drives were considered as part of a recent report on the Biological and Toxin Weapons Convention, led by the Royal Society,[1] which noted that it would be possible for a gene drive to be created that could "alter the traits of wild populations and ecosystems without regard for national borders". Gene drives are not specific to genome editing but the power of genome editing makes it more likely that relevant applications will emerge. As noted in the report, there are only a few research groups currently working on CRISPR-gene drives and representatives from the groups and related areas are advocating for transparency for anyone doing work with gene drives. This includes what experiments are being conducted and what safeguards are being employed to prevent accidental release and for these details to be publicly disclosed. Potential uses for gene-drives currently being considered are in the areas of public health, sustainable agriculture and ecological conservation.

As noted in a recent House of Lords Science and Technology Committee report on Genetically Modified Insects, there is promise in this area but progress from the research to application can only occur once the regulatory and governance issue of the use genetically modified insect technology is resolved.

Methods to biologically contain organisms modified by gene drive techniques and/or restrict their spread, as well as to make the gene drive process conditional, and even reversible, are all being explored.

Genome editing in plants

Uses of genetic editing in plants

Genetic techniques are used widely as a routine tool in research and they have greatly facilitated major advances in plant biology over the last 25 years. They are particularly important in the ongoing task of assigning function to each of the thousands of genes that have been identified in each species and in elucidating the cellular mechanisms in plant biology. The application of GM techniques in crop plants, however, has been controversial in some parts of the world.

[1] IAP (2015) *Assessing the implications of science and technology development for the Biological and Toxin Weapons Convention*

The drive in using these techniques has been to enhance characteristics that are considered useful or to provide novel functions. For example, increasing yield in crops, new colours of ornamental plants, growth rate of trees in forestry and turning plants into biological production factories e.g. vaccines produced in tobacco plants.[2] The use of newer gene editing techniques will continue these trends.

As highlighted in the Royal Society report, *Reaping the benefits*, the pressures of soil degradation, water shortages and climate change are going to put pressure on crop plants and production will need to be sustainably intensified. The application of genetic methods has the potential to refine existing crops and provide incremental improvements e.g. disease, pest or drought resistance, or increased nutritional properties for humans or animals and drought resistance.

Genetic techniques could also be used to introduce radical and highly significant improvements to crops for example: increasing photosynthetic efficiency, reducing the need for nitrogen or other fertilisers and changing annual plants to perennials. The potential benefits and risks will vary depending on the nature of the gene being manipulated or transferred and the plant being modified.

As noted in the report, in trying to address problems as complex as sustainable intensification, no technology should be ruled out and different strategies may need to be employed in different regions and circumstances. The 2014 *Public Attitudes to Science*[3] survey found that eight-in-ten people feel that no food producing techniques and technologies that might raise world food production should be rejected out of hand. Genetic technologies are not a 'silver bullet' and they will need to be combined with other expertise, for example agronomy to support crop production.

Influence of the GM debate

Genetically modified (GM) crops have been the subject of at least 15 years of polarised debates. In the UK there is considerable public concern over the use of GM food and feed, particularly around the safety of these products in the food chain. The 2014 *Public Attitudes to Science*[4] survey found that most people do not feel informed about genetically modified (GM) crops and a sizable minority (28%) say the risks outweigh the benefits for GM crops.

Currently in the UK GM crops are used only in research labs and a few field trials. Recent changes to EU law mean that individual member states can now opt to prevent cultivation of EU-approved GM crops within their countries or to be excluded from the approval applications for future products. Within the UK, Scotland, Northern Ireland and Wales have indicated that they will exercise this opt-out.

The newer genetic editing techniques, such as TALENS, ZFN[5] and most recently CRISPR, are often referred to as 'new breeding techniques' when discussed in reference to their use in plants. Statements on 'new breeding techniques' have been released by the UK's Biotechnology and Biological Sciences Research Council (BBSRC) and the European Academies Science Advisory Council (EASAC). Both statements highlight the importance of the way these technologies are regulated in the EU for future

[2] http://www.reuters.com/article/us-flu-vaccine-analysis-idUSKCN0HQ2YO20141001

[3] Ipsos MORI 2014 *Public attitudes to science*

[4] Ipsos MORI 2014 *Public attitudes to science*

[5] Transcription activator-like effector nucleases (TALENs); clustered regularly interspaced short palindromic repeat (CRISPR); Zinc-finger nucleases (ZFNs)

development and importantly call for trait-based approaches to regulation. The European Commission is currently considering whether or not 'new breeding techniques' fall under current regulation for genetically modified organisms, and their report is expected in March 2016.

Relative to existing technologies, gene editing techniques in plants do not raise any new issues in relation to ecological stability, biological diversity, technology transfer and equitable sharing of benefits.

The benefits and risks of any genome-edited plant should be considered individually. Genome editing techniques do not themselves create risks or benefits, these arise depending on what genetic change they are used to make.

One way in which gene editing techniques differ from previous techniques is that they may not leave any readily-detectable indication that genetic modification has occurred. If just one or a few base pairs have been altered, the change could have arisen by either induced mutation (with a chemical mutagen or ionising radiation) or spontaneous mutation. So, it would be difficult to identify plants that had been genome-edited were they not reported as such, making regulation difficult if they were to be considered genetically modified organisms under EU regulations.

Genome editing in animals

As with plants, the drive in using genome editing techniques is to understand the function of genes, enhance characteristics that are considered useful or to provide novel functions. At present this is mostly the subject of research rather than in commercial applications, although there are notable exceptions in genetically modified pets.

The Royal Society considers that all research should be carried out with a high regard for animal welfare and only proceed where the research offers considerable benefits, where there are no alternatives and while upholding a commitment to the 3Rs.[6]

In our 1998 report, *The use of genetically modified animals*, the following uses of genetically modified animals were discussed:

- In research e.g. to create animal models of disease
- GM animals that produce substances of benefit to humans in their milk or tissues
- agricultural GM animals to increase desirable traits
- GM insects that are incapable of transmitting disease
- GM fish for research into developmental biology and enhancing growth for food production
- Xenotransplantation to make animal organs more suitable for transplantation into humans

Research

Genetically modified animals are used significantly in research to understand gene function and create models of disease. According to 2014 statistics from the Home Office, the numbers of procedures involving animals has decreased but there has been an increase in the number of these procedures involving genetically modified animals, 60% of which are mice.[7]

[6] https://royalsociety.org/topics-policy/publications/2015/animals-in-research/

[7] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/469508/spanimals14.pdf

The use of CRISPR/Cas9 gene editing, which can be achieved directly through modification of the zygotic genome, could reduce the number of animals used in research, since the resulting modified embryos and live young can be analysed in the first generation without the need to transmit mutant alleles to create homozygous mutant embryos and live young.

For example, a viral delivery platform has been used to introduce CRISPR/Cas9 into the mouse lung to create an improved mouse model of lung cancer and mouse lines with endogenous expression of Cas9 have been created so that only the guide RNA needs to be introduced to create and investigate gain-of or loss-of function mutations in lung cancer.

Bio-farming

Genetically modified animals have also been used in bio-farming, for example goats which are able to produce spider silk proteins in their milk.[8] Researchers have also used gene editing in livestock animals to produce cows without horns.[9] Animals can also be engineered to produce humanised antibodies for therapeutic purposes, for example camel antibodies as research tools.

Livestock

There is high genetic variability in livestock populations, unlike monocultures often used in crop agriculture. Livestock animals have traditionally been bred based on phenotypic differences and multiple traits and this practice is unlikely to change until the understanding of which genetic changes produce desired phenotypes and traits improves. Regulatory considerations will also be important if by using gene editing techniques farmers face a significant regulatory burden, or if regulation prevents gene edited animals from being farmed or used for consumption.

Only one genetically modified animal has been approved for human consumption worldwide and that is AquAdvantage® salmon from AquaBounty[10] which was approved by the FDA in the USA in November 2015.[11] The genetic alterations turn on growth promoters so the salmon grows to market size faster. The initial application was almost 20 years ago, so it has taken considerable time for the FDA to review and approve this application. Although GM food is not required to be labelled in the US the FDA have required that AquAdvantage salmon should be labelled as genetically engineered.

Current efforts are largely focused on increasing resistance to disease. Genome editing techniques have greatly accelerated this work, for example in experiments designed to develop resistance to influenza in poultry.

Pets

Chinese researchers have also used gene editing techniques to modify pets, including beagles with bigger muscles[12] and 'micropigs'.[13] Beyond aesthetic uses, it is envisaged by some researchers that

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[8] http://www.bbc.co.uk/news/science-environment-16554357

[9] http://discover.umn.edu/news/food-agriculture/scientists-use-gene-editing-dehorn-dairy-cattle

[10] https://aquabounty.com/

[11] http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm472487.htm

[12] http://www.technologyreview.com/news/542616/first-gene-edited-dogs-reported-in-china/

[13] http://www.nature.com/news/gene-edited-micropigs-to-be-sold-as-pets-at-chinese-institute-1.18448?WT.mc_id=SFB_NNEWS_1508_RHBoxHP

gene editing techniques could lead to pets with longer life spans or which are smarter.[14] One clearly beneficial use might be to edit out disease-associated alleles that are very frequent in some breeds of dogs and cats in a way that does not alter the desired characteristics of such breeds.

Xenotransplantation

Genome editing techniques have also been used to make animal organs more suitable for transplantation into humans.[15]

Genome editing in microorganisms

The use of genetic techniques in microorganisms is now well established and there are an increasing number of bacteria in which it is possible to use complex techniques, such as editing multiple genes at once.

Gene editing techniques in bacteria are being used to modify bacterial strains for a range of uses e.g. biofuel production, high-value chemicals and pharmaceuticals production, biocatalysis/green chemistry and food processing.

Genome editing is continuous with synthetic biology, the accepted definition of which includes redesign of living organisms for a specified application or purpose. Genome editing introduces a new tool to modify or 'design' the genetic sequence, and either explore and test a large number of possible designs in parallel or use the single design-build-test cycle preferred by many synthetic biologists.

Biomedical and human applications

In using genome editing techniques in humans there is a sharp distinction made between those changes that happen to the cells of the body (somatic cells) and reproductive cells (germ line cells) through which changes would be passed on to the next generation. Calls for international moratoria on the use of gene editing in humans have focussed on excluding the clinical use of techniques that introduce heritable changes in germ line cells.

The statement from the Hinxton Group, the joint statement from Wellcome Trust, MRC, BBSRC, AMS and AMRC and the statement from the International Gene Editing Summit, all highlight the differences between somatic and germ line changes and between research and clinical application, all support research and clinical application in somatic cells. They also support research on germ line cells using gene editing techniques, with clinical applications in germ line cells considered not appropriate until the techniques are shown to be safe and there has been public engagement to inform how these applications might be used, if at all. With the Human Fertilisation and Embryology Authority (HFEA), the UK has the advantage of having a robust regulatory system that will prevent use of gene editing methods to make heritable changes unless there is both a public and political will to change the existing laws.

CRISPR/Cas9 gene editing technique is currently being used to study early stages of human development, including early human germ cells and somatic cells generated from human pluripotent embryonic stem cells. It may be possible eventually to obtain more advanced germ line cells and

[14] http://www.technologyreview.com/news/542616/first-gene-edited-dogs-reported-in-china/

[15] http://www.nature.com/news/new-life-for-pig-to-human-transplants-1.18768

possible human gametes in culture. The use of patient-derived induced pluripotent stem cells (iPSCs) makes it possible to modify genes by CRISPR/Cas9 to examine the consequences of mutations that affect cell fates and cause human diseases.

Currently, the main driver of the use of genetic editing techniques in humans is to treat disease using somatic therapies, as in the treatment of leukemia in baby Layla.[16] To address most diseases caused by a single gene mutation there are alternative methods, such as preimplantation diagnosis and embryo selection, which require elective termination of embryos carrying the genetic mutation being screened for. Some of the recent developments in the use of gene editing techniques which were noted in our work in relation to the Biological and Toxin Weapons Convention[17] are:

- the use of CRISPR/Cas9 to edit human genetic components linked with disease as cancer immunotherapies and cell-based therapies for HIV, primary immune deficiencies and autoimmune diseases. It is too soon at present for these methods to have reached the clinic. ZFNs and TALENs have progressed to clinical applications.
- the creation of a programmable tool using CRISPR/Cas9 to replace genetic sequences in mature immune cells, which could be used to modulate T-cell function.

The UK has strong regulation for new medical products, reproductive medicine and human tissue use and any use of gene editing techniques in humans should be governed within this framework.

Military and security considerations

As the Society's recent work on the Biological and Toxin Weapons Convention highlighted,[18] gene editing techniques are already widely used and similar to other areas of research there is the possibility of dual use of concern. Due to the speed of the development in the sciences, the decreasing costs and the increasing ease of use, the technological barriers to acquiring a biological weapon have been eroded. The skills and resources required remain considerable implying that it would likely require the backing of a nation state, however these barriers are likely to be rapidly eroded over the next few years with new technologies. As highlighted previously, the increased precision of gene editing technique also mean that changes introduced may be effectively 'invisible', making forensic investigation and attribution difficult.

The technical report noted some problems that may arise from the use of gene editing techniques:

- the use of gene editing tools to produce novel pathogens and/or alter entire populations
- reduction of risk by removing potential agents from naturally occurring crops e.g. removing the ricin gene from the castor oil plant *Ricinus communis.*
- The difficulty of distinguishing between a 'natural' and 'unnatural' disease outbreak. The lack of 'fingerprints' from the use of gene editing techniques may hamper forensic investigations
- the possible use of CRISPR gene drives against wild populations and ecosystems, for example plants or livestock, by actors intent on doing harm
- use of gene editing techniques to change the characteristics of an infectious disease so that it resists treatment or controls that prevent it from spreading

[16] https://www.newscientist.com/article/dn28454-gene-editing-saves-life-of-girl-dying-from-leukaemia-in-world-first/

[17] https://royalsociety.org/~/media/policy/projects/biological-toxin-weapons-convention/biological-weapons-technical-document.pdf

[18] https://royalsociety.org/topics-policy/projects/biological-toxin-weapons-convention/

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