Scoping for EASAC project on Genome Editing

1. Introduction

As discussed in the EASAC Biosciences Steering Panel meeting in November 2015, the field of genome editing has seen some very rapid recent advances because of the availability of programmable nucleases, particularly TALEN and CRISPR-Cas9. These new tools are relatively easy to design and use, with high activity, good specificity, and applicability in a wide range of cells.

Genome editing for targeted deletion, disruption, correction and integration has significant potential in basic research and, broadly, in applications in microbial biotechnology, plant and animal breeding, and human health (Carroll and Charo, 2015). The science is advancing rapidly but the technology is sufficiently mature to warrant EASAC work to take a wide perspective on scientific opportunities, applications, policy implications and issues for EU strategy. Following the Biosciences Steering Panel recommendations and the decision by Council in November 2015, a project on genome editing will be initiated within the Biosciences Programme leading to production of an EASAC Statement. To stimulate further discussion, the following sections briefly consider scope, introduce key questions and the particular value of EASAC work.

2. Contribution to fundamental research

There is now little doubt that the new tools of genome editing have significant potential in basic and translational research including the elucidation of poorly understood genetic functions. For example, recent research used CRISPR to identify essential genes in human cells (and tumour-specific vulnerabilities) (Osorio, 2015) and to re-programme adult into stem cells (Howden et al, 2015). As noted in the Statement by the German academies (2015), the now feasible concurrent introduction of several targeted mutations can reconstruct complex disease pathways in model organisms and help efforts to identify and characterise therapeutic targets.

3. Applications

There will be specific issues raised for different applications of genome editing (with regard to particular drivers and obstacles), but there are also some generic questions that are relevant to any application, as observed in the consultation for the UK Nuffield Council on Bioethics inquiry (2015). For example: To what extent can the development of new genome engineering techniques be regarded as distinct from, or continuous with, existing techniques? What is the current state of the art and rate of progress?

3.1 Micro-organisms and the bioeconomy

Various applications are underway or can be envisaged. For example, in producing “third generation” biofuels (modified yeast degradation of wood xylose for biofuel), and microbial modification to increase the yield of key precursors of pharmaceuticals and other high value chemicals. There are also potential opportunities for microbial modification in

bioremediation but their use outside of contained facilities may raise environmental concerns.

One underlying question is – how similar are the issues raised for microbial genome editing to those for synthetic biology more broadly? This consideration may be relevant for the European Commission as they develop their recommendations on synthetic biology in 2016.

3.2 Plant breeding

Genome editing can be used to tackle various targets to improve plant traits, e.g. for yield, stress- and disease-resistance and allergen reduction, in support of societal objectives for increased food production, conservation of resources, less pollution and healthier food. The opportunities are illustrated by the recent commercial applications for cold-storable potatoes and no-trans-fat soybean oil and by recent research advances in the induction of targeted, heritable mutations in barley and brassica (Lawrensen et al, 2015) and in combatting invading virus DNA in plants (e.g. Zhang et al, 2015).

One underlying question for the EU is – to what extent will the regulation of plants/food products developed using genome editing be influenced by previous controversies and current legislation on GMOs? The products of genome editing contain no foreign DNA and EASAC has previously advised in our Statement on New Breeding Techniques (encompassing genome editing tools) that such processes should not be regulated in the same way as GMOs. Recommendations from the European Commission are anticipated before the end of 2015 and continuing discussion with the European Commission, European Parliament and Council of Ministers is expected in 2016.

3.3 Animal breeding

Proposed applications in agriculture include genetic de-horning of dairy cattle (for improved husbandry) and mutation of the myostatin gene in cattle and pigs for increased production of skeletal muscle. Such applications may raise issues for animal welfare and, in some cases, for food safety.

There will also be opportunities for developing animal models of human disease in laboratory research. This may have implications for the principle of the 3Rs and, therefore, may receive attention by the European Commission in 2016 in preparation of the review of the Directive on animal use for research in 2017.

3.4 Animals as organ donors for xenotransplantation

Scientific advance in the field of xenotransplantation has been considered relatively disappointing until recently but genome editing brings new opportunities, e.g. to edit pig genes which could cause rejection or infection in human recipients. Genome editing is encouraging new options for, e.g., kidney and lung transplantation (Reardon et al, 2015b), but there remains a lot to do to assess long-term efficacy and safety. Presumably the EU and Member States would regulate according to current mechanisms for advanced therapy/medical products relating to cells and tissues.

3.5 Modification of populations in the wild

Genetic manipulation of wild populations is a potentially effective approach for ameliorating the impact of pathogens, disease vectors and agricultural pests. It also has potential to do harm through accidental or purposeful release. Using gene drives to distort inheritance in favour of a particular attribute can eventually affect a whole population. It has been proposed, e.g., to alter mosquitoes to control their transmission of malaria and dengue fever. Concerns have been raised that the spread of gene drive may be difficult to control and might have ecological consequences beyond those intended. Genome editing is a reversible process but ecosystem change might not be undone. Various control and containment measures have been suggested, e.g. to curtail the spread of a modified organisms if escaped from laboratory research.

Prior modelling of the manipulation of natural populations is likely to be an essential part of research studies (e.g. Unckless et al, 2015) and there will also need to be extensive risk assessment to consider the possible consequences for ecosystems and use of retrieval measures. This area is controversial and it is important for researchers to be open in discussing proposed experiments before they are undertaken – good practice is exemplified by genome editing researchers working on Lyme disease and schistosomiasis (Anon 2015).

3.6 Human health

As observed in the UK Joint Statement from the Academy of Medical Sciences and research funding bodies (2015), there is need to distinguish (i) between the use of genome editing in the research context and in the clinical setting; and (ii) between its use in somatic cells and in germ cells. As emphasised in the Statement by the German academies, support for human applications requires more research to understand complex interactions between genes, and the molecular mechanisms involved in editing to increase efficiency, selectivity and safety. As discussed in the Statement of the Hinxton Group (2015), safety research is important both to clarify the extent and impact of off-target events (unintended genetic alterations) and mosaicism (variation across cells). Such research also requires improving *in silico* tools to predict off-target effects and whether they are likely to be deleterious, and to guide design in genome editing.

3.6.1 Biomedicine/somatic changes

These include gene, cell and regenerative therapies. The new approach to gene therapy has advantages over vector-mediated gene delivery. One of the first examples was modification of the CCR5 gene in T cells to treat HIV patients. A more recent example, the treatment of a child with acute lymphoblastic leukaemia using TALEN-modified designer immune cells has aroused significant public interest. It is easier to envisage *ex vivo* treatment (modification of the patient's cells in the laboratory and returning them to the patient) because direct delivery of gene editing to tissue within the body presents challenges for targeting. Nonetheless, *in vivo* trials may start in 2016, e.g. on factor IX therapy of haemophilia B (Reardon 2015a).

As with other innovation in healthcare, these advances raise questions as to whether benefits will be distributed equitably (or differently from existing treatments) and in what ways the interests of people in vulnerable groups may be affected.

3.6.2 Reproduction/germline changes For example, removing hereditary disease traits. Recent Chinese research on editing human embryos has stimulated extensive discussion on what research and applications should be allowed. There have been various proposals for a moratorium, e.g. from the UNESCO International Bioethics Committee[1].

The German academies Statement endorses suggestions for an international moratorium on all forms of human germline engineering that could have an impact on the genome of offspring. From this perspective, the moratorium would provide an opportunity to discuss unresolved questions and develop recommendations for regulation, but it should not constitute a general restriction on methodological developments and limit any promising new genome editing approaches. In the UK, research can be conducted on germ cells, including human embryos up to 14 days, when justified and supported by rigorous scientific and ethical review.

Although ethical aspects (see Box 1) are a national/local responsibility for EU Member States, the EU Clinical Trials Directive 2001/20/EC and Clinical Trials Regulation EU No. 536/2014 (effective after May 2016) include the provision "… no gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity."

Box 1: Some ethical considerations in human germline applications

1. Safety

2. Respect for human life (if embryos were to be destroyed)

3. Dignity, with regard to the boundary between treatment and design (although this distinction is not always clearcut, designing enhanced functions might be perceived to jeopardise inherent/equal dignity of all human beings)

4. Justice, with regard to equity in the sharing of benefits

Sources: UNESCO, Hinxton Group

While germline applications are currently not allowed, consideration of issues for future options has to take account of the wide spectrum of possible interventions – from correction of serious disease-causing mutations through to biological enhancement. It should also be noted (Mathews et al, 2015) that use of genome editing, if permitted, in human sperm, eggs and embryos could yield insight in basic research, e.g. how cell types are specified in the early human embryo, understanding biology and genetics of stem cell lines, and the role of specific genes in the differentiation of sperm and eggs.

[1] "Updating its reflection on the human genome and human rights" calls for a moratorium on germline applications and hereditary modifications. In surveying the legislative position worldwide, 29 of 39 countries reviewed by UNESCO had a ban on editing the human germline. In 25 countries, the ban was legally binding, 4 had guidelines, not laws (China, Japan, Ireland, India) while rules in the remaining 10 countries were ambiguous.

Some options will be more controversial than others (even in a well-regulated context): technical and safety concerns may be resolved by scientific research but moral considerations require public debate. It has been suggested (Mathews et al, 2015) that national academies are well placed to take the lead on efforts to ensure that debates on genome editing applications are geographically and demographically inclusive and inform policy discussions.

Active discussion in this area raises some general questions for the scientific and policy-making communities. For example, as noted in the Nuffield Council on Bioethics consultation: What influence do international ethical debate and agreements have on the pace or organisation of research? Who should lead in setting policy for research and for human applications? Is the use of genome editing techniques significantly different from other kinds of reproductive medicine?

3.7 Biosecurity

Are there military interests in genome editing? Are there biosecurity concerns related to use of genome editing for non-military purposes? Examples of genome editing were discussed in the Warsaw meeting of the IAP Biosecurity Working Group (www.iapbwg.pan.pl/index.php) but it is not yet clear if genome editing raises new issues, e.g. for the Biological Weapons Convention.

4. Relevant academy work

The German academies Statement ("Opportunities and limits of genome editing") has been discussed in previous sections. It emphasises the great scientific potential of genome editing, that it is ethically and legally acceptable in many areas and that new techniques should not automatically be equated with sporadic cases of improper use or with applications whose ethical and legal ramifications have not yet been assessed.

The US National Academies have initiated two relevant projects:

(i) Human gene editing: scientific, medical and ethical considerations. This is an international expert group (and also involving UK Royal Society and Chinese Academy of Sciences) that is examining the scientific underpinnings as well as the clinical, ethical, legal and social implications of the use of human genome editing technologies in biomedical research and medicine, including editing of the human germ line. See http://www8.nationalacademies.org/cp/projectview.aspx?key=49750

(ii) Committee on "Gene drive research in non-human organisms: recommendations for responsible conduct". See http://dels.nas.edu/Study-In-Progress/Gene-Drive-Research-Human/DELS-BLS-15-06?bname=bls

EASAC has previous relevant work on genome editing as part of the New Breeding Techniques in plants (Statement, 2015) and more generally in synthetic biology (Report, 2010 and responses to European Commission consultation 2014-2015).

FEAM has initiated a project proposal with a request for IAMP funding in 2016 to discuss the current European landscape relevant to health research and applications involving human genome editing. Whether the focus of this project would be mainly on human germline editing or would take a broader perspective on other health applications remains to be clarified.

5. EASAC next steps

A timely EASAC Statement would add value to the work of other groups, some cited previously, in taking a broad perspective of the science and range of opportunities, but highlighting where issues are distinctive for particular applications and relevant for regulation. These matters will be of interest to the EU Institutions and Member States. It is important for EASAC to take account of what work has been done by other academies (worldwide) and what may be achievable in the FEAM project, clarifying what policy objectives are relevant at the EU level, what is reserved for Member States and how Europe can contribute to global strategy development, where that is appropriate.

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