Nuffield Council for Bioethics: Working Party on genome editing and human reproduction call for evidence

Submission from the Medical Research Council and Biotechnology and Biological Sciences Research Council

28th July 2017

Summary

In the UK our strong ethical and regulatory framework has allowed us to find ways forward through complex ethical issues. We support the continued assessment, refinement and use of genome editing ('GE') techniques alongside open debate and responsible, proportionate and robust regulation. This includes the use of these technologies in preclinical research, including in human reproductive cells and early embryos, where fully justified scientifically, ethically and legally.

Introduction:

1. In February 2016 the Biotechnology and Biological Sciences Research Council (BBSRC) and the Medical Research Council (MRC) submitted evidence[1] to the Nuffield Council on Bioethics *Ethical Review of Genome Editing*. Respecting the current call's spotlight on human germline editing, here we reiterate and expand upon elements of our previous response to focus on the potential use of genome editing to make heritable genetic changes to the human germline.

2. We would also like to highlight to the Working Group the House of Commons Science and Technology Select Committee's recent *Inquiry into Genomics and Genome Editing*[2] which sought evidence on issues including the potential impact of genomics and GE and related ethical, social and safety concerns. The Research Councils UK submitted evidence to this Inquiry on behalf of BBSRC, MRC, the Engineering and Physical Sciences Research Council (EPSRC), the Natural Environment Research Council (NERC) and the Science and Technology Facilities Council (STFC).

Further perspectives on genome editing:

3. Researchers have employed genetic engineering technologies for many years to develop tools for genetic modification, some of which have offered potential gene therapy applications to counteract missing or faulty DNA and restore healthy gene expression in cells, or have allowed immune cells to recognize and kill cancer cells. However, the emergence of techniques to edit the genome in a much more efficient and targeted way, such as CRISPR-Cas9, has accelerated the field to such an extent that UK researchers now routinely edit *in vitro* cell lines and somatic and germline cells in animal models, and are actively researching GE as a somatic therapeutic application. Some researchers are also using GE to edit human embryos (donated by patients who have undergone *in vitro* fertilisation (IVF)) for research purposes. This use is in accordance with UK legislation and embryos are destroyed before the 14 day post-fertilisation legal limit (*see **6** below*).

4. As outlined in our previous submission (*paras. 30-36*) we welcome innovation in GE as a means of manipulating genomes for biomedical research and for its potential in therapeutic treatment of diseases. Currently research includes the use of GE techniques to model disease, understand gene function in normal and pathophysiological settings, and to understand if gene correction in a model system presents a viable therapeutic approach. For example, as part of its research portfolio, the MRC funds studies at the Weatherall Institute of Molecular Medicine (WIMM) at Oxford University to explore the potential for somatic genome editing of white blood cells in treatment of leukaemias. We note with interest on-going research published in January 2017 illustrating clinical application of GE (TALEN)-modified non-autologous T cells in 2015 to treat two infants at Great Ormond Street Hospital

[1] https://www.mrc.ac.uk/documents/pdf/ncb-genome-editing-project-bbsrc-mrc-submission/
[2] http://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/inquiries/parliament-2015/inquiry2/ and http://www.rcuk.ac.uk/documents/submissions/rcukresponse-hocstgenomicsgenomeediting-pdf/

with relapsed refractory CD19+ B cell acute lymphoblastic leukaemia[3]. Although the current focus of clinical research is somatic editing, this and wider research will be essential to develop the body of knowledge to inform decisions on the possibility of editing the human germline for therapeutic purposes.

5. Internationally, numerous developments around GE of somatic tissues continue to emerge: a December 2016 publication from the Belmonte Lab at the US Salk Institute demonstrated use of GE technologies to partially restore the sight of blind adult rats[4]. In June 2016, US regulators approved plans to use CRISPR–Cas9 to modify several genes within T cells to enable them to effectively target cancer cells[5] (similar studies are also at Phase I stage in the UK). In China, several somatic GE human clinical trials are planned or recruiting participants. These include a planned study to assess use of CRISPR-Cas9 and TALEN GE approaches to challenge cervical cells infected with HPV16 and HPV18[6] and an HIV study to explore the use of CRISPR-Cas9 to disrupt the CCR5 gene in CD34+ hematopoietic stem/progenitor cells for patients that develop AIDS and hematological malignancies[7]. Other Chinese studies planned, or underway, include use of PD-1 knockout engineered T cells in treating different cancers (for example see [8]).

6. Genome editing research in embryos has also been undertaken: 2015 research in China used non-viable embryos to explore CRISPR-Cas9 efficacy[9]. This generated concerns and led to calls for an effective moratorium on germline genome editing for clinical application in humans until the implications had been fully considered[10]. More recently, a 2017 report by a China-based group investigated efficiency of CRISPR-Cas9 editing at several sites in very early embryos[11]. In both the UK (Kathy Niakan at the Crick Institute) and Sweden (Fredrik Lanner at the Karolinska Institute), research is underway which uses CRISPR-Cas9 as a tool to understand the role of key genes in early embryonic development, using viable donated human embryos. These latter two studies do not seek to take forward research through to clinical application, however such studies may indirectly inform our understanding of the penetrance, specificity and persistence of CRISPR-Cas9 modifications in early human embryos.

7. The Research Councils note that the many challenges facing implementation of GE as a human therapeutic approach are discussed in the Hinxton Group statement[12]. This notes that the ease and rapidity of making specific genomic changes has shifted, bringing human application closer, but that there are significant implications for the existing regulatory framework and a need for a societal debate around the ethical concerns before implementation of such biologically complex interventions is considered. As with other advanced therapies, the costs will be high in the first instances and many of the challenges found in regenerative and stratified medicine, such as access and cost, will need to be played out.

8. The Research Councils have also taken careful note of the US National Academy of Science, Engineering and Medicine (NASEM) report "Human Genome Editing: Science Ethics and Governance"[13], published in February 2017. The report sets out principles to guide the governance of human genome editing research and its applications and makes recommendations on oversight and use of GE. The report states that clinical trials for genome editing of the human germline could be permitted in the future in the US, but only for serious, otherwise intractable conditions under stringent oversight. It outlines several criteria that should be met before allowing GE clinical trials to go forward. The report recommended that while GE has already entered clinical trials for non-heritable applications,

[3] Quasim *et al*. Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells. **Science Translational Medicine** 9(374) 2017
[4] Suzuki *et al*., *In vivo* genome editing via CRISPR/Cas9 mediated homology-independent targeted integration. **Nature** 540 (*144-149*) 2016
[5] http://www.nature.com/news/first-crispr-clinical-trial-gets-green-light-from-us-panel-1.20137
[6] https://clinicaltrials.gov/ct2/show/NCT03057912
[7] https://clinicaltrials.gov/ct2/show/NCT03164135?term=CRISPR&rank=2
[8] http://www.nature.com/news/chinese-scientists-to-pioneer-first-human-crispr-trial-1.20302
[9] Liang et al., CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. **Protein & Cell** 6(5) (*363-372*) 2015
[10] http://science.sciencemag.org/content/348/6230/36/tab-pdf
[11] Tang *et al*., CRISPR/Cas9-mediated gene editing in human zygotes using Cas9 protein. **Molecular Genetics and Genomics** 292(3) (*525-533*) 2017
[12] http://www.hinxtongroup.org/Hinxton2015_Statement.pdf
[13] http://nationalacademies.org/gene-editing/index.htm

this should be allowed only for treating or preventing diseases or disabilities at this time.

9. As discussed in depth in the Hinxton and NASEM reports and elsewhere, there are risks common to all applications of GE that researchers must consider and seek to minimize before clinical application. For example, both somatic and germline editing technologies can cause off-target changes (in relation both to target cells/tissue and genomic region). Particularly careful research will be needed to ensure that, for example:

    - Where somatic genome editing components are to be administered to a patient, they are delivered to their target organ(s) precisely and do not reach, and edit, the germline.
    - Where genome editing is carried out on cells removed from a patient for modification (e.g. white blood cells, germ cells or embryos), they do not acquire harmful changes during this process.

10. Before GE methodologies can be introduced routinely at the clinical level, for either somatic or germline editing, it is important that basic and pre-clinical research assesses the long-term impact of such therapeutic interventions on the edited cell and daughter cells in a physiologically relevant context. For example, research may be needed to explore the long-term impact of a cell's response to the introduction of a modification (e.g. in terms of gene expression levels) and any associated stress or immune responses that may be induced by this or the GE process. Stability of an engineered change across a cell and its progeny will also need to be explored.

11. Following from the above, the Research Councils support continued refinement of GE techniques to improve their accuracy, measure genome variation in individual cells and explore where application could offer health benefits to people. Research funders and research publishers must continue to engage with the research community to refine protocols and experimental design; areas quality assured through robust peer review mechanisms.

Open debate and responsible, proportionate and robust regulation:

12. The Research Councils support the continued assessment, refinement and use of GE techniques alongside open debate and responsible, proportionate and robust regulation. This includes the use of these technologies in preclinical research, including in human reproductive cells and early embryos, where fully justified scientifically, ethically and legally. It is our view that continued use of GE while its future applications are openly debated is the most effective way to push forward the frontiers of science. Consequently, we would not support a moratorium on the use of GE technologies within the UK.

13. In the UK our strong ethical and regulatory framework allows us to find ways forward through complex ethical issues. We highlight that, in recent years, the public, researchers and regulatory systems have come together to find a way forward both in research using human embryonic stem cells and in the use of mitochondrial donation. In the case of mitochondrial donation, a range of mechanisms were used to engage and inform policy makers, researchers and the public in an open debate. The Government's proposals to change the law followed several years of consideration, including scientific reviews and public consultations and debate. Like IVF before it, the new reproductive technique was subject to full scrutiny of Parliament.

14. An important marker of the debate around GE in the UK (referred to in paras **3** & **6** above) was the HFEA's approval in February 2016 for the application of CRISPR technology by Dr Kathy Niakan's group at The Francis Crick Institute to investigate healthy human embryo development during the first seven days of life[14]. The Nuffield Council's current GE Working Party, along with other activities such as those by the Hinxton Group[15], will play an important role in continuing this debate.

[14] http://www.mrc.ac.uk/news/browse/new-gene-editing-techniques-approved/
[15] http://www.hinxtongroup.org/. The Hinxton Group is funded by the MRC, the Wellcome Trust and others.

15. There appear to be two foci for current debate: modification of embryos for research and modification of germ cells and/or embryos as a therapeutic intervention to combat Mendelian and other diseases. Another point for debate is the extent to which the gene-therapy endpoints of GE research can be of benefit to countries with relatively low national healthcare investment and limited infrastructure and consequently the extent to which UK funders should invest in a way that maximises benefit internationally. Additionally, the Research Councils recognize that there may be important ethical distinctions between engineering a pathogenic mutation to a non-pathogenic variant common in human populations and introducing genetic change(s) that are new to the human genepool.

16. The Research Councils engage in "science in society" activities to support informed debate and ensure broad input into our strategic decision-making. Activities range from supporting researchers we fund to communicate their research to the public and relevant stakeholder groups, through to directly communicating our policies and funded research across a range of formats, set in the context of their implications and relevance to society.