The Hinxton Group
An International Consortium on Stem Cells, Ethics & Law

Statement on Genome Editing Technologies and Human Germline Genetic Modification

PREAMBLE

While genetic modification methods have been used successfully for over 30 years to alter genes in experimental animals and animals of agricultural importance, these methods have been inefficient, and have often lacked specificity or otherwise relied on a series of steps that made them both inappropriate and unsafe to use in humans. More recent advances in genome editing technology[1], however, make it possible to insert, delete, or modify DNA with greatly increased specificity and efficiency. These techniques are already beginning to be used in human somatic gene transfer trials. The use of such technologies in pluripotent and other stem cells and in early stages of human development, to correct genetic defects or introduce other potentially therapeutic changes, now provides vast scope for applications in human disease and health. This includes the potential for modification of the human germline. It is this step, which has multigenerational implications, that has been cause for deep concern and demands wide-ranging and open debate.

It is important to note that this debate has happened before. Indeed, it has happened multiple times, in response to each incremental step toward the ability to create changes in the human genome that are inheritable down the generations. While the ethical issues raised by this prospect remain unchanged, the context in which they now arise is dramatically different. Science has grown enormously in both size and geographic diversity, now encompassing many more people from many different cultures and regulatory environments. In comparison with earlier techniques, modern genome editing technologies and CRISPR/Cas9 in particular are not only very precise, but also easy, inexpensive, and, critically, very efficient. In addition, since the last round of debates, other areas of science and medicine have likewise advanced; for example, we can now sequence entire genomes quickly and inexpensively. Further, there is increased acceptance and use of techniques of assisted conception, which are likely to be required for the use of genome editing in human embryos. *In vitro* fertilization and related techniques are regulated well in some countries, but not others. As a consequence, and especially given the recent experience with purported stem cell-based 'treatments' in unregulated clinics, there is serious concern that genome editing technologies might be used in reproductive contexts long before there are data sufficient to support such use, and before the international community has had the opportunity to weigh the benefits and harms of moving forward.

For these reasons and others, there are many conversations ongoing and being planned to grapple with the scientific, ethical and regulatory issues raised by both research and

[1] Zinc Finger Nucleases (ZFNs), TALE Nucleases (TALENs), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPRs) all work by guiding a DNA cutting enzyme (either the Fok1 nuclease for the first two and Cas9 for the last) to specific DNA sequences. ZFs and TALEs are DNA-binding proteins, CRISPR methods use an RNA guide.

clinical reproductive uses of this technology. The science will continue to progress rapidly, and there is and will be pressure to make decisions – scientifically, and for funding, publishing and governance purposes. There will also be pressure from individuals wishing to use the technology for their own medical, reproductive and other needs.

The goal of the Hinxton Group is to inform these ongoing debates and to provide useful guidance to decision-makers regarding use of these technologies in humans, and in particular their use to intervene in the human germline[2]. The focus of our discussions was genome editing in the early stages of human development, when any such intervention might reasonably be assumed to integrate into the germline, and therefore have the opportunity of being passed down to future generations[3].

In developing this statement, many scientific, ethical and regulatory issues were raised and discussed, triaged, and prioritized. We ultimately focused our attention on issues that we saw as more pressing and potentially tractable. For example, though we discussed many critical ethical issues, such as the moral status of the embryo, we did not attempt to come to consensus on those that we believe are unresolvable outside of particular cultural contexts. We were able to come to consensus on a number of issues related to basic research, clinical applications, public engagement and governance. Importantly, as will be detailed below, we all agreed that while this technology has tremendous value to basic research and enormous potential for somatic clinical uses, it is not sufficiently developed to consider human genome editing for clinical reproductive purposes[4] at this time.

THE VALUE OF BASIC SCIENTIFIC RESEARCH

While much of the focus of public discussions of human genome editing has been on potential clinical applications, the immediate and perhaps most exciting uses of this technology are in basic scientific research. However, it is important to keep in mind that this technology, and in particular the CRISPR/Cas system, is very new and there is still much to be learned. As such, we concur that:

1. Genome editing has tremendous value as a tool to address fundamental questions of human and non-human animal biology and their similarities and differences. There are at least four categories of basic research involving genome editing technology that can be distinguished: 1) research to understand and improve the technique of genome editing itself; 2) genome editing used as a tool to address fundamental questions of human and non-human animal biology; 3) research to generate preliminary data for the

[2] Our process includes not only the development of this statement, but also an extensive collection of background materials that are available at: www.hinxtongroup.org

[3] We included in this, stem cells able to give rise to gametes, notably spermatogonial stem cells in the testis or, potentially, germ cells derived from pluripotent stem cells *in vitro*.

[4] 'Human genome editing for clinical reproductive purposes' involves editing germline cells at any stage of development followed by fertilization *and* editing of early embryos around the time of fertilization, where the intent is to establish a pregnancy.

development of human somatic applications; and 4) research to inform the plausibility of developing safe human reproductive applications. These distinctions are important to make clear that, even if one opposes human genome editing for clinical reproductive purposes, there is important research to be done that does not serve that end. That said, we appreciate that there are even categories of basic research involving this technology that some may find morally troubling. Nevertheless, it is our conviction that concerns about human genome editing for clinical reproductive purposes should not halt or hamper application to scientifically defensible basic research.

2. Prior to any movement toward human reproductive applications, a number of crucial scientific challenges and questions must be addressed, including the extent and impact of off-target events (unintended genetic alterations, secondary to the intended modification) and mosaicism (variation across cells with respect to the intended genetic change). We recommend that a detailed but flexible roadmap is produced to guide the development of standards for safety and efficacy. Such a roadmap should include consideration of at least the following:
   - Use of appropriate models that reflect key aspects of human biology and genetics (e.g., heterogeneity) including: animal models, human somatic cells, human pluripotent stem cells and their differentiated derivatives, spermatogonial stem cells, gametes, and human embryos cultured *in vitro* and subject to the 14 day rule[5], to test efficacy and safety. Such efforts might be carried out in parallel.
   - Optimization of genome editing tools and their delivery to maximize efficiency and specificity, thus minimizing mosaicism and off-target events.
   - Assessment of mosaicism and its impact on developing embryos, and the health of individuals and their descendants.
   - Sequencing (to sufficient coverage) of the edited and the relevant control genomes (e.g. parental genomes and genomes from unedited sibling embryos or blastomeres isolated from them), as well as molecular and functional characterization (e.g., transcriptional analysis).
   - Comparison of the number of mutations in the genome with and without editing (bearing in mind that natural background mutation rates might differ based on age, sex and genetic background), to assess the degree to which mutations are the result of genome editing methods. This will be aided by *in silico* methods to analyze genomes, design guide RNAs, ZFNs or TALENs, and to predict likely off-target sites. Efforts will be needed to improve *in silico* tools to predict whether any induced mutations are likely to be deleterious.
   - Use of appropriate animal models that allow analysis of multigenerational effects other than those anticipated.
3. There are three categories of human embryos that have been used or considered for use in genome editing research: nonviable embryos left over following *in vitro* fertilization;

[5] The 14 day rule is a broadly agreed to limit on the length of time that intact human embryos can be cultured *in vitro*.

viable embryos left over following *in vitro* fertilization; and embryos created specifically for research. While the use of nonviable embryos does address to some degree the deep concern expressed by many about the genetic modification of human embryos, any experiment must first meet the criterion of scientific validity.[6] Of note, most supernumerary IVF embryos available for research will have progressed beyond the one-cell stage, such that the use of genome editing techniques will likely lead to mosaicism. Experiments where all cells need to be modified will probably require the creation of embryos specifically for research. We recommend that scientists wishing to carry out research using genome editing techniques in human embryos consider carefully the category of embryo to be used. Moreover, given that the number of embryos available for research is low and the tissue precious, the methods used and any data obtained should be made openly available, to maximize the scientific value derived from these human cells. In addition, jurisdictions that permit research with human embryos may need to review their policies to assess whether they are consistent with particular types of genome editing research.

THE PROSPECT OF HUMAN GENOME EDITING FOR CLINICAL REPRODUCTIVE PURPOSES

As noted above, we do not believe that sufficient knowledge is available to consider the use of genome editing for clinical reproductive purposes at this time. However, we acknowledge that when all safety, efficacy and governance needs are met, there may be morally acceptable uses of this technology in human reproduction, though further substantial discussion and debate will be required as detailed below.

4. All clinical uses of this technology (somatic and reproductive) require the manipulation of cells sufficient to fall under the jurisdiction of established medical licensing authorities and perhaps other governmental oversight. Any medical innovation in this arena is premature prior to the completion of the necessary basic and clinical research and the availability of data sufficient to justify use of this technology in human reproductive contexts from the perspective of safety and efficacy. This same standard applies to medical innovation in somatic interventions.

5. International and regional debate will be required to assess and make decisions about the ethical acceptability/permissibility of different potential uses of human genome editing for clinical reproductive purposes, even once standards for safety, efficacy, and robust governance have been met.

6. As with most emerging biomedical technologies, human genome editing raises substantial concerns about justice and equity, such as questions about for whom treatments are developed and who will have access. Before moving forward with

[6] For example, because genome editing relies on endogenous DNA repair mechanisms, which may either be compromised or over-active in nonviable embryos, little may be learned as to how the methods might work in normal embryos.

clinical applications, attention should be paid to how applications are prioritized and based on what criteria, such as magnitude and frequency of need, nature of the genetic change being made, anticipated feasibility, and the presence of accepted alternative approaches—all of which bear directly on the risk/benefit analysis and the justification for any given use.

7. There are and will be a spectrum of proposed or requested interventions—from correction of serious disease-causing mutations, through introduction of disease-preventing changes, to enhancements—some of which will be more contentious than others. Individual societies will need to decide which, if any, interventions along this spectrum, should be permitted in the context of well-regulated clinical research.

8. There is important ethical, scientific and regulatory work to be done to identify and explore the issues that are common and divergent across *in vitro* and *in vivo* gamete modification, *in vitro* and *in vivo* embryo modification, and *in vivo* fetal modification.

9. Oversight structures must be in place prior to any attempts to use genome editing in human reproduction. Effective oversight requires the development of appropriate standards for preclinical data (e.g., What are acceptable thresholds for off-target events and mosaicism? What are appropriate methods for determining the impact of off-target events?). Initial attempts should be conducted only in the context of formal clinical research or trials. In addition, the health and well-being of participants, developing fetuses, and pregnancy outcomes should be monitored carefully. The health and well-being of those born should also be monitored in long-term follow-up and research, albeit with a mind toward the burdens this would impose.**

THE IMPORTANCE OF GOVERNANCE AND MEANINGFUL ENGAGEMENT

Critical to scientific and societal decisions about the use of genome editing for basic research and clinical reproductive purposes are appropriate governance and oversight, and meaningful and substantial public engagement. As such, we recommend the following:

10. Decisions about research and clinical uses of genome editing technologies should be made through inclusive, deliberative processes that will make engagement with the public and policymakers substantive, and should aim to strike the best possible balance between free scientific inquiry and social values. Further, best methods for integrating the outputs of public engagement into the policymaking process should be identified and utilized.

11. In considering policies governing the regulation of clinical applications, a distinction should be made between objections that are based on technical or safety concerns and objections that reflect additional moral considerations. Technical and safety concerns have the potential to be resolved over time by further scientific research and advances,

while the additional moral considerations may continue to be the focus of public debate.**

12. Scientific journal editors should support and promote high standards for papers that report research involving genome editing of human tissues. Editors should require a statement from scientists that their research conforms to local laws and policies, and that, where applicable, it has been approved by all appropriate oversight committees. Authors should provide statements of all conflicts of interest that affect their research. On request from editors, authors should provide protocols approved by relevant oversight committees, consent forms, information provided to potential human subjects and tissue donors, and other related documents or information that may bear on the ethics of the research.*

13. Public policies carry great power to facilitate or restrict scientific exploration in the area of human genome editing. Policymakers should be circumspect when regulating science. When enacted, policies governing science nationally and internationally ought to be flexible, so as to accommodate the rapidity of scientific advance as well as changes of social values.**

14. Societies have the authority to regulate science, and scientists have a responsibility to obey the law. However:
    a. Any constraint of scientific inquiry should be derived from reasonable concerns about demonstrable risks of harm to persons, societal institutions, or society as a whole. Policymakers should refrain from constraining scientific inquiry unless there is substantial justification for doing so that reaches beyond disagreements based solely on divergent moral convictions.
    b. In the case of human genome editing, as with all science, it is important to target restrictive policy specifically to those dimensions of the research or its applications that have proved to be unacceptable, and that these policies be proportionate to the magnitude of what is morally at stake.**

While there was consensus about the above statements, there were nonetheless a set of issues with which we felt it was important to engage, but on which we could not agree. These include a small number of uses of human embryos in research and, while all participants were willing to consider the prospect of using the methods for clinical reproductive purposes, we could not come to a consensus on the specific uses that might be acceptable, as we could not agree, in absence of the details, whether any specific case was sufficiently compelling to warrant the use of this technology.

* This consensus point was based in whole or in part on a similar point made in the 2006 Hinxton Group Statement on International Cooperation in Stem Cell Research.
** This consensus point was based in whole or in part on a similar point made in the 2008 Hinxton Group Statement on Pluripotent Stem Cell-Derived Gametes.

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