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Current Opinion in Genetics & Development

Ethical issues in genetic modification and why application matters

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Advances in genome editing techniques have generated renewed interest in the ethical implications of genetic modification. In this article, we review the recent literature and discuss in detail ethical issues pertaining to the application of this technology to five areas; human embryo research, organoid research, the prospect of genetically modified babies, mitochondrial replacement therapy and the creation of chimeric organisms. We point to a central issue which cuts through these different areas: the need to clearly frame how using the technology provides benefit that cannot be met by other means. Failure to provide reasonable justification, and address how risks — if any — will be mitigated, is likely to erode public trust and undermine progress in medical research and its clinical translation.

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Current Opinion in Genetics & Development 2018, **52**:7–12

This review comes from a themed issue on **Cell reprogramming, regeneration and repair**

Edited by **Knut Woltjen** and **Alex Bortvin**

https://doi.org/10.1016/j.gde.2018.05.002

Introduction

For over 40 years, scientists have been able to genetically modify the genome of mammalian cells. The first 'transgenic' mouse was created by Rudolf Jaenisch in 1974 [1]. Since this time various techniques have been used to insert, delete or modify DNA, in order to create animals with altered physical [2], cognitive [3] and social [4] characteristics. While invaluable to advance basic research, the potential clinical applications have been hampered by the challenge of reliably modifying the desired genome sequence without any off-target effects. However, advances over the past six years have led to more precise and efficient methods for genetic engineering, raising the spectre of 'editing' the genomes our own cells or even those of our descendants at will.

The most notable of these advanced 'genome editing' techniques is the clustered regularly interspaced short palindromic repeats (CRISPR-Cas9) system. This approach, developed by a team at UC Berkeley in 2012, showed that CRISPR-Cas9 could be modified so that it could target virtually any DNA sequence [5], giving researchers the ability to delete, add, or modify DNA sequences with greatly increased precision. The CRISPR-Cas9 approach has since been used to modify the genome of mice [6], dogs [7], pigs [8] and primates [9].

These developments have brought to focus a number of important ethical questions. In this review, we discuss the ethical issues raised by genome modification technologies and why application remains a paramount consideration for the future.

Recent controversy — editing the human germline

In April 2015, a team in China became the first to use genome editing technologies on human embryos [10]. The study, which attempted to correct the gene responsible for β-thalassaemia using 'non-viable' IVF embryos, sparked a worldwide debate about how research involving germline genome editing (a practice we will call GGE[3]) should be regulated. Some scientists and public interest groups, including the United Nations Educational Scientific and Cultural Organization have called for an international ban on any gene editing research in human embryos [11]. The U.S. based National Institutes of Health, maintained that performing such research passed 'a line that should not be crossed' [12]. Opinion articles in the leading journals *Nature* and *Science* called for a moratorium on any GGE research [13,14].

In response to this development, some called for collective efforts to carefully analyse the ethical, legal, and social implications for altering the germline, and called for broad public discussion on the issue [15]. In December 2015, the Hinxton Group, an international consortium of scientists, ethicists and policy experts, convened a meeting to analyse the ethics of gene editing technologies. The Hinxton Report resisted calls for moratorium on all GGE research. While it makes clear that any reproductive

[3] By GGE, we mean the editing of any cells, including gametes and cells in early cleavage stage embryos, in which the changes made to the genome *could* be inherited by decedents of that cell.

use of GGE is premature, it highlights the important roles that GGE could achieve in basic research, such as helping us understand the mechanisms that underlie early human development [16].

In 2016, International Society for Stem Cell Research released its 'Guidelines for Stem Cell Science and Clinical Translation'. Like the Hinxton Report, this publication highlighted the importance of basic research which could be accomplished with GGE. However, it takes a harder line on the use of these technologies for reproductive purposes, starting that that such uses ought to be prohibited; and that there needs to be 'a deeper and more rigorous deliberation on the ethical, legal, and societal implications of modifying the human germ line is essential if clinical application is ever to be sanctioned' [17].

In 2017, a comprehensive joint report from the U.S. National Academy of Sciences and U.S. National Academy of Medicine, was released which looked at the ethical and regulatory implications for human genome editing. This report builds on fundamental ethical principles [18] to describe the overarching considerations for the conduct and oversight of genome editing technologies for basic research and clinical application [19••]. Notably, the report states that clinical trials using GGE *could* be considered if 10 steps are met, importantly whether the clinical objectives are unable to be reached through reasonable alternatives (see Table 1).

The recent public attention on modifying human embryos has generated much discussion on the ethics of such research; but also the ethical issues raised by genetically modifying human cells more generally. We review the major issues below, distinguishing between issues raised by genetic modification in basic research and issues raised through areas of future clinical application of genetic modification.

Ethical issues raised in research

Genetically modifying embryos

To date, all of the research involving the germline modification has taken place during early embryo development; at, or immediately after, fertilisation (see Table 2). For those who think that early embryos have the same moral status as adult humans, this is morally problematic [20]. Initial GGE studies using human embryos tried to mitigate these concerns by using 'non-viable' IVF embryos[4] that were identified as being abnormally fertilised and therefore not suitable for infertility treatment. As Savulescu *et al.*, commented 'as trialling the CRISPR system in these zygotes had no chance of resulting in a live birth, it is unclear how the study could harm or wrong anyone directly . . . ' [21]. However, it is also unclear how informative experiments using genetically abnormal embryos are in advancing the technology given that information about off-target mutations, mosaicism and about human development, cannot be easily extrapolated [16].

These limitations raise the question of how 'normally' fertilised human embryos could be *ethically* sourced. Most human embryos used in research are 'left-over' from IVF treatment. These embryos, normally fertilised and at the early stages of pre-implantation embryonic development, are no longer required by the couple and maybe available to donate to research. Using CRISPR-Cas9 on these embryos (often 4–8 cell or blastocyst stage) is likely to give variable results with genetic modification being achieved in some cells and not others, resulting in a mosaic of edited and non-edited expression across the embryo. Normally fertilised zygotes are rarely available for research. Therefore, from a research perspective, it has been argued that it may be better to specifically create zygotes using donated eggs and sperm for the purpose of research — an approach adopted in two recent gene editing studies [22,23]. While such a strategy may be acceptable to some, and has received ethics approval, such an approach opens these studies up to objections that they are unethical by creating an embryo whose sole purpose is to be used as a means for research [24]. How, where and from whom to source appropriate material to progress GGE using human gametes and embryos, and how to regulate such research, is likely to be an ongoing challenge for the field.

Organoids

Research involving organoids — clusters of cells derived from tissue or pluripotent stem cells that self-organize in ways which mimic tissue and organ function — allows scientists to create models which can further our understanding of biological processes underpinning development and the progression of disease [25]. It has also been proposed that in the future organoids may be a source of functional tissues and organs for transplantation, a quest that still has many challenges in terms of meeting necessary standards of scale and maturity. However, the recent report where gene editing techniques were used to restore normal function in intestinal organoids derived from cystic fibrosis patients provide an indication of future therapeutic applications [26].

Organoid research raises a number of important ethical issues [27]. Specifically, organoid research raises questions around moral status of these structures, about whether their creation constitutes 'life' or if they hold independent interest and rights. This is particularly relevant for research involving gastruloids, structures that are made in the lab from pluripotent stem cells and that mimic post-implantation embryonic development [28]. While most jurisdictions limit the development of human

[4] Researchers used one-cell embryos, also referred to as zygotes, that displayed more than two pro-nuclei following fertilisation; indicating abnormal fertilisation.