Ethics in Action

The elusive consensus on human gene editing

The scientific community has been aflutter since the Human Fertilisation and Embryology Authority (HFEA) early this year approved the UK's first gene editing research project using human embryos, on the condition that it be sanctioned by a research ethics committee. Under the three-year HFEA licence, scientists at the Francis Crick Institute in London will use the revolutionary CRISPR/Cas9 technology to gain a greater understanding of early human development.

CRISPR/Cas9 acts as molecular scissors that can snip out and replace, correct or inactivate faulty genes. Its precision in cutting the DNA at the exact location of the mutation and its relative ease of use have opened up a whole new realm of possible therapeutic applications, and many are excited at the prospect of potentially eliminating previously untreatable genetic diseases such as cystic fibrosis, sickle-cell anaemia, Huntington's disease and certain types of cancer.

The project's lead researcher, Kathy Niakan, will be looking at genes which she believes play a crucial role in the early stage of human development to understand which, if any, of these genes are important in an embryo being viable (i.e. in terms of developing into a foetus). This could eventually help doctors gain a greater understanding of fertility and improve pregnancy outcomes, especially in the context of in vitro fertilisation (IVF).

Dr Niakan will study fertilised eggs during the first seven days of development, after which they will be destroyed. This is well within the maximum legal limit of 14 days under UK law, which also stipulates that such embryos are not allowed to be used to impregnate a woman.

Ethical considerations

As reported in the October 2015 issue of *MedNous*, the ethical debate surrounding gene editing of human embryos (germline editing) was already heating up last year, sparked by a Chinese study using CRISPR/Cas9. The conclusions revealed serious obstacles to using the method in medical applications and created quite a stir amongst a broad range of interested parties, from academics to corporations to patient groups. As such, many have called for a moratorium on any such research until there is an international consensus on how to do it responsibly.

The concerns have led to some stakeholders bandying about terms such as "playing God," "consumer eugenics" and "slippery slope" during debates on the subject – especially since the HFEA's approval of Dr Niakan's project.

The HFEA committee that approved the research agreed the use of human embryos was necessary because, among other things, human embryonic development is significantly different to that of animal model species in a number of respects. Furthermore, it noted that not all functions required for preimplantation development can be modelled in embryonic stem cells.

According to a Francis Crick Institute spokesperson, the research ethics committee has reviewed Dr Niakan's project and a decision is expected soon. The role of the committee is to ensure research participants (i.e. the women who are donating their embryos) are treated ethically. For example, it will make sure the informed consent forms meet ethical requirements. In other words, the fate of the overall project does not hang on the ethics committee's decision, although it could cause delays if any changes need to be made to documents such as the consent form.

Some groups believe this project represents a slippery slope. For example, the UK's Human Genetics Alert is apprehensive about any research that creates genetically modified (GM) embryos, "because it's part of a normal step-by-step process which is likely to end up with the legalisation of the creation of GM babies," the independent watchdog's director David King told *MedNous*.

Dr King's worry is that even if studies involving germline editing yield nothing on the topic they're researching, they will help create the protocols for efficient and accurate germline genome editing. It would thus be "the first step in a well mapped-out process leading to GM babies, and a future of consumer eugenics," he said. He was keen to emphasise that Human Genetics Alert is not pro-life, nor is it opposed to scientific research using human embryos.

Others such as the Alliance for Regenerative Medicine in the US have previously called for a moratorium on all human germline editing, including for research, while companies such as Intellia Therapeutics and Crispr Therapeutics have expressed opposition to using it in clinical applications.

The two companies released a joint position in December 2015 stating that the vast majority of genetic and other diseases can be addressed by gene editing of somatic (non-germline) cells and do not require modification of germline cells, i.e. the source of genetic information passed on to subsequent generations.[1]

Intellia and Crispr also mentioned ethical implications in the context of the regulatory framework. Because there are already robust regulations in place for testing somatic cell gene editing technologies in patients, they said, any delays in research or product development caused by modifying existing regulations to cover germline gene editing would "adversely impact patients whose lives are dependent on the availability of new treatments for severe and sometimes fatal genetic diseases."

As for germline gene editing in the lab, Jennifer Smoter of Intellia has confirmed that the company will continue to refrain from this type of research, although she did not explicitly say Intellia was opposed to it. "When it comes to the germline, more discussion and rules are needed," she said.

An international debate

The growing global debate over human gene editing led to the US National Academy of Sciences (NAS) and National Academy of Medicine (NAM), along with the Chinese Academy of Sciences and the UK's Royal Society organising a summit in early December 2015 to further discuss the issue. Some 500 participants from around the world gathered in Washington,

DC for three days of presentations and deliberations on the associated scientific, ethical, legal, social and governance issues.[2]

Some of the arguments in favour of germline gene editing included:

- The positive impact on basic biological and biomedical research, namely understanding the mechanisms of action of genes, proteins and cells;
- The ability to change genes that cause inherited diseases;
- The capacity to modify variants that cause infertility; and
- The ability to alter genes to protect against diseases, e.g. those that cause heart disease.

There were also plenty of sceptics, who pointed out some of the potential downsides, for example:

- Many genetic diseases are not amenable to germ cell gene editing, including those caused by new mutations or chromosomal aneuploidies in germline cells;
- For common diseases that have genetic components (e.g. heart disease and cancer), many genes contribute to the disease and the expression of these genes is often related to an individual's environment and experiences;
- Genes typically have more than one function, so changing a gene to achieve a desired effect might also have negative consequences; and
- All humans carry some genetic variants that could cause harm in offspring and altering all of these variants would be impossible.

The meeting's organisers issued a final statement concluding that an inclusive, ongoing global conversation would be essential. A Royal Society spokesperson told *MedNous* that discussions were already under way for a follow-up summit, possibly to be held in China.

There was agreement that clinical use of germline gene editing should not be allowed unless and until the relevant safety and efficacy issues have been resolved and there is broad societal consensus about the suitability of any proposed application. Also, appropriate regulatory oversight would have to be in place, which it is not at present. However, the statement said that the clinical use of germline editing should be revisited on a regular basis, leaving the door open.

Regarding lab research involving germline gene editing, the statement says: "Intensive basic and preclinical research is clearly needed and should proceed, subject to appropriate legal and ethical rules and oversight, on (i) technologies for editing genetic sequences in human cells, (ii) the potential benefits and risks of proposed clinical uses, and (iii) understanding the biology of human embryos and germline cells. If, in the process of research, early human embryos or germline cells undergo gene editing, the modified cells should not be used to establish a pregnancy." Thus, there was no recommendation for a moratorium or ban on such research as some had hoped for.

What's next?

With the conclusion of the December 2015 summit, the NAS and NAM have moved into the second phase of their Human Gene Editing Initiative, which is a year-long study of the scientific underpinnings of human gene-editing technologies, their potential use in biomedical research and medicine, and the clinical, ethical, legal and social implications of their use.

To this end, a multidisciplinary committee of experts held a meeting on 11 February 2016 in Washington, DC to gather information for the study, and another public meeting will take place in Paris, France on 29 April 2016.

Following its in-depth independent review, the committee will release its findings and conclusions in a peer-reviewed consensus report, expected in late 2016. This will represent the official views of NAS and NAM.

Meanwhile, there are growing concerns about gene editing in non-human organisms. Matthew Cobb, professor of zoology at the University of Manchester in the UK, believes that the application of CRISPR technology to so-called 'gene drives' has much more far-reaching implications than that of human germline editing.

With gene drives, genetic modifications are intentionally and rapidly spread throughout a population of wild organisms. An example is the genetic modification of malaria-carrying mosquitoes to spread infertility, thus potentially eradicating the disease.

"The impact is huge and needs to be the subject of an informed debate," Dr Cobb told *MedNous*. "There are the same biological concerns about effectiveness as with human gene editing, but with wild organisms we need to consider how this would affect the ecosystem as a whole," he explained.

Pointing to increasing fears about the spread of the Zika virus, he noted that "it's being transmitted by invasive mosquito species; gene-altered mosquitoes could invade new ecosystems, too. It's too important an issue to leave up to scientists, even though they generally agree there needs to be an international consensus on a regulatory structure."

Currently, the application of gene drive technology to non-human organisms is being discussed by various organisations, including the NAS, which is due to publish a report later this year with recommendations on responsible conduct.[3] In the UK the Nuffield Council on Bioethics held a public consultation on this issue and on human germline editing for research purposes which closed on 1 February 2016.[4] The UK House of Lords Select Committee on Science and Technology is also looking into gene drives.[5]

References:

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