EDITORIAL

Live births following genome editing in human embryos: a call for clarity, self-control and regulation

Just hours away from the opening of the *Second International Summit on Genome Editing* in Hong Kong on 27 November 2018, and following a report in Technology Review (*Regaldo, 2018*), the Associated Press (*Marchione, 2018*) reported that a Chinese researcher, Dr Jiankui He, was claiming to have performed genome editing in human embryos, resulting in the birth of twin girls this month. Dr He maintains that he transferred embryos that had been edited to inactivate a gene called *CCR5*, a chemokine receptor, which, in its active state, forms a protein that allows HIV to enter a cell. The babies are reportedly healthy, but information is scattered and inconsistent, with no formal peer-review verification or published data accompanying the claims.

There is no doubt that adoption of germline editing for clinical use is far too premature, but perhaps it is not entirely surprising under the category of 'rogue science'. Despite doubts over the veracity of the claims, there is decent evidence to suggest that Jiankui He and his team have indeed edited embryos, and transferred the embryos to patients with the intention to establish pregnancy. This intent is cause for great concern. Many details are still lacking regarding the methods used and the validation protocols implemented to ensure the well being of the children. But what is clear is that safety was entirely overlooked in favour of the desire to be 'the first'. While much research has been done in this area, edited human embryos have not been investigated sufficiently for off-target editing effects, as the controversy surrounding a recent paper from the Mitalipov team has shown (Ma et al, 2017) where human embryos were corrected for a mutation in a gene called *MYBPC3*, which causes a condition known as hypertrophic cardiomyopathy. This work divided the field, as many believed there was insufficient evidence to prove the mutation had been fixed and by which cellular repair pathway.

How should we, the scientific community, respond to this act? Undoubtedly, we must ensure that improper use of this powerful technology, as appears to have been the case here, does not continue and that others are strongly, perhaps even forcefully, discouraged from following in the footsteps of Jiankui He. At the same time, there is a need to manage patient expectations for would-be therapies, which are certain to come. The scientific community at large has embraced the technology using animal models, is actively engaged in improving its various components, and has shown commitment to developing a full understanding of the underlying science. Yet, the alleged work of Jiankui He demonstrates a lack of respect for this process, and ignores known and unknown complexities and consequences of the application of this technology to the germline.

Genome editing technology, which has been harnessed from a bacterial immune system, has seen global uptake and expansion of research across all areas of biology and technology. The relative rate of discovery and 'problem solving' has therefore far surpassed any previous revolutionary tool. Biology being an unpredictable and fluid medium, one could pose the question whether gene editing will ever be fully safe for germline use, but only rigorous basic research can provide that answer.

The Jiankui team set out to transfer embryos whose genes were altered to withstand later infection by HIV. The decision to focus on a gene associated with a non-heritable disorder and a preventable and treatable disease is as surprising as it is indefensible. The research is not yet published, but trial data submitted as part of the human trial listing shows that genetic tests were to be carried out on the fetuses up to 24 weeks (or 6 months) gestation as well as throughout their lives, up to 18 years old.

Around 1 in 100 HIV patients are protected by a mutation, delta32, which occurs naturally in the population, and can confer innate resistance to HIV-1. Previously published work by Tsui et al (2018) used a method of genome editing called zinc finger nuclease (ZFN) technology to create this change in non-human primates. While they successfully edited these cells, the monkeys still needed anti-retroviral therapy to suppress infections as the percentage of *CCR5*-edited cells was too low to effect remission. Jiankui He claims that one twin carries both copies of the mutated *CCR5* gene and the other twin, only one copy but it is not yet known if this is due to mosaicism or whether she is heterozygous for the mutation. If the latter, then she will not have resistance to HIV.

A statement from the Southern University of Science and Technology (SUSTech) declares that Dr Jiankui He has been on unpaid leave since February 2018 (until January 2021). The University has expressed deep shock at the news and has taken immediate action for an emergency meeting of the Department Academic Committee. The preliminary statement from SUSTech states:

1 "The research was conducted outside of the campus and was not reported to the University nor the Department. The University and the Department were unaware of the research project and its nature.
2 The SUSTech Department of Biology Academic Committee believes that Dr Jiankui HE's conduct in utilizing CRISPR/Cas9 to edit human embryos has seriously violated academic ethics and codes of conduct.

3 All research conducted at SUSTech is required to abide by laws and regulations, and comply with international academic ethics and codes of conduct. The University will call for international experts to form an independent committee to investigate this incident, and to release the results to the public."

The rationale for hosting a genome-editing summit in China was partly to facilitate revelations regarding the current status of such research in the region and to understand what 'evidence of safety' means to researchers. Contrary to common assumption, ethical and legislative frameworks do exist in China for research in embryos but, in this instance, it is assumed that documents may have been forged. Earlier this year, a newer form of genome editing called 'base editing' was used to correct the mutation that causes Marfan syndrome in IVF embryos, which were not intended for transfer. The Chinese government has supported research led by Xingxu Huang, who spoke at the summit (*Liu et al, 2018, Zeng et al., 2018*). In the UK and the USA, it is illegal to implant genome-edited human embryos. Indeed, in the USA, any government-supported pre-clinical research with human zygotes and embryos is prohibited, but a National Academy of Science (NAS) Report commissioned by the Food and Drug Administration (FDA) and published in 2016, advised in favour of applying cytoplasmic donation in women at risk for transmitting mitochondrial disease. In the UK, following a 2-year investigation and call for evidence from scientists, ethicists, policy-makers and the public, the *Nuffield Council on Bioethics (2018)* released its report on 'Human Genome Editing and Human Reproduction', which goes further than the NAS report, stating that they found no categorical moral objection to germline genome editing. However, importantly, the report set out principles upon which the technology might be permitted in some circumstances. The news from China highlights the urgency in setting a legal framework that allows for research to pave a path toward application of gene editing in the context of ART while exercising the highest standards of clinical safety, but that prevents the adoption of the technology by any clinics except through a robust and rigorous licencing process.

It is yet to be seen what impact this act will have on research efforts of the scientific community at large, but there is hope that the actions of one do not hamper the efforts of others.

REFERENCES

Marchione, M. **Chinese researcher claims first gene-edited babies.** Associated Press 2018. https://www.apnews.com/4997bb7aa36c45449b488e19ac83e86d

Regaldo, A. **Exclusive: Chinese scientists are creating CRISPR babies.** MIT Technology Review 2018. https://www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/

Liu, Z., Lu, Z., Yang, G., Huang, S., Li, G., Feng, S., Liu, Y., Li, J., Yu, W., Zhang, Y., Chen, J., Sun, Q., Huang, X. **Efficient generation of mouse models of human diseases via ABE- and BE-mediated base editing.** Nat Commun. 14 2018; 9: 2338

Nuffield Council on Bioethics. **Genome editing and human reproduction: social and ethical issues** 2018**.** http://nuffieldbioethics.org/project/genome-editing-human-reproduction

Zeng, Y., Li, J., Li, G., Huang, S., Yu, W., Zhang, Y., Chen, D., Chen, J., Liu, J., Huang, X. **Correction of the Marfan Syndrome Pathogenic FBN1 Mutation by Base Editing in Human Cells and Heterozygous Embryos.** Molecular therapy: the journal of the American Society of Gene Therapy 2018; 26: 2631–2637

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