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Sorcerer's apprentices at work

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Abstract

Heritable human genetic modifications pose serious risks, and the therapeutic benefit still dubious. Therefore, there are concerns regarding the ethical and safety implications of this research as well as the negative impact it could have on studies involving the use of genome-editing techniques in non-reproductive (somatic) cells.

Keywords: academic research; public-health research; commercial research; medical research; advancement of learning

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1. A troubling announcement

He Jiankui, a molecular biologist from the Southern University of Science and Technology of China in Shenzhen, claimed that he implanted an embryo that had been edited to disable the genetic pathway that allows a cell to be infected with HIV. For such a purpose, he used a CRISPR-Cas9 genome-editing tool to modify the CCR5 gene, which forms a protein that allows HIV to enter a cell.

The Chinese scientist presented the data at the Second International Summit on Human Genome Editing in Hong Kong on November 28. However, he provided few useful information about the procedure, keeping much of his research secret in pursuit of a larger goal. In doing so, He took advantage of the loosely worded and irregularly enforced regulations and generous funding available today in China while skirting local protocols and possibly laws. He's ambitions appear to be in line with prevailing social attitudes in China, including the idea that the larger communal good can transcend ethical principle and even shared international rules.

He's presentation appears to have done little to allay strong condemnation from other researchers in the field, who allege that his work breaches ethical and scientific norms. As a consequence, scrutiny of He's research methods has also grown, with China's National Health Commission requesting an investigation.

2. Main questions

This event raises two main questions.

1) Did CRISPR technique really 'edit' the genome? Because Results and Methods have yet to be published, and we can only 'retrace' how the experiments may have been done. From He's presentation we infer that the twins cells harbor multiple edited versions of the CCR5 gene, with different-size DNA deletions. Such 'mosaicism' can be caused when CRISPR edits some early embryo cells differently to others, or fails to edit some. He claimed he targeted the CCR5 gene because some people naturally carry a mutation in CCR5 — a 32-DNA-letter deletion known as delta-32 — that inactivates the gene. However, the CCR5 deletions that He claims to have introduced by CRISPR gene editing are not identical to the delta-32 mutation. Sean Ryder, a RNA scientist commented that "The point is that none of the three match the well-studied delta 32 mutation, and as far as I can tell, none have been studied in Indeed, it has long been known that CRISPR techniques

may lead to unwarranted outcomes. Studies using gene-editing methodologies in different animals indicate that it is possible to delete or disable genes in an embryo in only some of the cells. Others opined that "The current ability to perform quality controls on only a subset of cells means that the precise effects of genetic modification to an embryo may be impossible to know until after birth. Even then, potential problems may not surface for years" (Lanphier et al., 2018). As recognized by He himself, there was evidence of mosaicism in both embryos, as some cells carry the edited gene while others carry the original. During his talk, He also recalled that in one embryo, there was evidence of a possible "off target" effect, namely, a wrong spot was targeted by the molecular tools that scientists use for genome editing, thus altering genes that the researchers did not mean to change.

Ultimately, the current ability to perform quality controls on only a subset of cells means that the precise effects of genetic modification to an embryo may be impossible to know until after birth. Even then, potential problems may not surface for years. It is unclear what the possible off-target alteration could mean for the twins' health. The girls themselves could be fine, but future generations might suffer from unexpected, collateral effects. Off-target effects could happen anywhere along these (added) molecules, so they would be hard to detect. Namely, we should be concerned that the CCR5 gene, thought to enable the HIV virus to sneak into cells, is – paradoxically – proven to protect the lungs, liver and brain during some other serious infections and chronic diseases, like West Nile virus disease or encephalitis. Indeed, people without a functional CCR5 gene are four times more likely than those with the gene to develop these serious conditions (Lim et al., 2011; Pulendran et al., 2008). Overall, the chemokine receptor CCR5 plays a key role in the early memory CD8+ T cell response, thus improving a critical step in immunity activation (Kohlmeier et al., 2008). Are we sure that the cell can efficiently cope with non-HIV infection without that gene? I am wondering if these effects seems have been communicated to the parents of the girls. We can suppose that it did not happen .

Established methods, such as standard prenatal genetic diagnostics or in vitro fertilization (IVF) with the genetic profiling of embryos before implantation, are much better options for parents who both may carry the same mutation for a disease. Moreover, this experiment exposes healthy normal children to risks of gene editing for no real necessary benefit, given that reliable, pharmacological alternatives do exist for preventing HIV infection in newborns. Evidently, this specific issue cause "regret and concern over the fact that gene editing—a powerful and useful technique—was put to use in a setting where it was unnecessary. Indeed, studies are already under way to edit the same gene in the bodies of adults with HIV" . Finally, even if the editing might have worked allowing the twins carrying the edited genes in their cells, it is unclear whether those modifications will do them any good. Therefore, it is nearly impossible to validate if they work in the real world.

2) Are there unmet ethical concerns? More than 100 Chinese biomedical researchers have posted a strongly worded statement online condemning He's experiment. "Directly jumping into human experiments can only be described as crazy," the statement reads. These scientists have asked Chinese authorities to investigate the case and introduce strict regulations on this procedure. The question is a rather simple one, namely, Should scientists do what they actually can do?

CRISPR-based editing experiment brings forward core ethical questions, questions that will need to be addressed carefully to avoid the potential for catastrophic missteps. Key to all discussion and future research is making a clear distinction between genome editing in somatic cells and in germ cells. A voluntary moratorium in the scientific community could be an effective way to discourage human germline modification and raise public awareness of the difference between these two techniques.

Yet, it is not only a matter of 'technical efficiency. We are facing the possibility that unpredictability genetic changes can be introduced, and transmitted to the progeny, and, ultimately, to humankind. Moreover, projects to obtain genetically tailored humans - the post-modern version of eugenics - are emerging from the mists of the dream (or is it a nightmare), becoming reality.

3. Can we be worried?

As other scientists concluded, this experiment "is premature, dangerous and irresponsible".

This is not science. This development appears as an updated, modern version of the old famed story of Frankenstein. Thereby, is even too easy recalling what has been wrote some time ago,

> Revolutionary man perform experiments with everything, from the juxtaposition of words (as in surrealism) to the new uses of dialectics, science and the rearrangement of political institutions. [...]

> At the heart of the revolutionary philosophy, is the firm conviction that man is the master of himself, not subject to any order or human nature, and that he is free playing with elements at his disposal or by itself invented.

That is the point. We are moving in the darkness, on a land littered with dangers. However, can we really afford it?

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