THE ETHICS OF GERMLINE THERAPY

CRISPR babies
Is it acceptable to genetically modify embryos?

By Martin Lindner

Using sophisticated 'molecular scissors', we can, in principle, now make specific changes to an embryo's genetic material. However, any such changes would not just affect the child that develops from that embryo – they would also affect all of that child's descendants. In 2018, a Chinese researcher claimed to have carried out the first ever germline therapy intervention in humans – sparking a huge furor. What purpose would modifying the embryonic genome serve? And what about the ethical issues?

Lulu and Nana

It's a real-life scientific thriller. In November 2018, Chinese researcher He Jiankui announced the birth of twin sisters who he claimed to have genetically modified as embryos while still in a Petri dish. The two girls are believed to be the first babies in the world to have had their germline genetic material deliberately modified. The girls were nicknamed "Lulu" and "Nana".

In a talk at an international conference in Hong Kong, He stated that his goal had been to make the children resistant to HIV. During the IVF process, He had used gene-editing techniques on the developing embryos to modify a cell receptor called CCR5. This receptor is used by HIV to get into somatic cells, and people with specific mutations in this receptor gene are immune to most strains of the virus.

The case made headlines worldwide. Instead of publishing it in a peer-reviewed scientific journal – the usual practice among scientists – He announced the birth of Lulu and Nana on YouTube. He emphasized that HIV-positive people suffer discrimination in many countries, and that his experiments represent a major scientific breakthrough. The case unleashed a storm of protest.

A Brave New World? Gene editing and what happened next

The tool He used is known as CRISPR/Cas9. It has been compared to molecular scissors. CRISPR/Cas9 is an enzyme complex which can be used to easily modify specific genes and remove existing or insert new stretches of DNA. The process is sometimes referred to as gene editing or genome engineering. CRISPR/Cas9 is already used in plant breeding and for genetically modifying animals in the laboratory. There are, however, technical complications to its use. The technique can result in only some of an embryo's calls being genetically modified. This is known as mosaicism. In addition, unintended mutations away from the target gene (known as off-target effects) can also sometimes occur, giving rise to unforeseen risks.

And the gene editing process in Lulu and Nana was indeed only partially successful. It remains unclear what the consequences of this will be for the two girls. Researchers worldwide accused He and his team – which included his American doctoral supervisor – of being irresponsible in their use of what remains an immature technology.

He's experiments make a mockery of the international consensus that, as things stand today, researchers should not be using gene editing techniques in the context of fertility treatment. Furthermore, He did not properly inform his own university what he was up to and did not properly brief the couple involved. Shortly after his lecture in Hong Kong, the Chinese authorities suspended He's research activities, and in late 2019 sentenced him to three years in prison and a substantial fine. By then, in addition to Lulu and Nana, this unique set of experiments had also resulted in the birth of a third CRISPR baby.

The ethical debate – is it acceptable to modify someone's genetic inheritance?

Is it acceptable to genetically modify human embryos? Assuming it proved possible at some future date to resolve the scientific uncertainties around the process, could gene editing be ethically acceptable in some circumstances? A key point in the debate is that genetically modifying an early embryo doesn't just affect the child that develops from that embryo. The modifications will also be passed on to all of that child's descendants via the child's germ cells (egg cells or sperm). Changes to germline cells affect a person's genetic inheritance. The issue of the ethics of germline modification is highly controversial. Points of view include the following:

» **As a matter of principle, gene editing in embryos should be prohibited entirely:**
A developing embryo and its potential descendants are possessed of an intrinsic dignity and identity. Its genome should be sacrosanct. This point of view may be motivated by respect for the principles of human life or by religious conviction.

» **Germline therapy is acceptable where the benefits clearly outweigh the risks:**
Future gene editing techniques could be used to help prevent serious genetic disorders such as cystic fibrosis, hereditary breast cancer, or Huntington's disease (a progressive, degenerative brain condition which causes locomotor problems). As long as the risks are controllable, prohibiting the use of such therapies would be unethical. Doctors in particular often tend towards this view. It is frequently bound up with a conviction that genome editing should only be used for treating or preventing disease, and not for genetic "enhancement", e.g. for enhancing intelligence. It should also be noted that genetic modification of an embryo is always carried out in the context of IVF, which carries its own risks.

» **There are usually alternatives to germline therapy available, rendering it unnecessary:**
Some genetic defects can also be treated after a child is born – for example, using gene therapy which targets the relevant somatic cells (somatic gene therapy). In addition, using preimplantation genetic diagnosis (PGD), it is possible to identify embryos with serious genetic diseases prior to implantation, and these embryos can then be discarded. But PGD is of no help where both parents suffer from cystic fibrosis, for example, since all of the couple's embryos will also have the disease. In rare cases like this, gene editing would enable such couples to have a healthy child who is biologically theirs.

» **Genetically modified babies harm society, as they create an impression that illness and disability are abnormal and are something to be prevented:**
This argument comes up in the context of various debates in the reproductive medicine field, for example in the debate revolving around PGD. It is raised in particular by organizations representing disabled people, as well as other critical voices. They are concerned that people with genetic defects will suffer discrimination.

» **Parents should be able to decide for themselves:**
On the other hand, parental freedom of choice –

reproductive autonomy – is also of high value Advocates of this position often cite the rights of the individual in a liberal society.

Genetically modified embryos in research

Whether germline modification will eventually become established medical practice remains unclear. Researchers nonetheless continue to look for ways to develop these techniques further and to minimize the risks involved. One approach to doing so is to genetically modify laboratory animals, breed several generations of offspring and see if any long-term effects are observable.

In some places research is also being conducted on spare human embryos that are not destined to be implanted to produce a pregnancy. A team from the Francis Crick Institute in London, for example, is editing the genome of embryos left over from IVF and studying them in the lab for a period of one week. Their research is aimed at enhancing our understanding of how genes control early embryonic development. Similarly, researchers from Oregon Health and Science University in the US are exploring the possibility of correcting inherited heart diseases in the embryo.

This kind of research is not without controversy. Although it will not result in the birth of genetically modified babies, such research nonetheless involves the 'consumption' of human embryos for the purpose of research. In Germany, the Embryo Protection Act (Embryonenschutzgesetz) prohibits all such research.

Changing values – technology, culture, and society

In the 1990s, the boom in genetic research and the development of techniques for cloning animals – and theoretically therefore humans – led to international agreements aimed at protecting human genetic material. The Council of Europe's Bioethics Convention, for example, permits genetic modification only where it will not modify the genome of subsequent generations in any way – effectively banning germline therapy.

Views on gene editing techniques have altered significantly in recent years, particularly in response to newer, more precise techniques such as CRISPR/Cas9. But if something was wrong yesterday, can it be right today? Or do ethical judgments always depend on the extent to which a technology is viewed as normal by the population? It's certainly true that bioethical questions – and with them our understanding of what it is to be human – are subject to constant debate and renegotiation.

In 2018, for example, an online survey in the Netherlands found that, in principle, many people would be open in principle to the idea of using gene editing to protect their descendants (who can't be asked for their consent) from, for example, an inherited neuromuscular disease. Naturally, the results from surveys like this will vary from country to country, even within Europe. What would such a survey find in Germany? There are also differences between different religions. While the Catholic Church, for example, traditionally objects vigorously to all reproductive technologies, Islam tends to be much more relaxed about these things. That was the finding of a 2020 research project on gene editing by Malaysian scientists. Provided that there are clear rules to prevent abuse and protect human dignity, their research found that CRISPR babies may be entirely compatible with the Islamic world view.

Three-parent babies – the special case of mitochondrial donors

The availability of fertility treatments has also given rise to a further genetic engineering scenario – the creation of children with three genetic parents. In some rare inherited disorders affecting the brain or muscles, the problem lies, not in the genes found in the cell nucleus, but in a mutation in the mitochondria. Mitochondria – the powerhouses of the cell – have their own DNA. Because mitochondria are passed on to the embryo in the egg cell (and not or only to a very small extent in sperm), mitochondrial defects are inherited exclusively from the mother.

During IVF, genetic material from the mother and father can be transferred into an egg cell from a healthy donor from which the nucleus has been removed. The technique is also known as mitochondrial donation. This produces an embryo with the parents' genetic material in the cell nucleus, and around three dozen mitochondrial genes from the egg donor. These mitochondrial genes are important for energy metabolism.

The first three-parent baby produced using this technique was born in April 2016. The baby was a healthy boy born to a Jordanian couple following mitochondrial transfer performed by US doctors at a clinic in Mexico. Many scientists internationally have reservations about this technique, and it remains illegal in Germany. In the UK, by contrast, following extensive debate around serious illnesses, it has been legalized.

Surprisingly, in the UK mitochondrial donation is not classified as germ line therapy. This is despite the fact that girls born using this technique will pass the donor mitochondrial genes on to their own children. Today, it might even be possible to treat mitochondrial mutations using CRISPR/Cas9 gene editing techniques similar to those used with Lulu and Nana, rather than through egg donation.

About the lesson series "Understanding Stem Cells - The Conference for Schools"

In this four-part series of lessons, the German Stem Cell Network and the Ernst Schering Foundation provide teachers with fact-checked knowledge about stem cells. The freely usable material allows students from 14 years onwards to actively immerse themselves in current research. The scientific experts at the German Stem Cell Network ensure the technical and professional quality of the material.The Schering Foundation uses its experience in science education to introduce young adults to current research topics using new methods and to encourage their interest in science. This material is available online at: http://www.understanding-stemcells.info

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