NEWS IN FOCUS

Molecular biologist Denis Rebrikov is planning controversial gene-editing experiments in women diagnosed with HIV.

GENE EDITING

Russian biologist plans more CRISPR-edited babies

The proposal follows the birth of twins from embryos edited by a Chinese scientist last year.

BY DAVID CYRANOSKI

A Russian scientist says he is planning to produce gene-edited babies, an act that would make him only the second person known to have done this. It would also fly in the face of the scientific consensus that such experiments should be banned until an international ethical framework has been agreed on the circumstances and safety measures that would justify them.

Molecular biologist Denis Rebrikov has told *Nature* that he is considering implanting gene-edited embryos into women, possibly before the end of the year if he can get approval by then. Chinese scientist He Jiankui prompted an international outcry when he announced last November that he had made the world's first gene-edited babies — twin girls.

The experiment will target the same gene, called *CCR5*, as He did, but Rebrikov claims his technique will offer greater benefits, pose fewer risks and be more ethically acceptable to the public. Rebrikov plans to disable the gene, which encodes a protein that allows HIV to enter cells, in embryos that will be implanted into women who have been diagnosed with HIV, reducing the risk of them passing on the virus to the baby *in utero*. By contrast, He modified the gene in embryos from fathers with HIV, which many geneticists said provided little clinical benefit because the risk of a father passing on HIV to his children is minimal.

Rebrikov heads a genome-editing lab at Russia's largest fertility clinic, the Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology in Moscow. He is also a researcher at the Pirogov Russian National Research Medical University in Moscow. ▶

According to Rebrikov, he already has an agreement with an HIV centre in the city to recruit women infected with HIV who want to take part in the experiment.

But scientists and bioethicists contacted by *Nature* are troubled by Rebrikov's plans.

"The technology is not ready," says Jennifer Doudna, a molecular biologist at the University of California, Berkeley, who pioneered the CRISPR–Cas9 genome-editing system that Rebrikov plans to use. "It is not surprising, but it is very disappointing and unsettling."

Alta Charo, a researcher in bioethics and law at the University of Wisconsin–Madison says Rebrikov's plans are not an ethical use of the technology. "It is irresponsible to proceed with this protocol at this time," adds Charo, who sits on a World Health Organization (WHO) committee that is formulating ethical governance policies for human genome editing.

LEGAL UNCERTAINTY

The implanting of gene-edited embryos is banned in many countries. Russia has a law that prohibits genetic engineering in most circumstances, but it is unclear whether or how the rules would be enforced in relation to gene editing in an embryo.

Rebrikov expects the health ministry to clarify the rules on the clinical use of gene-editing of embryos in the next nine months. Rebrikov says he feels a sense of urgency to help women with HIV, and is tempted to proceed with his experiments even before Russia hashes out regulations.

To reduce the chance that he would be punished, Rebrikov plans first to seek approval from three government agencies, including the health ministry. That could take anywhere from one month to two years, he says.

George Daley, a geneticist at Harvard Medical School in Boston, Massachusetts, who also heard about Rebrikov's plans from *Nature*, says that before any scientist attempts to implant gene-edited embryos into women, there needs to be a transparent, open debate about scientific feasibility and ethical permissibility.

One reason that gene-edited embryos have created a huge global debate is that, if they are allowed to grow into babies, the edits can be passed on to future generations — a far-reaching intervention known as altering the germ line. Researchers agree that the technology might, one day, help to eliminate genetic diseases such as sickle-cell anaemia and cystic fibrosis, but much more testing is needed before it is used to alter human beings.

In the wake of He's announcement, many scientists renewed calls for an international moratorium on germline editing. Although that has yet to happen, the WHO and other prominent organizations have discussed how to stop genome editing in humans that poses unnecessary or excessive risks.

"It is irresponsible to proceed with this protocol at this time."

Although He was criticized for conducting his experiments using sperm from men with HIV, his argument was that he just wanted to protect people from the infection. But researchers countered that there are other ways to decrease the risk of infection, such as contraceptives. There are also ways to prevent maternal transmission of HIV, says Charo.

Rebrikov agrees, and plans to implant embryos only into a subset of mothers with HIV who do not respond to standard treatment and have an increased risk of transmitting the infection to their child. If editing disabled the *CCR5* gene, that risk would be greatly reduced, Rebrikov says. "This is a clinical situation which calls for this type of therapy," he says.

Most scientists say that even so, there is no justification for editing the *CCR5* gene in embryos, because the risks don't outweigh the benefits. Even if the therapy goes as planned, and both copies of the *CCR5* gene in cells are disabled, there is still a chance that such babies could become infected with HIV. The cell-surface protein encoded by *CCR5* is thought to be the gateway for some 90% of HIV infections, but getting rid of it won't affect other routes of infection.

There are also concerns about the safety of gene editing in embryos more generally.

One big concern about He's experiment — and other such research — is that CRISPR–Cas9 can cause unintended 'off-target' mutations away from the target gene, and that these could be dangerous if, for instance, they switched off a tumour-suppressor gene. But Rebrikov says that he is developing a technique that can ensure that there are no off-target mutations; he plans to post preliminary findings online within a month, possibly on the preprint server bioRxiv.

Scientists contacted by *Nature* were sceptical that such assurances could be made about off-target mutations, or about another known challenge of using CRISPR–Cas9 — 'on-target mutations', in which the correct gene is edited, but not in the way intended.

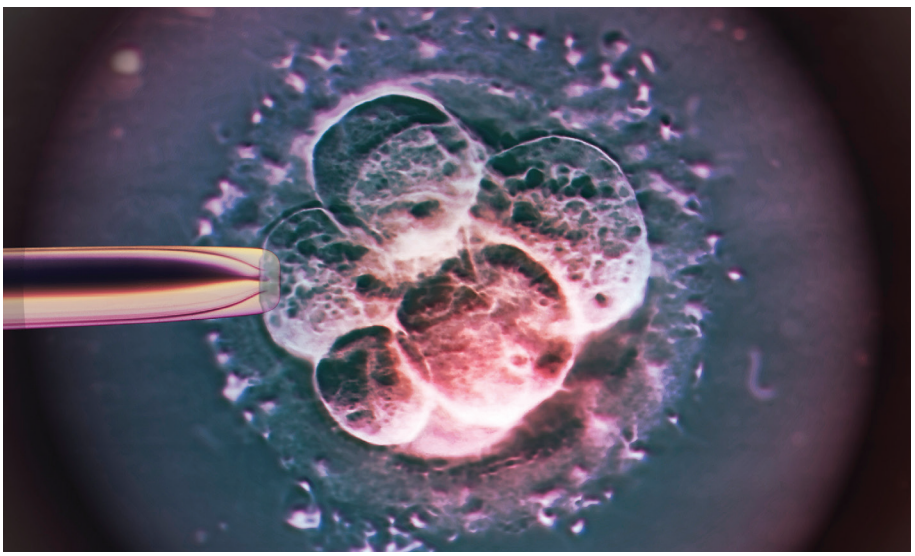
Rebrikov wrote in a paper published last year in the *Bulletin of the Russian State Medical University*, of which he is editor-in-chief, that his technique disables both copies of the *CCR5* gene more than 50% of the time (T. A. Kodyleva *et al. Bull. Russ. State Med. Univ.* http://doi.org/c642; 2018). He says publishing in this journal was not a conflict of interest because reviewers and editors are blinded to a paper's authors.

But Doudna is sceptical of his results. "The data I have seen say it's not that easy to control the way the DNA repair works," she says. Geneticist Gaetan Burgio at the Australian National University in Canberra also thinks that the edits probably led to other deletions or insertions that are difficult to detect, as is often the case with gene editing.

Misplaced edits could mean that the gene isn't properly disabled, and so the cell is still accessible to HIV, or that the mutated gene could function in a completely different and unpredictable way. "It can be a real mess," says Burgio.

What's more, unmutated *CCR5* has many functions that are not yet well understood, but which offer some benefits, say scientists critical of Rebrikov's plans. For instance, it seems to offer some protection against major complications following infection by the West Nile virus or influenza. "We know a lot about its role in HIV entry, but we don't know much about its other effects," says Burgio. A study published last week also suggested that people without a working copy of *CCR5* might have a shortened lifespan (X. Wei & R. Nielsen *Nature Med.* **25**, 909–910; 2019).

Rebrikov understands that if he proceeds with his experiment before Russia's updated regulations are in place, he might be considered a second He Jiankui. But he says he will only do so if he's sure of the safety of the procedure. "I think I'm crazy enough to do it," he says. ■



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Embryos for implantation into humans cannot legally be edited in many countries.