NATURE | NEWS

Chinese scientists genetically modify human embryos

Rumours of germline modification prove true — and look set to reignite an ethical debate.

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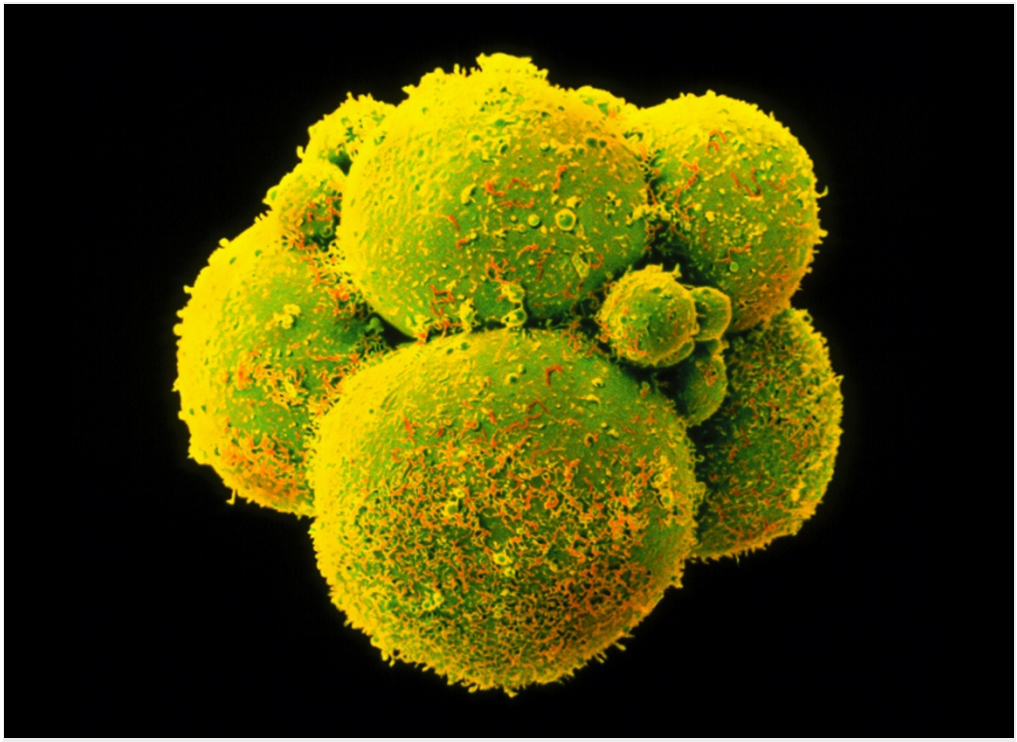


Dr. Yorgos Nikas/SPL

Human embryos are at the centre of a debate over the ethics of gene editing.

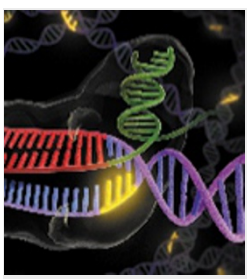
In a world first, Chinese scientists have reported editing the genomes of human embryos. The results are published[1] in the online journal *Protein & Cell* and confirm widespread rumours that such experiments had been conducted — rumours that sparked a high-profile debate last month[2, 3] about the ethical implications of such work.

In the paper, researchers led by Junjiu Huang, a gene-function researcher at Sun Yat-sen University in Guangzhou, tried to head off such concerns by using 'non-viable' embryos, which cannot result in a live birth, that were obtained from local fertility clinics. The team attempted to modify the gene responsible for β-thalassaemia, a potentially fatal blood disorder, using a gene-editing technique known as CRISPR/Cas9. The researchers say that their results reveal serious obstacles to using the method in medical applications.

"I believe this is the first report of CRISPR/Cas9 applied to human pre-implantation embryos and as such the study is a landmark, as well as a cautionary tale," says George Daley, a stem-cell biologist at Harvard Medical School in Boston, Massachusetts. "Their study should be a stern warning to any practitioner who thinks the technology is ready for testing to eradicate disease genes."

Some say that gene editing in embryos could have a bright future because it could eradicate devastating genetic diseases before a baby is born. Others say that such work crosses an ethical line: researchers warned in *Nature*[2] in March that because the genetic changes to embryos, known as germline modification, are heritable, they could have an unpredictable effect on future generations. Researchers have also expressed concerns that any gene-editing research on human embryos could be a slippery slope towards unsafe or unethical uses of the technique.

The paper by Huang's team looks set to reignite the debate on human-embryo editing — and there are reports that other groups in China are also experimenting on human embryos.



***Nature* special: CRISPR**

Problematic gene

The technique used by Huang's team involves injecting embryos with the enzyme complex CRISPR/Cas9, which binds and splices DNA at specific locations. The complex can be programmed to target a problematic gene, which is then replaced or repaired by another molecule introduced at the same time. The system is well studied in human adult cells and in animal embryos. But there had been no published reports of its use in human embryos.

Huang and his colleagues set out to see if the procedure could replace a gene in a single-cell fertilized human embryo; in principle, all cells produced as the embryo developed would then have the repaired gene. The embryos they obtained from the fertility clinics had been created for use in *in vitro* fertilization but had an extra set of chromosomes, following fertilization by two sperm. This prevents the embryos from resulting in a live birth, though they do undergo the first stages of development.

Huang's group studied the ability of the CRISPR/Cas9 system to edit the gene called *HBB, w*hich encodes the human β-globin protein. Mutations in the gene are responsible for β-thalassaemia.

Serious obstacles

The team injected 86 embryos and then waited 48 hours, enough time for the CRISPR/Cas9 system and the molecules that replace the missing DNA to act — and for the embryos to grow to about eight cells each. Of the 71 embryos that survived, 54 were genetically tested. This revealed that just 28 were successfully spliced, and that only a fraction of those contained the replacement genetic material. "If you want to do it in normal embryos, you need to be close to 100%," Huang says. "That's why we stopped. We still think it's too immature."

His team also found a surprising number of 'off-target' mutations assumed to be introduced by the CRISPR/Cas9 complex acting on other parts of the genome. This effect is one of the main safety concerns surrounding germline gene editing because these unintended mutations could be harmful. The rates of such mutations were much higher than those observed in gene-editing studies of mouse embryos or human adult cells. And Huang notes that his team likely only detected a subset of the unintended mutations because their study looked only at a portion of the genome, known as the exome. "If we did the whole genome sequence, we would get many more," he says.

Ethical questions

Huang says that the paper was rejected by *Nature* and *Science*, in part because of ethical objections; both journals declined to comment on the claim. (*Nature*'s news team is editorially independent of its research editorial team.)

He adds that critics of the paper have noted that the low efficiencies and high number of off-target mutations could be specific to the abnormal embryos used in the study. Huang acknowledges the critique, but because there are no examples of gene editing in normal embryos he says that there is no way to know if the technique operates differently in them.

Still, he maintains that the embryos allow for a more meaningful model — and one closer to a normal human embryo — than an animal model or one using adult human cells. "We wanted to show our data to the world so people know what really happened with this model, rather than just talking about what would happen without data," he says.

But Edward Lanphier, one of the scientists who sounded the warning in *Nature* last month, says: "It underlines what we said before: we need to pause this research and make sure we have a broad based discussion about which direction we're going here." Lanphier is president of Sangamo BioSciences in Richmond, California, which applies gene-editing techniques to adult human cells.

Huang now plans to work out how to decrease the number of off-target mutations using adult human cells or animal models. He is considering different strategies — tweaking the enzymes to guide them more precisely to the desired spot, introducing the enzymes in a different format that could help to regulate their lifespans and thus allow them to be shut down before mutations accumulate, or varying the concentrations of the introduced enzymes and repair molecules. He says that using other gene-editing techniques might also help. CRISPR/Cas9 is relatively efficient and easy to use, but another system called TALEN is known to cause fewer unintended mutations.

The debate over human embryo editing is sure to continue for some time, however. CRISPR/Cas9 is known for its ease of use and Lanphier fears that more scientists will now start to work towards improving on Huang's paper. "The ubiquitous access to and simplicity of creating CRISPRs," he says, "creates opportunities for scientists in any part of the world to do any kind of experiments they want."

A Chinese source familiar with developments in the field said that at least four groups in China are pursuing gene editing in human embryos.

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References

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2. Lanphier, E. *et al*. *Nature* **519**, 410–411 (2015).
3. Baltimore, D. *et al*. *Science* **348**, 36–38 (2015).