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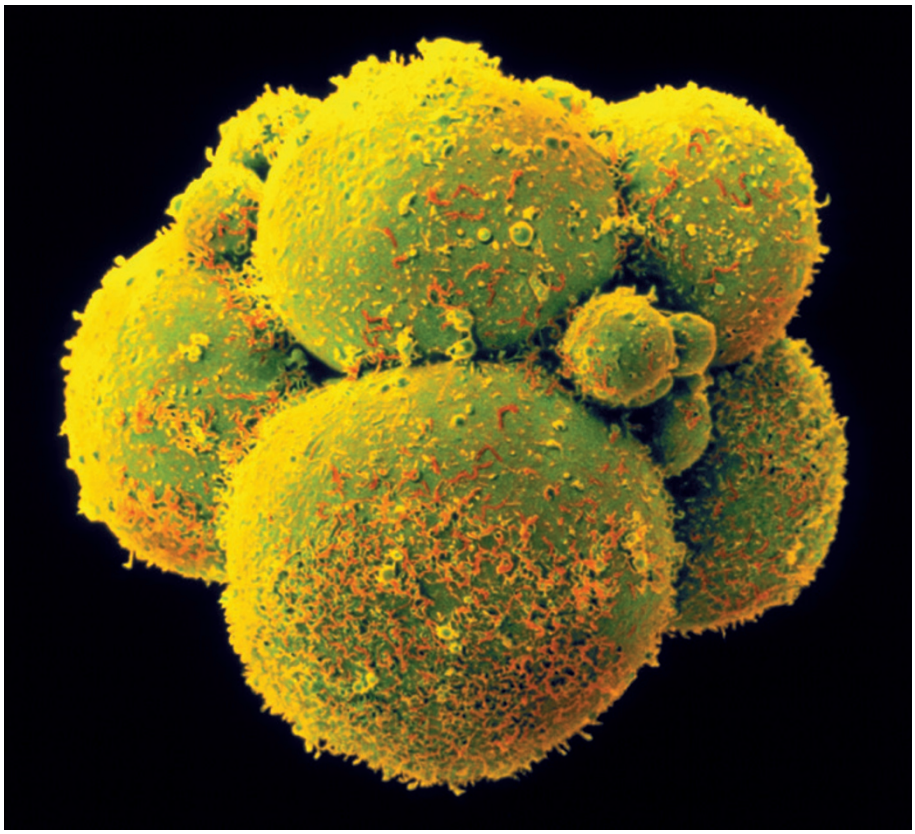

Human embryos are at the centre of a debate over the ethics of gene editing.

GENETIC MODIFICATION

Embryo editing sparks epic debate

In wake of paper describing genetic modification of human embryos, scientists disagree about ethics.

BY DAVID CYRANOSKI AND SARA REARDON

In a world first, Chinese scientists have reported that they have used powerful gene-editing techniques to modify human embryos. Their paper[1], published in the Beijing-based journal *Protein & Cell* on 18 April, came as no surprise to the scientific community, but it has ignited a wide-ranging debate about what types of gene-editing research are ethical. The publication also raises questions about the appropriate way to publish such work (see 'Publishing policy').

In the paper, researchers led by Junjiu Huang, a gene-function researcher at Sun Yat-sen University in Guangzhou, describe how they used a system of molecules called CRISPR/Cas9, known for its ease of use, to cut DNA in human embryos and then attempted to repair it by introducing new DNA.

In a deliberate attempt to head off ethical concerns, the team used non-viable embryos obtained from fertility clinics, in which eggs had been fertilized by two sperm and so could not result in a live birth.

Gene-editing techniques such as those that rely on CRISPR/Cas9 had previously been used to modify DNA in adult human cells and animal embryos. Earlier this year, rumours were circulating that the methods were being applied in human embryos too, but the Huang paper is the first published report of this.

The team used CRISPR/Cas9 to modify a gene that can cause a potentially fatal blood disorder called β-thalassaemia when it is mutated. Some researchers have suggested that such a procedure, if done in a viable embryo, could eradicate devastating genetic diseases before a baby is born. Others say that such work crosses an ethical line: in response to the rumours that the work was being carried out, researchers warned in *Nature*[2] and *Science*[3] in March that because the genetic changes to embryos — a procedure 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 in human embryos could be a slippery slope towards unsafe, unethical or non-medical uses of the technique.

SERIOUS OBSTACLES

Huang's team says that its results reveal serious obstacles to using the method in a clinical setting. The team injected 86 embryos with CRISPR/Cas9, along with other molecules designed to add in new DNA. The researchers then waited 48 hours, by which time the embryos would have grown 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 4 of those contained the genetic material designed to repair the cuts. "That's why we stopped," says Huang. "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. The effect is one of the main safety concerns surrounding ▶

PUBLISHING POLICY

Gene editing poses challenges for journals

Amid the discussion generated by a paper that reports gene editing in human embryos, the process behind its publication has also aroused curiosity.

Lead author Junjiu Huang of Sun Yat-sen University in Guangzhou, China, says that the paper, published on 18 April in the Beijing-based online journal *Protein & Cell*, was rejected by *Nature* and *Science*, in part because of ethical objections. Both journals keep details of their review processes confidential (*Nature*'s news team is editorially independent of its research editorial team), but acknowledge that gene-editing of human embryos is a complicated issue for them.

"This is a rapidly evolving and complex area for which we cannot — and should not — easily offer simplistic policies," says Ritu Dhand, editorial director for *Nature*. Nature Publishing Group is consulting with a range of experts to develop a "progressive policy" on the issue, she says.

Science, meanwhile, told *Nature*'s news team: "We believe strongly that the potential of genome editing must be viewed in terms of social mores and that the path forward must be developed through a consensus-building process."

The editors of *Protein & Cell* say that they published the paper to "sound an alarm" about such work. "In this unusual situation, the editorial decision to publish this study should not be viewed as an endorsement of this practice nor an encouragement of similar attempts," wrote Xiaoxue Zhang, managing editor at *Protein & Cell*, in an editorial published on 28 April (X. Zhang *Protein Cell* http://doi.org/35n; 2015). "We had serious discussion about the ethics of this issue," adds the journal's editor-in-chief, Zihe Rao. "We expected there might be difference of opinions, but it needs to be published to start discussion."

Springer, the publisher of *Protein & Cell*, confirmed that the journal had checked the researchers' institutional approval and the consent forms from the embryo donors. They also confirmed that the study was compliant with the Helsinki declaration on human-medical-research ethics and with Chinese law.

The paper sped through *Protein & Cell*'s review process: it was submitted on 30 March and accepted on 1 April. A spokesperson for Springer said that the paper was submitted with peer-review comments from *Nature* and *Science* and that the authors had made revisions on the basis of these, which facilitated the fast review. Another round of peer review was conducted in the two-day gap between submission and acceptance, said the spokesperson.

Two days is "quite long", says Rao. "You can e-mail the article to everyone at once. It's not like the old days." **Daniel Cressey and David Cyranoski**

▶ germline 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 probably detected just a subset of the unintended mutations because their study looked at only a portion of the genome known as the exome. "If we did the whole genome sequence, we would get many more," he says.

Huang wonders whether there might be something intrinsically different that makes the human embryo more susceptible to extra mutations than animal embryos are. Another possibility — suggested by some critics of the work, he says — is that CRISPR/Cas9 worked differently in the embryos that his team used because they were the product of two sperm fertilizing an egg.

For some, these technical challenges support arguments for a moratorium on all research on human germline modification. "I think the paper itself actually provides all of the data that we kind of pointed to," says Edward Lanphier, president of Sangamo BioSciences in Richmond, California, and a member of the group that wrote the *Nature* article[2] calling for a moratorium.

But George Church, a geneticist at Harvard Medical School in Boston, Massachusetts, disagrees that the technology is so immature. He says that the researchers did not use the most up-to-date CRISPR/Cas9 methods and that many of the researchers' problems could have been avoided or lessened if they had.

"Some questions about early human development can only be addressed by studying human embryos."

Although researchers agree that a moratorium on clinical applications is needed while the ethical and safety concerns of human-embryo editing are worked out, many see no problem with the type of research that Huang's team did, in part because the embryos could not have led to a live birth. "It's no worse than what happens in IVF all the time, which is that non-viable embryos are discarded," says John Harris, a bioethicist at the University of Manchester, UK. "I don't see any justification for a moratorium on research," he adds. Church, meanwhile, notes that many of the earliest experiments with CRISPR/Cas9 were developed in human induced pluripotent stem cells, adult cells that have been reprogrammed to have the ability to turn into any cell type, including sperm and eggs. He questions whether Huang's experiments are any more intrinsically problematic.

Modifying human embryos is legal in China and in many US states. Asked whether Huang's study would have been funded under its rules, the US National Institutes of Health says that it "would likely conclude it could not fund such research", and is watching the technology to see whether its rules need to be modified.

Because the embryos Huang's team used were initially created for *in vitro* fertilization, not for research, the work would already have overcome many of the ethical hurdles it would face in other countries too, adds Tetsuya Ishii, who studies bioethics and policy at the University of Hokkaido in Sapporo, Japan.

NEXT STEPS

Applying gene editing to human embryos could answer plenty of basic scientific questions that have nothing to do with clinical applications, says George Daley, a stem-cell biologist at Harvard Medical School, who supports editing of human embryos *in vitro* for research purposes.

For instance, altering developmental genes with CRISPR/Cas9 could help to reveal their functions. "Some questions about early human development can only be addressed by studying human embryos," he says.

Gene editing could also be used to engineer specific disease-related mutations in an embryo, which could then be used to produce embryonic stem cells that could act as models for testing drugs and other interventions for disease, says Daley.

Huang now plans to work out how to decrease the number of off-target mutations using adult human cells or animal models.

Still, researchers expect to see more gene-editing studies in human embryos. "The ubiquitous access to and simplicity of creating CRISPRs," says Lanphier, whose company applies gene-editing techniques to adult human cells, "creates opportunities for scientists in any part of the world to do any kind of experiments they want." He expects that more scientists will now start work on improving on the results of the Huang paper. A Chinese source familiar with developments in the field said that at least four groups in China are pursuing gene editing in human embryos. ■

1. Liang, P. *et al. Protein Cell* http://dx.doi.org/10.1007/s13238-015-0153-5 (2015).
2. Lanphier, E. *et al. Nature* **519,** 410–411 (2015).
3. Baltimore, D. *et al. Science* **348,** 36–38 (2015).