

patients weren't turned away, she says.

On the other hand, distrust of the government, resentment against teams raising awareness, and rumors have hampered the response more in Guinea than elsewhere. The worst setback happened in September, when eight Ebola workers and journalists were killed with machetes and clubs in a remote village called Womey. (Eleven people were sentenced to life in prison for the murders last week.) In April, two people were seriously wounded when an Ebola team was attacked in Boffa prefecture; the only functioning ambulance there was badly damaged. In Forécariah, now the virus's main holdout, resistance to the anti-Ebola efforts has been fierce as well.

As part of the endgame, hundreds of local workers have gone house to house in the remaining Ebola pockets the past few weeks, to explain how Ebola spreads, encourage people to report suspected cases, and try to find any hidden Ebola patients or corpses. So far, the campaigns have been well received, Sakoba says. In Forécariah, the teams reached 91% of the population and identified 12 new Ebola cases, seven of whom were already dead.

William Perea, who has coordinated the World Health Organization's (WHO's) Ebola response in Guinea since last September, says he'd rather see those resources go to a focused, in-depth investigation of every new case to better understand the remaining routes of transmission—the kind of serious sleuthing that wasn't possible when the country had more patients. Even after the mass drive in Forécariah, some Ebola patients died at home, Perea says; that means that despite all the efforts, some people still don't understand the importance of reporting suspected cases. “We are missing things, and we need to understand exactly what they are,” he says. “I think that's what will get us to zero.”

Guinea's stubborn epidemic means that it may soon be the last place where researchers can do real-world tests of Ebola treatments and vaccines. Three treatment studies and two vaccine trials are already under way, and just last week, a delegation from the U.S. National Institutes of Health, already active in Liberia, was in town to gauge whether it can set up research partnerships in Guinea as well. An end to the epidemic—which Keita now tentatively predicts will come in June—may mean that most of the studies will not yield clear answers, says Mandy Kader Kondé, a former WHO epidemiologist who recently started his own research and training institute in Conakry and is involved in several of the studies. But, he says, that's a price that the country is more than happy to pay. ■

BIOETHICS

Embryo engineering study splits scientific community

First test of gene-editing technique on human embryos illustrates clinical risks

By Jocelyn Kaiser and Dennis Normile

A Chinese team's recent report that they have genetically altered human embryos for the first time has ignited a firestorm of controversy worldwide and renewed recent calls for a moratorium on such work. Scientists appear united in opposing any clinical use of such genome editing at the moment, whether to treat genetic diseases or create “designer babies.” But some biologists are equally adamant that basic research on genome editing in human embryos is scientifically and ethically justifiable.

In China, where the precedent-setting research is big news and some in the public have expressed concern about it on the Internet, “most scientists are more positive,” says Guo-Qiang Chen, a microbiologist at Tsinghua University in Beijing. “My personal opinion is that as long as they can control the consequences they should continue this work.” That view is echoed by many outside of China. “I personally would defend the fundamental scientific value of [such] research,” in part to explore the risks of any potential clinical use, says George Daley, a stem cell biologist at Harvard Medical School in Boston.

The paper at the heart of the debate appeared online on 18 April in *Protein & Cell*, a little-known journal co-published by Springer and an affiliate of China's Ministry of Education, but drew widespread attention only after *Nature* News reported it on 22 April. An editorial posted online on 28 April says the journal's objective in publishing the study was “the sounding of an alarm to draw immediate attention to the urgent need to rein in applications of gene-editing technologies, especially in the human germ cells or embryos.”

The paper makes sobering reading for anyone optimistic about genetically altering human embryos. In it, Junjiu Huang and colleagues at Sun Yat-sen University in Guangzhou described how they attempted to use

the CRISPR-Cas9 system, a new technology that makes it easy to modify genes in cells, to edit the human β -globin (*HBB*) gene in 86 human embryos donated for research by couples at an in vitro fertilization (IVF) clinic. In theory, such editing could be a way to prevent IVF-produced newborns from having beta thalassemia, a blood disorder resulting from a mutation in the *HBB* gene.

Two days after the single-celled embryos, or zygotes, had been injected with gene-editing molecules, 71 had survived and grown. But only four of 54 tested carried the desired genetic changes, and they were genetic mosaics, meaning only some of their cells had the intended changes to *HBB*. The edited embryos also had a large number of off-target effects, or mutations in genes other than *HBB*, which could be potentially harmful. The performance of the technique proved so poor that the researchers emphasized that any clinical use of CRISPR-Cas9 for embryo editing is “premature at this stage.”

The project was reviewed by a medical ethics board at Huang's university and complied with international and national

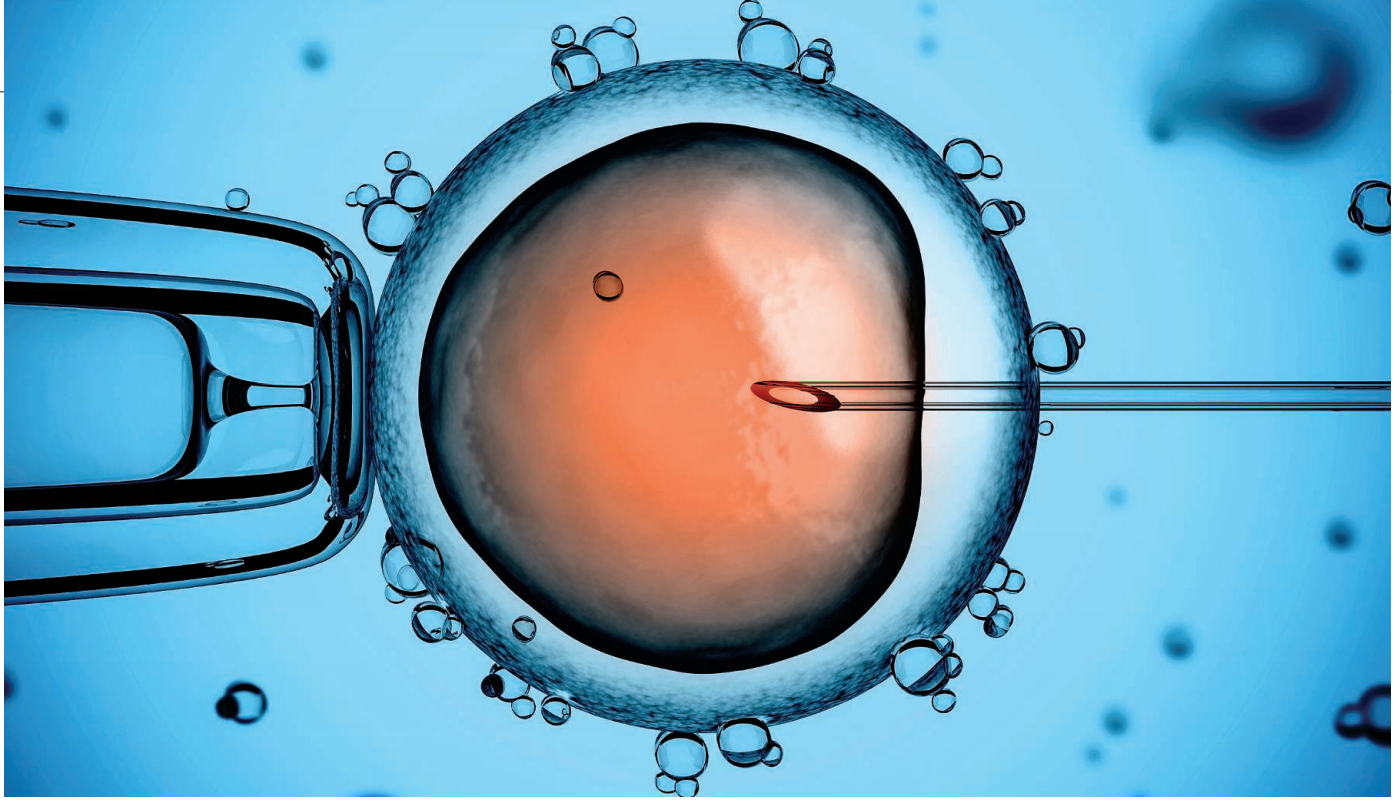
ethical standards, according to the paper. The researchers used abnormal zygotes that were not viable because they had an extra set of chromosomes as a result of being fertilized by two sperm and would have otherwise been discarded. “They did the research ethically,” says Tetsuya Ishii of Hokkaido University in Sapporo, Japan, who studies ethical issues

surrounding genome editing.

Still, the paper set off alarms. The Center for Genetics and Society in Berkeley, California, a watchdog group, called for a halt to such experiments. The Society for Developmental Biology in Bethesda, Maryland, called for a voluntary moratorium as well. Huang told *Nature* News that the paper was rejected by *Science* and *Nature* in part because of ethical concerns. (In an e-mail, Huang initially welcomed an inquiry from *Science* and asked for questions by e-mail, but then did not reply.)

“I personally would defend the fundamental scientific value of [such] research.”

George Daley, Harvard Medical School



A team has published the first report of using a new gene-editing method on human embryos created by in vitro fertilization (illustration).

Rumors that such a paper was in the works sparked two published commentaries about a month ago. In *Nature*, Edward Lanphier, CEO of Sangamo BioSciences in Richmond, California, and several others from industry and elsewhere called for a voluntary moratorium on all research involving gene modification of human embryos, eggs, or sperm. “We said ‘Let’s not perfect these technologies ahead of a conversation about whether we should allow this technology’” to be used in the clinic, or even need it, Lanphier explains. In a *Science* commentary, however, Nobel Prize-winning molecular biologist David Baltimore, president emeritus of the California Institute of Technology in Pasadena, and 17 co-authors limited their call for restraint to clinical applications (*Science*, 3 April, p. 36).

Some of the authors of the *Science* article say that they are comfortable with basic research like the Huang experiment. Daley points out that international guidelines developed by stem cell researchers allow for experiments with human embryos as long as the cells are not allowed to grow for more than 14 days. “To further inform any debate on whether this technology could be useful for eradicating disease, one has to understand the range of efficacy and off-target mutagenesis,” Daley says. Harvard molecular geneticist George Church, another author, agrees that the research does not appear to violate ethical guidelines.

Yet Church and several others are unimpressed with the Chinese group’s results.

One reason the researchers got so many off-target effects, Church suggests, is that they did not use the latest version of the gene-editing technology. University of California, Berkeley, molecular biologist Jennifer Doudna, who organized a workshop that led to the *Science* commentary, adds that the Huang experiment was premature because scientists are still a long way from perfecting the CRISPR-Cas9 gene-editing method. “I don’t see the value in working with human embryos right now. There’s a lot to be learned by working in other systems,” she says.

Doudna is also troubled that, according to

“I don’t see the value in working with human embryos right now.”

Jennifer Doudna, University of California, Berkeley

the dates noted in the paper, *Protein & Cell* apparently accepted the study 2 days after it was submitted. “I have to conclude this was not peer reviewed,” she says.

On the contrary, says *Protein & Cell* Editor-in-Chief Zihao Rao, a structural biologist at Nankai University in Tianjin. “Due to the scientific value and ethical dispute of this study, we not only conducted scientific peer-review, but also consulted related publishing and ethical experts,” he says. “The authors also revised the manuscript based on our suggestions.” Rao explains that the journal typically reviews submitted papers within 2 weeks, but for significant work they expedite the process.

Neither *Science* nor *Nature* would confirm that the journals reviewed the paper and rejected it in part because of ethical concerns. Asked whether it has a policy that would preclude considering such a paper, a *Nature* representative said the journal sometimes has papers reviewed by a bioethicist. *Science* issued a statement saying it supports recommendations in its earlier commentary and that while a consensus about germline genome editing is being developed, the journal “will carefully scrutinize all submissions for both technical and societal concerns and consult broadly.”

Scientists in China defend the country’s ethical oversight of research. The reviews in the United States and in China are very similar and based on the same principles, says Kehkooi Kee, a stem cell scientist also at Tsinghua, who earned his advanced degrees in the United States.

Chen adds that in light of the current controversy, review boards “will probably be more strict,” but he’s adamant that the newly published research was worth doing. Determining if these embryo engineering techniques can be useful in curing disease can be achieved “only by doing this kind of research,” Chen says.

Doudna is now helping organize an international meeting later this year that she says aims to “identify a broader consensus about the appropriate way to proceed with these experiments.” Now that the first human embryo gene-editing paper has been published, Doudna adds, “we feel some urgency.” ■

Science

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