NEWS IN FOCUS

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Reproductive biologist Shoukhrat Mitalipov and his team used genome editing to correct a gene that causes a potentially fatal heart condition in humans.

BIOTECHNOLOGY

CRISPR fixes embryo error

Gene-editing experiment in human embryos pushes scientific and ethical boundaries.

BY HEIDI LEDFORD

An international team of researchers has used CRISPR–Cas9 gene editing — a technique that allows scientists to make precise changes to genomes with relative ease — to correct a disease-causing mutation in dozens of viable human embryos. The study represents a significant improvement in efficiency and accuracy over previous efforts.

The researchers targeted a mutation in a gene called *MYBPC3*. Such mutations cause the heart muscle to thicken — a condition known as hypertrophic cardiomyopathy that is the leading cause of sudden death in young athletes. The mutation is dominant, meaning that a child need inherit only one copy of the mutated gene to experience its effects.

In the gene-editing experiment, published online this week in *Nature*[1], the embryos were not destined for implantation.

The team tackled two safety hurdles that had clouded discussions about applying CRISPR–Cas9 to gene therapy in humans: the risk of making additional, unwanted genetic changes (called off-target mutations) and the risk of generating mosaics, in which different cells in the embryo contain different genetic sequences. The researchers say that they have found no evidence of off-target genetic changes, and generated only a single mosaic in an experiment involving 58 embryos.

Several teams in China have already reported using CRISPR–Cas9 to alter disease-related genes in human embryos; work is also under way in Sweden and the United Kingdom to use the technique to study the early stages of human embryo development (see *Nature* **532,** 289–290; 2016). That research is aimed at understanding basic reproductive and developmental biology, as well as unpicking some of the causes of early miscarriages.

For the latest *Nature* paper, embryo experiments were conducted in the United States and led by Shoukhrat Mitalipov, a reproductive-biology specialist at the Oregon Health and Science University in Portland. The United States does not allow federal money to be used for human embryo research, but the work is not illegal if it is funded by private donors.

Mitalipov's team took several steps to improve the safety of the technique. The system requires an enzyme called Cas9, which cuts the genome at a site targeted by an ▶

RNA guide molecule. Instead of taking the typical approach of inserting DNA encoding CRISPR components into cells, Mitalipov's team injected the Cas9 protein itself, bound to its guide RNA, directly into the cells. Because the Cas9 protein degrades faster than the DNA that encodes it, the enzyme is left with less time to cut DNA, says genome engineer Jin-Soo Kim of the Institute for Basic Science in Daejeon, South Korea, and a co-author on the study. "There is little time for off-target mutations to accumulate."

But just because the team did not find off-target changes does not mean that the changes aren't there, cautions Keith Joung, who studies gene editing at the Massachusetts General Hospital in Boston.

MOSAICS MINIMIZED

The researchers also attempted to reduce the risk of mosaics by injecting the CRISPR–Cas9 components into the egg at the same time as they injected the sperm to fertilize it. This is earlier in development than previous human-embryo editing work had tried[2], and studies in mouse embryos have shown that the technique can eliminate mosaics when the father's genome is targeted[3].

In an experiment Mitalipov's group performed in 58 human embryos fertilized with sperm carrying the *MYBPC3* mutation, 42 contained two normal copies of *MYBPC3*. Because the sperm donor contained one normal copy and one mutated copy of *MYBPC3*, some of those embryos would have inherited the normal copy. The others were successfully edited to generate a normal gene. Only one was a mosaic. By comparison, the team found that 13 of 54 treated embryos were mosaics when the CRISPR–Cas9 machinery was injected 18 hours after fertilization.

The low rate of mosaics and the unusually high efficiency of gene editing make the study stand out, says stem-cell biologist Fredrik Lanner of the Karolinska Institute in Stockholm, who co-authored a commentary accompanying the article[4]. Additional testing is needed to show that the low rate of mosaics holds true for other gene-editing targets, but for now, he says, "it's a huge step in that direction".

The efficiency of gene editing in the study is exciting, adds stem-cell biologist George Daley of Boston Children's Hospital. "It puts a stake in the ground that this technology is likely to be operative," he says. "But it's still very premature." ■

1. Ma, H. *et al. Nature* http://dx.doi.org/10.1038/nature23305 (2017).
2. Tang, L. *et al. Mol. Genet. Genomics* **292,** 525–533 (2017).
3. Suzuki, T., Asami, M. & Perry, A. C. F. *Sci. Rep.* **4,** 7621 (2014).
4. Winblad, N. & Lanner, F. *Nature* http://dx.doi.org/10.1038/nature23533 (2017).

Princess Sumaya bint El Hassan is one of Jordan's leading science advocates.

MIDDLE EAST

Jordan stakes its future on science

The country wants to use a focus on research to solve its problems and build diplomatic ties in the Middle East.

BY AMY MAXMEN

When the World Science Forum kicks off on the shore of the Dead Sea in November, it will be the latest jewel in the crown for one of Jordan's biggest champions of science. Princess Sumaya bint El Hassan successfully lured the high-profile biennial conference to the Middle East for the first time — part of Jordan's ongoing push to transform itself into a regional research powerhouse. The country hopes to emphasize the power of science to transcend politics and war in the increasingly volatile Middle East.

It's a tall order, but there are signs that these efforts are beginning to pay off for Jordan, which created its first national science fund in 2005. In February, the country cemented plans for a reticular-chemistry foundry, the world's first. And in May, the Middle East's first synchrotron, SESAME, opened near Amman with the backing of seven nations and the Palestinian Authority.

Jordan's leaders see science, engineering and technology as an engine of economic growth for their 71-year-old country, which lacks the oil resources of many neighbouring states. The nation's political stability and central location have aided these ambitions. So has its diplomacy: Jordan is one of the only places in the Middle East where scientists from Israel and Arab countries can meet. "We are all in the region facing issues with energy, water and the environment," El Hassan says. "A bird with avian flu does not know whether there is a peace accord between Israel and Jordan, it just flies across the border."

The princess did not set out to be an architect of Jordan's science ambitions, however. In 1994, her father — the brother of King Hussein — asked the then-24-year-old art-school graduate to lead the board of trustees for an information technology college in Amman (now the Princess Sumaya University for Technology). El Hassan initially declined the job, but relented on the condition that she would first earn a computer-science diploma from the school.

Through that experience, El Hassan says, "I came to see science as a tool for human dignity. I began to see myself as a science enabler." In 2006, she became president of the Royal Scientific Society, an applied-science institution in Amman that also facilitates research collaborations across Jordan.

CORRECTION

The News story 'CRISPR fixes embryo error' (*Nature* **548,** 13–14; 2017) incorrectly stated that all 42 embryos with normal copies of *MYBPC3* were successfully edited. All 42 contained normal copies, but some of those inherited the normal copies, rather than have them edited in.