NEWS IN FOCUS

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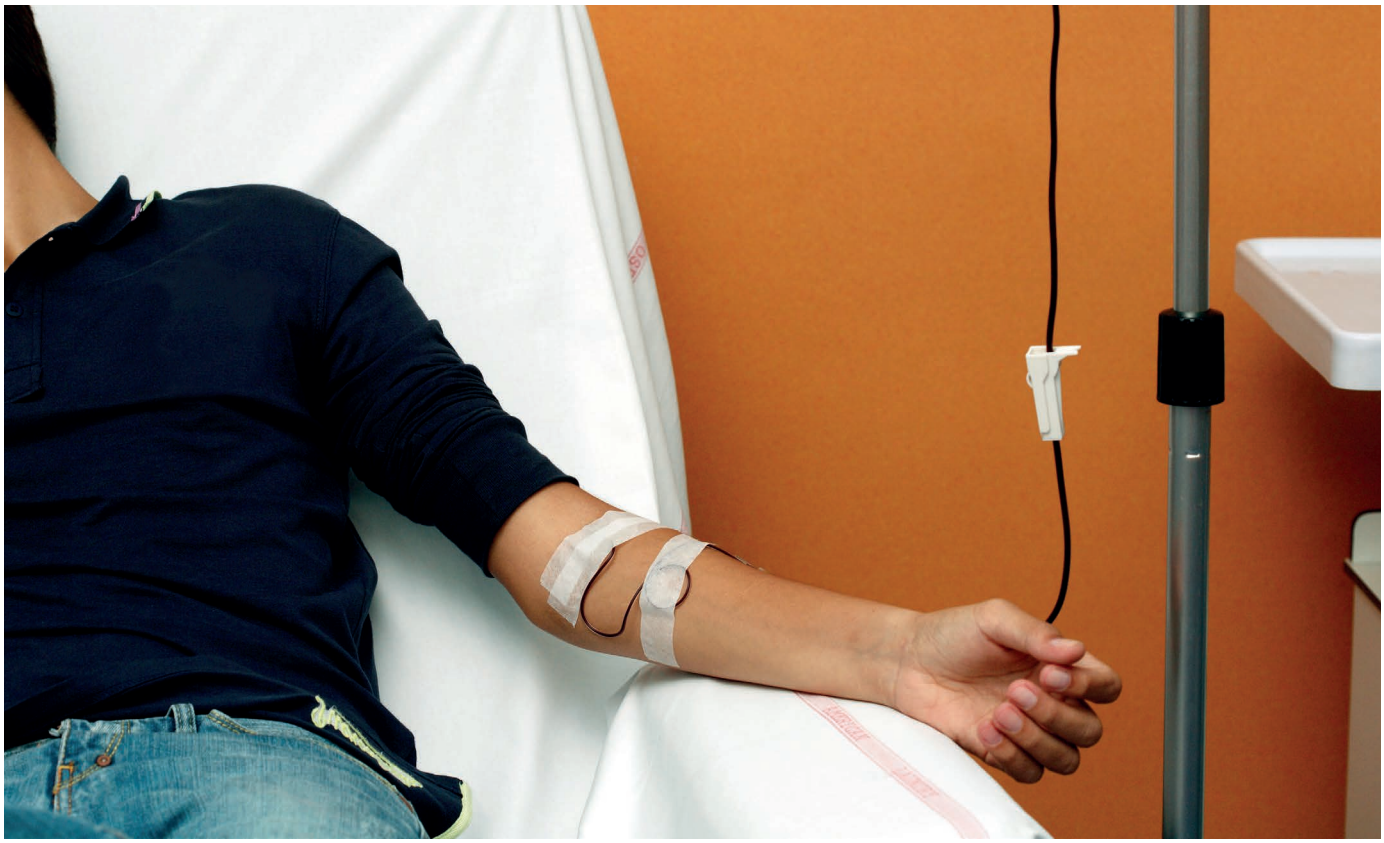

Correcting the genetic mutation linked to β-thalassaemia would save individuals with the condition from having to get life-sustaining blood transfusions.

GENETICS

Cloned-embryo DNA fixed

A method of precisely editing genes in human embryos hints at a cure for a blood disorder.

BY DAVID CYRANOSKI

A team in China has taken a new approach to fixing disease-related genes in human embryos. The researchers created cloned embryos with a genetic mutation for a potentially fatal blood disorder, and then precisely corrected the DNA to show how the condition might be prevented at the earliest stages of development.

The report, published on 23 September in *Protein & Cell*[1], is the latest in a series of experiments to edit genes in human embryos. And it uses an impressive series of innovations, scientists say. Rather than replacing entire sections of genes, the team, led by Junjiu Huang at Sun Yat-sen University in Guangzhou, China, tweaked individual DNA letters, or bases, using a precision gene-editing technology developed in the United States[2].

Huang's team is also the first to edit out the mutation responsible for a 'recessive' disease: one caused by having two faulty copies of a gene. Because it would be difficult for researchers to find dozens of embryos that all have this rare double mutation, the team worked around this roadblock by developing embryonic clones from their patient's skin cells.

"I thought, 'Why would they do cloning?' Then I read the paper, and thought, 'Wow, that's fascinating,'" says Shoukhrat Mitalipov, a reproductive-biology specialist at the Oregon Health and Science University in Portland who pioneered human-embryo cloning (see *Nature* **497,** 295–296; 2013) and also works on gene editing in embryos. "I would not have thought to do this."

Scientists around the world have now published eight studies reporting on gene editing in human embryos, five in the past two months. None has permitted the embryos to grow beyond 14 days, and the research has had ▶

different purposes: some to test gene-editing technologies; others to edit various disease-related genes; and some to unravel the mechanisms behind early embryonic development. Huang's team led the first report, published in April 2015, in which the researchers used the CRISPR–Cas9 enzyme complex to snip chromosomes at specific locations, excise DNA and replace it with other genetic material[3].

In the latest study[1], Huang's team used 'base editing', a modification of CRISPR–Cas9. It guides an enzyme to specific gene sequences, but does not cut the DNA. Instead, the Cas9 enzyme is disabled and tethered to another enzyme that can swap individual DNA base pairs. For now, this technique can convert guanine (G) to adenine (A), and cytosine (C) to thymine (T). Hundreds of genetic diseases are caused by single-base changes, or 'point mutations', and so such editing at the embryonic stage could potentially stave off such conditions.

Huang's team chose one mutation common in the Chinese population: a switch from an A to a G at a certain spot in the *HBB* gene, which can lead to β-thalassaemia, a recessive blood disorder associated with severe or fatal anaemia. Researchers generally source embryos from *in vitro* fertilization (IVF) clinics, but it's rare for these facilities to have embryos with two copies of the same rare mutation. So Huang's team found a person with the blood disorder, extracted their skin cells and used cloning techniques to develop embryos with the same genetic make-up.

The team reported that in 8 of 20 cloned embryos, they were able to convert the errant G back into an A in one or both copies of the gene. (Repairing only one copy might be enough to cure a recessive disease.) That rate is too low for the technique to be considered for clinical use, but is high relative to that achieved in other gene-editing studies. "The repair rate is pretty good, and certainly promising," says Gaetan Burgio, a geneticist at the Australian National University in Canberra. "Our study opens new avenues for therapy of β-thalassaemia and other inherited diseases," says Huang.

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But scientists caution that not all cells in the eight embryos were fixed. Such embryos are 'mosaic', meaning that they have a patchwork of cells with different genetic make-ups, which is potentially dangerous. "It looks like solid work, but highlights that the problem of mosaicism remains a challenge for any form of gene editing in the human embryo," says Dieter Egli, a stem-cell biologist at Columbia University in New York City.

Some scientists also question whether Huang's team looked thoroughly enough for unintended genetic changes, called off-target effects, that might have been caused by the base-editing procedure, although the authors reported that none was found.

Huang says that future experiments will be more comprehensive, but that this first study was a successful proof of principle that the base-editing technique can be used to correct a disease mutation in a human embryo. It may be that conventional CRISPR–Cas9 cannot fix embryos when both copies of a gene are faulty, although this isn't yet clear. In August, for instance, Mitalipov's team reported[4] using CRISPR–Cas9 to repair a mutation in a gene that can cause a potentially deadly heart disorder, by using the other, healthy copy of the gene as a template.

In the future, Huang says, he plans to ask for oocytes and sperm from donors who have one mutated copy of the gene — and so are unaffected by the condition, but are carriers of the disease — and use these to produce embryos. Some of those embryos would have two mutated copies, and some one, but Huang wants to edit both types. That raises the contentious idea that gene editing might be used not only to prevent severe disease, but also to eliminate the chance of people becoming carriers of the disorder. "Base editing can repair the mutant site and block it from being passed on to the next generation," he says. ■

1. Liang, P. *et al. Protein Cell* http://dx.doi.org/10.1007/s13238-017-0475-6 (2017).
2. Komor, A. C., Kim, Y. B., Packer, M. S., Zuris, J. A. & Liu, D. R. *Nature* **533,** 420–424 (2016).
3. Liang, P. *et al. Protein Cell* **6,** 363–372 (2015).
4. Ma, H. *et al. Nature* **548,** 513–519 (2017).

DATA SCIENCE

Internet research triggers scrutiny

Concern over the use of public data spurs guideline update.

BY ELIZABETH GIBNEY

British graffiti artist Banksy is renowned for his anonymity. But that status was dented last year when researchers published a paper that cross-referenced the locations of Banksy's street art with public information about people's addresses and likely movements (M. V. Hauge *et al. J. Spatial Sci.* **61,** 185–190; 2016). The team, led by academics at Queen Mary University of London, concluded that someone previously suspected to be Banksy probably was the secretive artist.

Because the study used public data, a university ethics committee said that the work was exempt from formal review — and informally advised academics that it would do no harm because a UK national newspaper had already identified the person in question as Banksy. But for some ethicists, the paper highlights growing concerns about the potential hazards of research that uses public data. "I think this study should never have been done," says Jake Metcalf, a technology ethicist at the think tank Data & Society in New York City.

Metcalf is one of several academics calling for new guidelines to steer scientists through ethical quandaries in Internet research. The unprecedented availability of online data — together with tools to draw patterns from it, such as machine learning — is opening up research possibilities that outpace existing ethics frameworks around privacy, consent and harm, says Charles Ess, a research ethicist at the University of Oslo and a member of the Association of Internet Researchers. The association will discuss how to update its guidelines at its annual meeting on 19 October in Tartu, Estonia.

A flurry of similar initiatives is under way. Earlier this year, the SATORI project, funded by the European Commission, published recommendations on Internet research as part of an effort to standardize and update research-ethics guidelines. In September, the US National Science Foundation funded a US$3-million, 4-year study called PERVADE — of which Metcalf is a part — that aims to chart attitudes to data-research ethics, produce best-practice guidelines and create tools to assess the potential harms of such work. And some British universities are preparing their first guidelines on the ethics of Internet research, after the UK Research Integrity Office, a national advisory body, published non-binding recommendations about it last December.

Common themes among these efforts include rethinking what counts as 'public' data, the ethical use of social media and the need to consider a study's potential harm to wider society, as well as to individuals. Many countries have long-standing ethical checks for research that intervenes in human lives. But those principles, set up for medical and psychological studies, apply to research on human subjects,