China's bold push into genetically customized animals

New kinds of dogs, goats, monkeys and pigs are being made quickly, though scientists voice worries about ethics.

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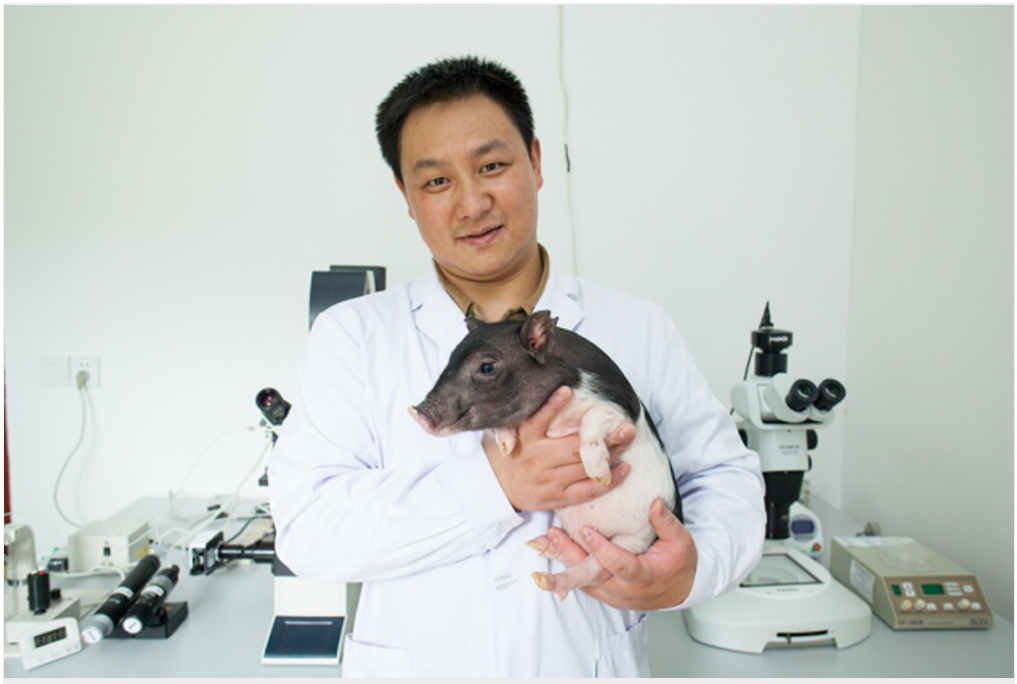
18 November 2015



BGI

A technician at the genomics institute BGI in Shenzhen, China, holds a genetically-modified micropig.

An article by Scientific American.

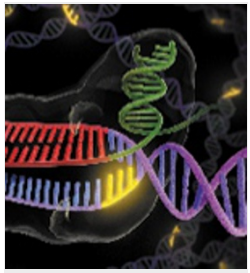
China's western Shaanxi Province is known for rugged windswept terrain and its coal and wool, but not necessarily its science. Yet at the Shaanxi Provincial Engineering and Technology Research Center for Shaanbei Cashmere Goats, scientists have just created a new kind of goat, with bigger muscles and longer hair than normal. The goats were made not by breeding but by directly manipulating animal DNA—a sign of how rapidly China has embraced a global gene-changing revolution.

Geneticist Lei Qu wants to increase goatherd incomes by boosting how much meat and wool each animal produces. For years research projects at his lab in Yulin, a former garrison town along the Great Wall, stumbled along, Qu's colleagues say. "The results were not so obvious, although we had worked so many years," his research assistant, Haijing Zhu, wrote in an e-mail.

hers adopted the new gene-customizing technology called CRISPR–Cas9, a technique developed in the U.S. about three years ago. CRISPR uses enzymes to precisely locate and snip out segments of DNA, much like a word-processor finding and deleting a given phrase—a process known as "gene-editing." Although it is not the first tool scientists have used to tweak DNA, it is by far more precise and cheaper than past technologies. The apparent ease of this powerful method now raises both tantalizing possibilities and pressing ethical questions.

Once the goat team began to deploy CRISPR, their progress was rapid. In September Qu and 25 other collaborating scientists in China published the details of their research in *Nature's Scientific Reports*. In early-stage goat embryos they had successfully deleted two genes that suppressed both hair and muscle growth. The result was 10 goat kids exhibiting both larger muscles and longer fur—designer livestock—that, so far, show no other abnormalities. "We believed gene-modified livestock will be commercialized after we demonstrate [that it] is safe," predicts Qu, who envisions this work as a simple way to boost the sale of goat meat and cashmere sweaters from Shaanxi. [*Scientific American* is part of Nature Publishing Group.]

The research is just one of a recent flurry of papers by Chinese scientists that describe CRISPR-modified goats, sheep, pigs, monkeys and dogs, among other mammals. In October, for instance, researchers from the country discussed their work to create unusually muscled beagles in the *Journal of Molecular Cell Biology.* Such research has been supported via grants from the National Natural Science Foundation of China, Ministry of Agriculture, Ministry of Science and Technology as well as provincial governments.



***Nature* special: CRISPR**

Dozens, if not hundreds, of Chinese institutions in both research hubs like Beijing and far-flung provincial outposts have enthusiastically deployed CRISPR. "It's a priority area for the Chinese Academy of Sciences," says Minhua Hu, a geneticist at the Guangzhou General Pharmaceutical Research Institute and one of the beagle researchers. A colleague, Liangxue Lai of the Guangzhou Institutes of Biomedicine and Health, adds that "China's government has allocated a lot of financial support in genetically modified animals in both [the] agriculture field [and the] biomedicine field."

This is raising a number of ethical worries about making new life forms. Unlike past gene therapies, changes made using CRISPR to zygotes or embryos can become "permanent"—that is, they are made to the DNA that will be passed onto future generations. For each zygote or embryo that scientists successfully transform, typically dozens, if not hundreds, of others do not work. But the technology is rapidly improving. "What is different about CRISPR is that the technology is vastly more efficient and so the possibility of it being practiced widely is that much more real," says George Daley, a stem-cell biologist at Harvard Medical School. Past efforts to manipulate the genetic code of life have been slower, more cumbersome and more unpredictable. "The ethical concerns are now upon us because the technology is real," he adds.

This applies to CRISPR experiments to "edit" the DNA of all plants and animals—as well as in the future, perhaps, humans, if scientists like Qu further hone the technique. "As with any intervention, there's always a trade-off in issues between human welfare and animal welfare and gauging the environmental impacts," says Daley, referring the quest for "improved" livestock, a current focus of China's gene-editing research. And on the even more complicated topic of potential CRISPR experiments involving human DNA, he wonders, "Can we draw a clear line between what might be allowable for medical research or applications and what we must strictly prohibit?" Finding an answer that the whole world can agree on is geneticists' and ethicists' next big task.

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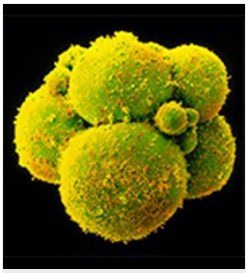
China is not the birthplace of CRISPR (currently there's an ongoing patent battle between scientists at Massachusetts Institute of Technology and the University of California, Berkeley, for that claim). China, however, has been an extremely rapid adopter, aided by a fast-growing research budget and the sheer scale of China's science establishment, which is largely state-affiliated. Between 2008 and 2012 China's research and development spending fully doubled, according to the Organization for Economic Cooperation and Development's *Science, Technology and Industry Outlook 2014*. (Now second in the world, China's research budget may surpass the U.S. by 2019, the report projects.) Yet despite its strengths, "China is a relative newcomer to international scientific community and doesn't have the same institutional-review traditions in place," says Daley, adding that scientists in the U.S. and Europe are now keenly watching how Chinese scientists will deploy such powerful tools.

The level and sophistication of work in China using CRISPR is already "about the same" as in Europe and the U.S., where the technology was codeveloped, says George Church, a professor of genetics at Harvard Medical School. An analysis by Thomson Innovation, a division of London-based Thomson Reuters, found that more than 50 Chinese research institutions have filed gene-editing patents.

Some experiments in China, as in the U.S. and U.K., are aimed at potential biomedical applications. For instance, scientists at Yunnan Key

Laboratory of Primate Biomedical Research have used CRISPR to augment the neurological development of monkeys in an effort to test the feasibility of creating primate disease models for better understanding human conditions like autism, schizophrenia and Alzheimer's disease. Many experiments, like the one on cashmere goats and a similar experiment that deleted the gene-inhibiting muscle growth in sheep, are aimed at transforming animal husbandry—more muscled livestock could help satiate China's fast-growing middle-class appetite for meat.

But what first brought widespread global attention, or infamy, to China's ambitions was a recent published experiment on human embryos, the first in the world. In April China became a lightning rod for criticism and anxiety when a team of Chinese scientists published a paper online in the journal *Protein & Cell* detailing attempts to use CRISPR to modify nonviable human embryos, obtained with consent from a fertility clinic. Their aim had been to delete a gene linked to a blood disorder called beta-thalassemia without creating other mutations, but the experiment failed on 85 attempted embryos.



Chinese scientists genetically modify human embryos

The research was legal within China, which bans experiments on human embryos more than 14 days old, and was supported in part by government grants. (Such research is not banned in most U.S. states but is probably ineligible for federal funding.)

Many international observers reacted with sharp rebuke, attributing nefarious intentions to the Chinese scientists. "No researcher has the moral warrant to flout the globally widespread policy agreement against altering the human germ line," Marcy Darnovsky, executive director of the California-based Center for Genetics and Society, a nonprofit advocacy group, wrote in a statement reacting to the report. Respected news organizations ran ominous headlines: "Chinese Scientists Edit Genes of Human Embryos, Raising Concerns" appeared in *The New York Times* and "Editing Humanity" in *The Economist*.

Because China is new to global scientific stage, its institutional standards for approving research projects are not fully transparent to the world, Daley says. Moreover, the researchers involved were not the heads of well-known global institutions, like the Broad Institute of M.I.T. and Harvard University or the Francis Crick Institute in London, whom global research community knows well and understands their motivations. Daley adds that now China's scientific establishment is "responsibly stepping up to discussion."

The controversy may have been a bit overblown. The Chinese scientists say they were not trying to edit human germ line or develop clinical uses. Junjiu Huang, co-author of the paper and a geneticist at Sun Yat-sen University in Guangzhou, wrote in an e-mail to *Scientific American* that "It is forbid[den] to do germ-line editing in clinic." Yet he defended the potential to learn about human disease s through future CRISPR experiments. "Using CRISPR–Cas9 technology, scientists could learn more about what are the real functions of key genes in [the] human preimplantation period. … We can also figure out the mechanism of gene repairing, which could lead to a new understanding of how genetic diseases occur during early development."

Later appraisals credit the carefulness of their method, including the choice to deliberately use nonviable embryos that could never become babies, Harvard's Church says. But the flap itself pointed to both the seriousness of the stakes and concern over whether Chinese scientists will accept same ethical principles as Westerners.

In early December scientists from the U.S., U.K. and China will meet at the U.S. National Academy of Sciences in Washington, D.C., in an effort to codify international consensus on editing DNA, focusing on the human germ line. Church, who has participated in preliminary meetings with Chinese and U.S. counterparts, says that the important takeaway from these debates may not be that China is an ethical outlier but rather that public discussion and clarification of guidelines, especially regarding the human germ line, is dearly needed. "I think China is behaving just as responsibly as others. I would not characterize China as being problematic in any way. Chinese scientists worked well within the legal system of most countries but I think there might have been some misunderstandings about consensus at that time," he says. "I think it's important to talk about it. I think many people want every opportunity to discuss this issue—sometimes you need an event to make it newsworthy."

Although scientists today offer a range of views on what is acceptable, the essential divide may not be between East and West. In September a researcher at the London-based Francis Crick Institute, Kathy Niakan, filed an application with U.K. regulators "to use new [CRISPR] 'genome editing' techniques on human embryos," according to an institution statement. "The work carried out at the Crick will be for research purposes and will not have a clinical application. However, the knowledge acquired from the research will be very important for understanding how a healthy human embryo develops."

Meanwhile Chinese scientists point out that the country is having its own internal debates about the ethics of editing DNA.

Whatever the discussions in Washington yield, Yaofeng Zhao at the State Key Laboratory of Agrobiotechnology, a geneticist working on

sheep, says that China is also grappling with its own internal ethical and safety debates about moving CRISPR experiments, for agriculture and biomedicine, beyond the lab. “I think there are different viewpoints on gene modification. Even in China there are different viewpoints on this issue. Some people in the general public, they are scared. But for most academics, I think most scientists support this kind of research—we need to do something for the future,” he says. In contrast to Qu, the cashmere-goat specialist, Zhao doesn’t think designer meat will be soon be on dinner plates. “If you want to use modified animals in agriculture, you must consider the public opinion—Can they accept this? Even if the technology is quite safe, it depends on many factors if you want to commercialize this kind of animal in agriculture.” There is already precedent for the Chinese government spending heavily on GMO crop research, including improved corn, wheat and rice, but delaying commercialization due to fierce public resistance.

In areas where science advances faster than regulation it may be possible for individual scientists or labs—in China or any country—to act outside of national consensus. At the Shenzhen International Biotech Leaders Summit on September 23, the private genomics firm BGI–Shenzhen, a maverick in the field, announced that it would begin selling gene-edited micro pigs as pets; the smaller pigs were originally created with the intention of biomedical research. Yong Li, technical director of BGI’s animal science platform, who turned down an interview request about the pigs for *Scientific American*, previously told *Nature* that he wanted to “evaluate the market.” (Pets are less regulated than agriculture, and do not supply national markets.) Some Chinese researchers clearly disapprove. Lai, co-author of the beagle paper, says he believes scientists should “not use CRISPR technique to create pets with special traits to satisfy some pet owner's special favor.”

Lai’s own work does not involve human embryos but he offered his opinion on the larger ongoing debate: If safety and efficacy issues can first be addressed, he is open to the future possibility of therapeutic uses, but not to eugenics. “In human beings CRISPR could be used to correct the mutation, which cause genetic human diseases, and it should not be used to generate any particular traits which some people may favor.” Other Chinese scientists working with CRISPR expressed similar views but none purported to predict the future—in China or elsewhere. Huang notes, “The gene-editing technology is very hot all over the world.”

Public debate over any powerful new technology reflects preexisting public hopes and fears, Church says. In the case of CRISPR that includes the desire to eliminate hereditary diseases as well as concerns about the commodification of parenting, the privileges of rich over poor and, newly, the rise of China.

Nature | doi:10.1038/nature.2015.18826

Nature ISSN 0028-0836 EISSN 1476-4687