

## GENOME EDITING

# China sprints ahead in CRISPR therapy race

## Human trials are using the genome-editing technique to treat cancers and other conditions

By **Dennis Normile**, in Shanghai, China

**C**RISPR, the wildly popular genome-editing research tool, was invented in the West, but it is speeding toward potential human applications in China. Last week, the Chinese team that sparked a worldwide debate in 2015 when it reported the first use of CRISPR to edit a human embryo's genome notched another first. In early embryos, they showed that a new CRISPR variant, which chemically modifies rather than cuts DNA, can correct the mutation that causes a debilitating blood disease. But the most striking evidence of progress in China can be found on the [clinicaltrials.gov](http://clinicaltrials.gov) database: Of the 10 listed trials of CRISPR in patients, nine are in China, where streamlined reviews have given researchers a head start.

Three groups confirmed to *Science* that they are infusing cancer patients with their own immune cells modified using CRISPR. The scientists leading those trials—on cancers of the stomach, lung, and esophagus—caution that routine use of CRISPR to treat disease is years away. Nevertheless, “If they are in the clinic and get good results, they will be in the lead for these particular applications,” says Donald Kohn, a gene therapist at the University of California, Los Angeles.

The groups targeting cancers use CRISPR

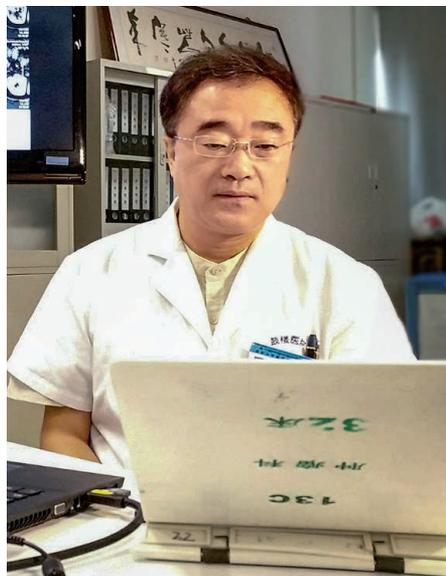
to unleash patients' T cells, immune warriors that can attack a tumor. Several teams are focusing on a gene that encodes programmed cell death protein 1 (PD-1), which prevents the immune system from overreacting to a viral infection or tumors when it induces T cells to die. Cancers can trigger PD-1 activity, protecting themselves by dampening the immune response. To block that defense, the researchers extract T cells from patients, use CRISPR to knock out PD-1, and reinfuse the altered cells to attack the cancer.

Because it is easier to cripple a single gene in a cell's genome than to add or replace genes, the strategy is seen as an ideal first test of CRISPR in the clinic. Moreover, targeting PD-1 with drugs or other gene-editing techniques has shown promise in clinical trials. All in all, Kohn says, “Knocking out PD-1 in autologous T cells should be pretty safe.”

Han Weidong's team at Chinese PLA General Hospital in Beijing is recruiting patients for a trial of a more ambitious approach. They will use CRISPR to knock out two genes that encode T cell receptor proteins and add an engineered receptor enabling the cells to recognize and attack leukemia cells. Instead of collecting and growing patients' own T cells, which can be difficult, Han is modifying donor cells, which he will bank for future use.

Scientists at the Academy of Military Medical Sciences in Beijing plan to unleash CRISPR on a different condition: HIV infections. Their goal is to disrupt the gene encoding a T cell surface protein that the virus uses to infect the cells. They will treat a donor's T cell precursor cells in vitro and then reinfuse them, hoping to establish a population of HIV-resistant T cells. Also targeting an infection, a group at Sun Yat-sen University in Guangzhou, China, is preparing a gel infused with gene-editing proteins that would be applied to the cervix of patients with a precancerous human papillomavirus infection. In what would be the first test of CRISPR administered in people, rather than in vitro, the team hopes the gene editor will penetrate the infected cells and knock out two key genes that promote tumor growth.

Many of China's CRISPR therapy pioneers say their trials grew out of long-running cancer research programs. Liu Baorui, an oncologist at the Nanjing Drum Tower Hospital of the Nanjing University Medical School in China, says his team is focusing on gastric and nasopharyngeal carcinomas because they impose a huge burden on China. CRISPR therapy could “provide new options for patients who have no choices after standard therapies,” Liu says. His group has treated two gastric cancer patients since April, and preliminary results look promis-



Liu Baorui is using CRISPR on two scourges in China: gastric and nasopharyngeal cancers.

### Bringing CRISPR into the clinic in China

Chinese researchers are pioneering the genome-editing tool CRISPR in human therapy. Their rapid advances are driven in part by a rising cancer burden and a paucity of experimental drugs when conventional treatments fail.

INSTITUTION	CONDITION	INTERVENTION	STATUS
Affiliated Hospital to Academy of Military Medical Sciences, Beijing	HIV infection	CCR5 gene modification	Recruiting patients
First Affiliated Hospital of Sun Yat-sen University, Guangzhou	Cervical cancer	Disrupt human papillomavirus	In planning
Chinese PLA General Hospital, Beijing	Leukemia	Modified T cell receptors	Recruiting patients
Peking University, Beijing	Prostate cancer	PD-1 knockout T cells	In planning
Peking University, Beijing	Bladder cancer	PD-1 knockout T cells	In planning
Peking University, Beijing	Bladder cancer	PD-1 knockout T cells	In planning
Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School, Nanjing	Gastric and nasopharyngeal cancers	PD-1 knockout T cells	Recruiting patients
Hangzhou Cancer Hospital, Hangzhou	Esophageal cancer	PD-1 knockout T cells	Recruiting patients
Sichuan University, Chengdu	Lung cancer	PD-1 knockout T cells	Recruiting patients

ing, he says. Wu Shixiu, an oncologist at the Hangzhou Cancer Hospital in China, is also focusing on a common and deadly disease: late-stage esophageal cancer. He says his team has treated 13 patients so far.

Other researchers are focusing on eliminating hereditary diseases before birth. Several groups already staged dramatic demonstrations, but in last week's issue of *Protein & Cell*, Huang Junjiu, a geneticist at Sun Yat-sen University, and colleagues reported taking the approach a step further. Earlier efforts used CRISPR to cut DNA's two strands at a point where a disease-causing mutation occurred, relying on the cell's own repair machinery to fix the gene. Huang's group, in contrast, used a variation of CRISPR to correct a single-letter genetic mutation that causes the blood disease  $\beta$ -thalassemia.

In embryos cloned from cells of a person with  $\beta$ -thalassemia, the procedure appeared to correct the mutation only about 20% of the time, and the group has not yet checked entire genomes for off-target effects. Experts hail it as a proof of principle. "This is another breakthrough in molecular editing," says Shirley Hodgson, a cancer geneticist at St. George's, University of London. "But clearly much more research needs to be done to perfect this method."

Chinese researchers pushing CRISPR into therapeutic trials must clear a single ethical and safety review, usually at their own institutions. In comparison, launching a similar trial in the United States typically requires reviews by the National Institutes of Health's (NIH's) Recombinant DNA Advisory Committee, the Food and Drug Administration, and the home institution. "It might be quite difficult to get approval here without extensive animal experiments," says Bryan Cullen, a virologist who has used CRISPR in mouse studies at Duke University Medical Center in Durham, North Carolina.

So far, only one U.S. trial has cleared that first NIH hurdle. A team at the University of Pennsylvania intends to use CRISPR to disrupt the gene for PD-1 in combination with a technique to add a receptor for NY-ESO-1, a protein often found on tumors, to a patient's T cells. The group got a green light from the Recombinant DNA Advisory Committee in June 2016 and is awaiting further approvals.

A long list of other U.S. groups is inching closer to CRISPR-related trials, Kohn says. Some target the same genes already in the crosshairs in China, but U.S. researchers also hope that the genome-editing tool can treat sickle cell anemia and a variety of immune deficiencies. Kohn says these trials could get underway "in 1 to 2 years." But in a fast-moving field, the Chinese teams may be another step ahead by then. ■

## ANCIENT DNA

# Neandertal genome reveals greater legacy in the living

## DNA inherited from interbreeding may influence diseases

By Ann Gibbons

**T**he insult "You're a Neandertal!" has taken on dramatic new meaning in the past few years, as researchers have begun to identify the genes many of us inherited from our long-extinct relatives. By sequencing a remarkably complete genome from a 50,000-year-old bone fragment of a female Neandertal found in Vindija Cave in Croatia, researchers report online in *Science* this week a new trove of gene variants that living people outside of Africa obtained from Neandertals. Some of this DNA could influence cholesterol levels, the accumulation of belly fat, and the risk of schizophrenia and other diseases.

The genome is only the second from a Neandertal sequenced to such high quality that it can reliably reveal when, where, and what DNA was passed from Neandertals to modern humans—and which diseases it may be causing or preventing today. "It's really exciting because it's more than two times better to have two Neandertal genomes," says evolutionary genomicist Tony Capra of Vanderbilt University in Nashville.

The first Neandertal genome was a composite drawn from three individuals from Vindija Cave (*Science*, 7 May 2010, p. 680). Then, over the past few years, ancient DNA researchers sequenced two more Neandertal genomes, including another high-quality sequence from an individual that lived 122,000 years ago in the Altai Mountains of Siberia. Together, the genomes showed that living Europeans and Asians carry traces of DNA from Neandertals who mated with members of *Homo sapiens* soon after our species left Africa. (Most Africans lack Neandertal DNA as a result.)

A key question has been: What does this archaic DNA do in living humans? Drawing largely on the Altai genome, researchers have published on about two dozen Neandertal gene variants that influence living humans' risk of allergies, depression, blood clots, skin lesions, immunological disorders, and other diseases (*Science*, 12 February 2016, p. 648).

But the Vindija Neandertal lived closer than the Altai one to the time and place where Eurasians' ancestors mated with Neandertals—likely 50,000 to 60,000 years ago, perhaps in the Middle East. So its DNA promised better insight, especially with recently improved methods to extract and sequence ancient DNA (*Science*, 31 August 2012, p. 1028). Evolutionary geneticist Kay Prüfer of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, and colleagues sequenced each base of the female's genome about 30 times on average. The team also used radiocarbon and genetic methods to date the bone.

As expected, this Neandertal's genome is

more closely related to today's Europeans and Asians than that of the Altai Neandertal. And Prüfer and his colleagues already have discovered 16 new Neandertal gene variants passed on to living humans. These include changes in genes already known to govern levels of cholesterol and vitamin D, and to influence the risk—for better or worse—of developing eating disorders, rheumatoid arthritis,

and schizophrenia, as well as the response to antipsychotic drugs. Researchers will now more closely study how each Neandertal version tips the balance in living people.

The new Vindija genome also allowed the researchers to better calculate how much Neandertal DNA different groups of humans outside of Africa have inherited. East Asians, with 2.3%–2.6% of Neandertal DNA, topped people from western Asia and Europe, who had 1.8%–2.4%. Prüfer and his colleagues confirmed that the ancestors of the 122,000-year-old Altai Neandertal had also interbred with *H. sapiens* in a much earlier encounter that took place more than 130,000 years ago.

The Altai and Vindija genomes are remarkably similar and that limited genetic diversity suggests that Neandertals lived in small, isolated populations of about 3000 individuals of reproductive age, Prüfer says. "This speaks to debates about why they went extinct," Capra says. "They probably were less robust in their response to disease, starvation, and changes in climate." ■

**"This speaks to debates about why [Neandertals] went extinct."**

**Tony Capra,**  
Vanderbilt University

# Science

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