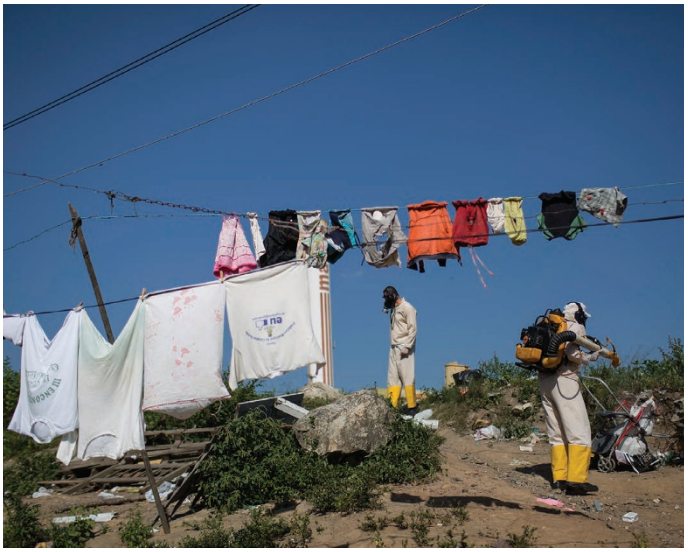
and Simon Hay, director of geospatial science at the Institute for Health Metrics and Evaluation in Seattle, Washington, to collaborate with researchers in Brazil. "The aim is to understand why we are only observing elevated rates in the northeast," says Brady, who flew into Brasilia this month to begin work.

The northeast was where the first reported surge in microcephaly cases in Brazil began a year ago. Health officials had expected that they would later see the same high rates in other parts of the country. "We were expecting an explosion of birth defects," says Marinho.



FELIPE DANA/AP

A health worker sprays insecticide to combat the mosquito that spreads Zika.

But as of 20 July, almost 90% of the 1,709 confirmed cases of congenital microcephaly or birth defects of the central nervous system reported in Brazil since last November were in a relatively small area: in the coastal hinterland of the country's northeastern tip. Particularly surprising, says Marinho, is that just three cases have been confirmed in Brazil's second-most populous state, Minas Gerais, which borders the most-affected part of the northeast region. Poor data on the scale and timing of Zika outbreaks across Brazil make it hard to tell whether increases in microcephaly elsewhere might have been delayed — but ministry scientists now think that the northeast represents a marked outlier, she says.

There are many hypotheses about what might be going on. Marinho says that her team's data, submitted for publication, hint that socio-economic factors might be involved. For example, the majority of women who have had babies with microcephaly have been young, single, black, poor and tend to live in small cities or on the outskirts of big ones, she says.

Another idea is that co-infections of Zika and other viruses, such as dengue and chikungunya, might be interacting to cause the high intensity of birth defects in the area.

In a paper published last month, researchers from Brazilian labs noted a correlation between low vaccination rates for yellow fever and the microcephaly clusters (L. P. de Goes Cavalcanti *et al. J. Infect. Dev. Countries* **10,** 563–566; 2016). Because yellow fever and Zika are in the same virus family, the scientists speculate that the vaccine might provide some protection against Zika.

And the Brazilian doctor who was the first to report a firm link between Zika and microcephaly — Adriana Melo at IPESQ, a research institute in Campina Grande — has another idea. In a preprint posted on the bioRxiv server on 15 July, Melo and her colleagues at the Federal University of Rio de Janeiro reported finding bovine viral diarrhoea virus (BVDV) proteins in the brains of three fetuses with microcephaly (F. C. S. Nogueira *et al.* Preprint at bioRxiv http://doi.org/bm4c; 2016).

BVDV causes birth defects in cattle but is not known to infect people. Melo and her team suggest that Zika infection might make it easier for BVDV to cause infections; however, they haven't ruled out the possibility that their findings might be due to contamination.

The Brazilian health ministry's study will test for BVDV among other ideas, says Brady. Researchers will reanalyse raw data on microcephaly cases, and will model connections with possible cofactors such as socio-economic status, water contamination and mosquito-borne diseases. Most of this information comes from health-ministry databases, but the team will also study experimental data, such as how people's immune response may change after past infection with other viruses such as dengue.

Until more is known about Zika and the causes of increased microcephaly rates in Brazil's northeast, public-health actions and advice must err on the side of precaution, says Ian Lipkin, a virologist and outbreak specialist at Columbia University in New York City. ■

BIOMEDICINE

First trial of CRISPR in people

Chinese team approved to test gene-edited cells in people with lung cancer.

BY DAVID CYRANOSKI

Chinese scientists are on the verge of being first in the world to inject people with cells modified using the CRISPR–Cas9 gene-editing technique.

A team led by Lu You, an oncologist at Sichuan University's West China Hospital in Chengdu, received ethical approval to test the cells in people with lung cancer on 6 July, and plans to start the trial next month.

That timeline puts the proposal ahead of a planned US trial to test CRISPR–Cas9-modified cells, also for the treatment of cancer.

"It's an exciting step forward," says Carl June, a clinical researcher in immunotherapy at the University of Pennsylvania in Philadelphia.

Last month, the US trial was approved by an advisory panel of the US National Institutes of Health (NIH) but had yet to receive a green light from the US Food and Drug Administration (FDA) and a university review board. There have also been a number of human clinical trials using an alternative gene-editing technique, including one led by June, that have helped patients to combat HIV — but none so far has used CRISPR.

The Chinese trial will enrol patients who have metastatic non-small cell lung cancer and for whom chemotherapy, radiation therapy and other treatments have failed. "This technique is of great promise in bringing benefits to patients," says Lu.

CHROMOSOME SNIP

Lu's team will extract immune cells called T cells from the participants' blood, and use CRISPR–Cas9 technology — which pairs a molecular guide able to identify specific genetic sequences on a chromosome with an enzyme that can snip the chromosome at that spot — to knock out a specific gene in the

cells. The target gene encodes a protein called PD-1 that normally acts as a check on the cell's capacity to launch an immune response.

The gene-edited cells will then be multiplied in the lab and re-introduced into the patient's bloodstream, where, the team hopes, they will home in on the cancer. The proposed US trial similarly involves knocking out the gene for PD-1, but also includes knocking out a second gene and inserting a third.

Last year, the FDA approved two antibody-based therapies that block PD-1 for use against lung cancer. Gene editing is expected to inhibit PD-1 with greater certainty, and by multiplying the cells, the scientists can increase the chance of triggering an immune response against tumours.

It is well known that CRISPR–Cas9 can result in edits at the wrong place in the genome, with potentially harmful effects. Chengdu MedGenCell, a biotechnology company in China and a collaborator on the trial, will validate the cells to ensure that the correct genes are knocked out before the cells are re-introduced into the patients, says oncologist Lei Deng of West China Hospital, a member of Lu's team.

Because the technique targets T cells — which are involved in various types of immune response — in a non-specific way, Chan worries that the approach might induce an autoimmune response in which T cells circulating in the blood might start to attack the gut, adrenaline glands or other normal tissue.

He suggests, instead, that the team take T cells from the site of the tumour because they would already be specialized for attacking cancer. But Deng says that the lung-cancer tumours targeted by their trial are not easily accessible. He also says that the team is reassured by the FDA-approved antibody therapies, which did not show a high rate of autoimmune response.

SAFETY FIRST

The phase I trial is designed foremost to test whether the approach is safe. It will examine the effects of three different dosage regimens on ten people, and, Deng says, the team plans to proceed slowly by increasing the dosage gradually and starting with just one patient, who will be monitored closely for side effects. But the researchers will also closely watch markers in the blood that would indicate that the treatment is working.

China has had a reputation for moving fast — sometimes too fast — with CRISPR, says Tetsuya Ishii, a bioethicist at Hokkaido University in Sapporo, Japan.

Lu says that his team was able to progress so rapidly because they are experienced with clinical trials of cancer treatments. The review process, which took half a year, included close communication with the hospital's internal review board (IRB). "There was a lot of back and forth," he says. The NIH's approval of the other CRISPR trial "strengthened our and our IRB's confidence in this study", he adds.

June is not surprised that a Chinese group has jumped out in front, he says, because "China places a high priority on biomedical research". Ishii notes that the clinical trial would be the latest in a series of firsts for China in the field of CRISPR — including the first CRISPR-edited human embryos and monkeys. "When it comes to gene editing, China goes first," he says.

Lu remains cautious. "I hope we are the first," he says. "And more importantly, I hope we can get positive data from the trial." ■

EUROPEAN UNION

Major funder tracks impact

European Research Council embarks on an unusual evaluation that could inspire others.

BY ALISON ABBOTT

Last month, neuroscientist Ileana Hanganu-Opatz began a risky project with a risqué name: Psychocell. With a grant of €2 million (US$2.2 million), she is studying whether a single type of neuron causes a miswiring in the developing brain that has been linked to psychiatric disease. But it may turn out that no 'psychocell' exists, or that her mouse models are unsuitable.

Supporting such blue-skies research is the mission of her funder, the prestigious European Research Council (ERC), which launched in 2007 to raise the quality of European science. "No one but the ERC would have funded such a high-risk project," says Hanganu-Opatz, from the University of Hamburg, Germany.

Now, the council, which sits within the European Union's Framework funding programmes and has a €1.7-billion budget this year, has embarked on an unusual exercise: to retrospectively evaluate the success of the projects it funds. By contrast, most funding agencies assume that the evaluation to select which projects they fund is sufficient.

"Virtually no basic research funding agency tries retrospectively to analyse its own performance and impacts," says Erik Arnold, chair of Technopolis, a European research and innovation consultancy headquartered in Brighton, UK. "It would be nice if the ERC effort would inspire others to do so."

On 26 July, at the European Science Open Forum in Manchester, UK, ERC president Jean-Pierre Bourguignon announced the results of a pilot investigation of 199 completed projects, almost three-quarters of which were deemed to have resulted in a scientific breakthrough or major advance (see 'To science and beyond').

"We push both scientists and grant-application reviewers to take a certain risk, so it is important to know that they are actually taking risks — and that we are selecting the right projects," says Bourguignon.

The ERC now plans to evaluate a selection of completed projects each year and to keep refining its methodology. Bourguignon hopes that this will help the council during discussions ▶