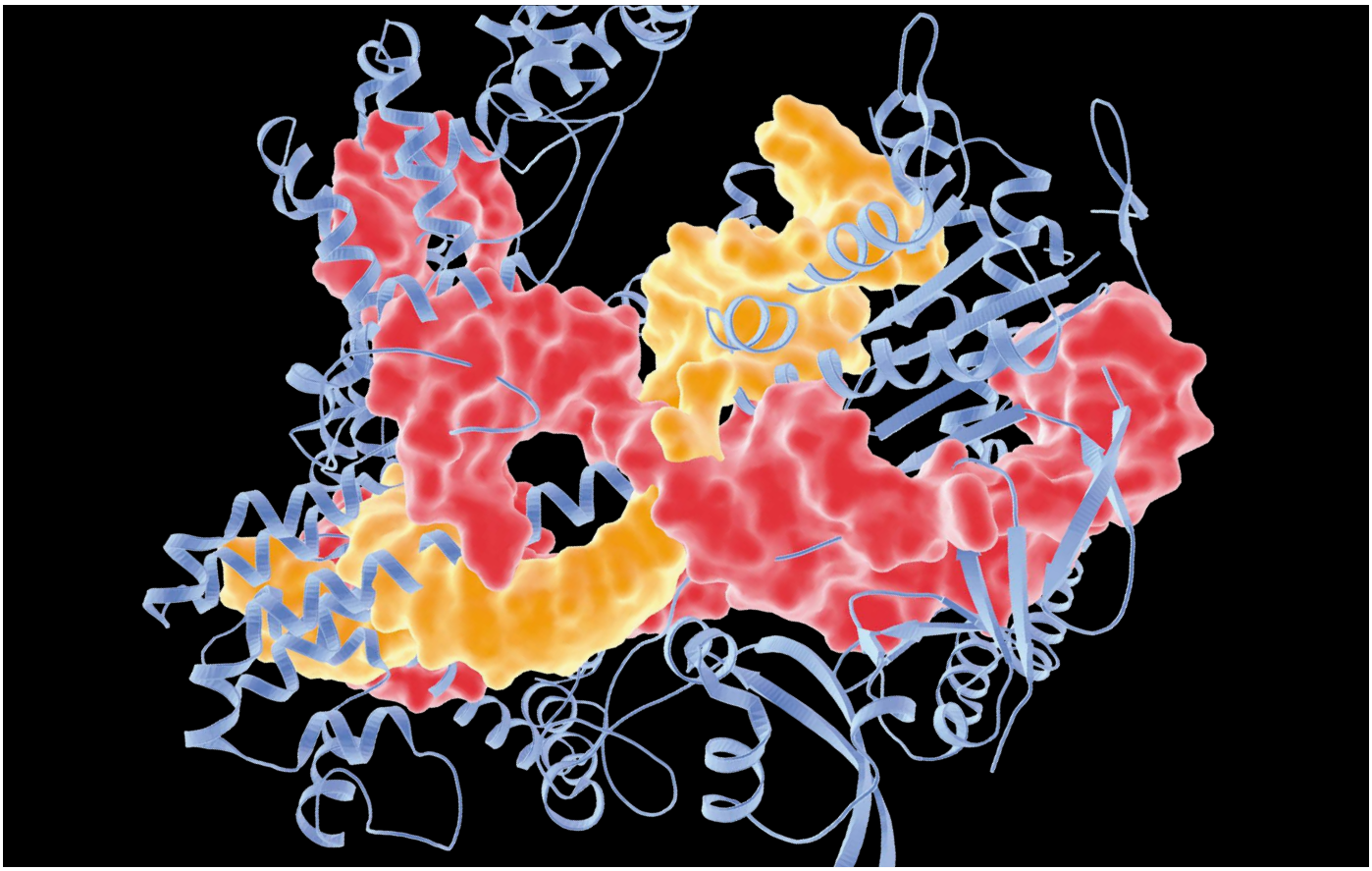
News in focus



ALFRED PASIEKA/SPL

The CRISPR–Cas9 complex (blue and yellow) can precisely cut DNA (red).

CRISPR CANCER TRIAL SUCCESS PAVES WAY FOR PERSONALIZED TREATMENTS

'Most complicated therapy ever' tailors bespoke, genome-edited immune cells to attack tumours.

By Heidi Ledford

A small clinical trial has shown that researchers can use CRISPR gene editing to alter immune cells so that they will recognize mutated proteins specific to a person's tumours. Those cells can then be safely set loose in the body to find and destroy their target.

It is the first attempt to combine two hot areas in cancer research: gene editing to create personalized treatments, and engineering immune cells called T cells so as to better target tumours. The approach was tested in 16 people with solid tumours, including in the breast and colon.

"It is probably the most complicated therapy ever attempted in the clinic," says study co-author Antoni Ribas, a cancer researcher and physician at the University of California, Los Angeles. "We're trying to make an army out of a patient's own T cells."

The results were published in *Nature* (S. P. Foy *et al. Nature* https://doi.org/jk4f; 2022) and presented at the Society for Immunotherapy of Cancer meeting in Boston, Massachusetts, on 10 November.

Ribas and his colleagues began by sequencing DNA from blood samples and tumour biopsies, to look for mutations that are found in the tumour but not in the blood. This had to be done for each person in the trial. "The mutations are different in every cancer," says Ribas. "And although there are some shared mutations, they are the minority."

The researchers then used algorithms to predict which of the mutations were likely to be capable of provoking a response from T cells, a type of white blood cell that patrols the body looking for errant cells. "If [T cells] see something that looks not normal, they kill it," says Stephanie Mandl, chief scientific

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officer at PACT Pharma in South San Francisco, California, and a lead author of the study. "But in the patients we see in the clinic with cancer, at some point the immune system kind of lost the battle and the tumour grew."

After a series of analyses to confirm their findings, validate their predictions and design proteins called T-cell receptors that are capable of recognizing the tumour mutations, the researchers took blood samples from each participant and used CRISPR to insert the genes encoding these receptors into their T cells. Each participant then had to take medication to reduce the number of immune cells they produced, before the engineered cells were infused.

"This is a tremendously complicated manufacturing process," says Joseph Fraietta, who designs T-cell cancer therapies at the University of Pennsylvania in Philadelphia. In some cases, the entire procedure took more than one year.

Each of the 16 participants received engineered T cells with up to three different targets. Afterwards, the edited cells were found circulating in their blood, and were present in higher concentrations near tumours than non-edited cells had been before the treatment. One month after treatment, five of the participants experienced stable disease, meaning that their tumours had not grown. Only two people experienced side effects that were probably due to the activity of the edited T cells.

Although the efficacy of the treatment was low, the researchers used relatively small doses of T cells to establish the safety of the approach, says Ribas. "We just need to hit it stronger the next time," he says.

And as researchers develop ways to speed up the therapies' development, the engineered cells will spend less time being cultured outside of the body and could be more active when they are infused. "The technology will get better and better," says Fraietta.

A solid start

Engineered T cells — called CAR T cells — have been approved for the treatment of some blood and lymph cancers, but solid tumours have posed a particular challenge. CAR T cells are effective only against proteins that are expressed on the surface of tumour cells. Such proteins can be found across many blood and lymph cancers, which means there is no need to design new T-cell receptors for each person with cancer.

But common surface proteins have not been found in solid tumours, says Fraietta. And solid tumours provide physical barriers to T cells, which must circulate through the blood, travel to the tumour and then infiltrate it to kill the cancer cells. Tumour cells also sometimes suppress immune responses, both by releasing immune-suppressing chemical signals and by using up the local supply of nutrients to fuel their rapid growth.

"The environment around a tumour is like a sewer," says Fraietta. "T cells are rendered less functional as soon as they hit the site."

With this initial proof of concept in hand, Mandl and her colleagues hope to be able to engineer T cells to not only recognize cancer mutations, but also be more active near the tumour. Mandl says there are several potential ways to toughen up T cells, such as removing the receptors that respond to immunosuppressive signals, or tweaking their metabolism so that they can more easily find an energy source in the tumour environment.

Such elaborate designs could be feasible thanks to recent technological advances in using CRISPR to edit T cells, says Avery Posey, who studies cell and gene therapies for cancer at the University of Pennsylvania. "It's become incredibly efficient," he says. "We'll see very sophisticated means of engineering immune cells within the next decade."

DENGUE VACCINE POISED FOR ROLL-OUT — BUT CONCERNS LINGER

Indonesia will be using the jab from next year, although some scientists say the safety data are insufficient.

By Smriti Mallapaty

A vaccine to prevent infection with dengue — a mosquito-borne disease that kills 20,000 people a year — is poised to be rolled out in Indonesia next year. But the jab is stirring debate: some researchers say that important safety concerns have been overlooked.

The vaccine, called Qdenga and developed by the pharmaceutical company Takeda, headquartered in Tokyo, is particularly significant because it is the first for people who have not previously contracted dengue. The virus infects up to 400 million people a year. The Indonesian drug regulator approved the vaccine for use without testing for previous exposure in August. Europe's drug regulator is also considering approving the vaccine for use without testing.

The only other approved vaccine, Dengvaxia, developed by Sanofi in Paris, can be given only to people who have already been infected. In individuals with no history of infection, Dengvaxia increases the risk of severe disease, including haemorrhagic fever, which might be caused by a rare but serious condition called antibody-dependent enhancement (ADE), in which vaccination induces antibodies that make a subsequent infection worse.

It is the possibility of ADE that is fuelling concerns about the new vaccine among some scientists, who say that it cannot be ruled out on the basis of clinical-trial data gathered so far. "I was really disappointed and surprised that the Indonesian government approved" the vaccine without restrictions, says Aravinda de Silva, a virologist at the University of North Carolina at Chapel Hill who has collaborated with Takeda and other dengue-vaccine developers.

A Takeda spokesperson says that clinical-trial data have been collected from more than 28,000 people over a period of 4.5 years, which is in line with World Health Organization recommendations. The data show that Qdenga is safe, regardless of past dengue exposure, the spokesperson says. And the European Medicines Agency (EMA) says there is no clear evidence of a higher risk of severe disease in people who have not been infected previously.

Other researchers say Qdenga will help to reduce the growing burden of dengue. The virus is endemic in more than 100 countries, predominantly in Asia. With no treatments and limited ways to control the spread of mosquitoes, vaccines are desperately needed. "I support the licensure of the vaccine in Indonesia," says Tedjo Sasmono, a virologist at the Eijkman Research Center for Molecular Biology in Jakarta. Indonesia has one of the world's highest numbers of dengue infections each year.

First approval

Dengue has four distinct 'serotypes' (DENV-1, DENV-2, DENV-3 and DENV-4) and protection from any two of them is needed to reduce the chance of serious disease. After a second infection, or vaccination followed by a breakthrough infection, people are typically protected against all four.

Qdenga is a two-dose live attenuated vaccine that uses DENV-2 as a backbone. Genes for key proteins from the other three serotypes are engineered into this backbone.

In 2019, Takeda published the results[1] of a trial across 8 countries, conducted in roughly 19,000 children aged between 4 and 16. One year after immunization, the vaccine had an

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