A more expensive reconnaissance instrument, which will do its first drilling tests this season at Dome C, should be ready to take a deeper look next year. Led by glaciologist Jérôme Chappellaz of Joseph Fourier University in Grenoble, France, the €3.2-million (US$3.4-million) SUBGLACIOR probe, which is about the same width as RAID, can penetrate the more than 3-kilometre-thick ice sheet in a single season.

Both the UK and French drilling projects are funded as part of the EU collaboration. But also this season, a US team led by climatologist Jeffrey Severinghaus of the Scripps Institution of Oceanography in La Jolla, California, and John Goodge of the University of Minnesota, Duluth, will test the $10.5-million Rapid Access Ice Drill (also abbreviated RAID) at Minna Bluff, near the US McMurdo Station on Ross Island. Producing a hole of about 8 centimetres — similar to the boreholes of the other drills — it is the only rapid drill that can extract rocks from the bottom of a core. Next Antarctic summer, the team will begin its hunt for the site of a 1.5-million-year-old core.

Dome C is one option for its first excavation. Another is the relatively unexplored Dome F in Antarctica's Queen Maud Land, which ground-based radar suggests is a promising candidate (see 'Ice search'). In January, a German team will run reconnaissance flights there. Funded by the same European grant as the UK RAID and SUBGLACIOR drills, this radar survey will give a more comprehensive view of the ice thickness. Severinghaus says that his team will watch for the data when deciding where to point the US RAID.

"You cannot trust a single core."

Both the US and European teams are working under an umbrella group. The International Partnerships in Ice Core Sciences (IPICS) aims to identify a suitable site to drill a core representing Antarctica's oldest ice in the next two years. That drilling could start by the end of 2020, says Eisen. But how the international teams would work together on a joint project, or share funding, is unclear.

There's a possibility that a record-breaking ancient core could show up sooner. For several years, scientists at the Polar Research Institute of China in Shanghai, who are also members of IPICS, have been probing the ice sheet that covers Dome A, a plateau close to the centre of the Antarctic continent. Using a conventional corer rather than a rapid exploratory drill, they are working on obtaining a deep, intact ice core from the region, says Eisen — and it is possible that it could stretch back to 1.5 million years. Such a surprise success would increase pressure on teams from other nations to produce their own record, he says.

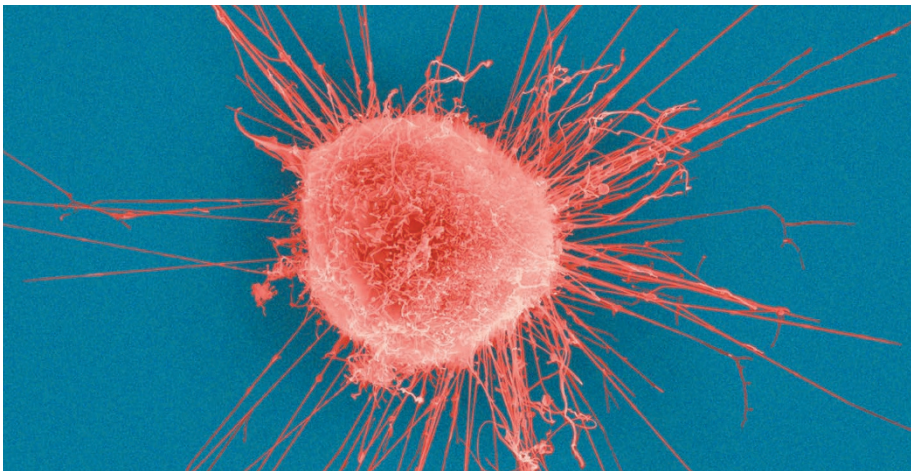
Multiple cores would benefit science. "We would carry on with our project," says Eisen. The IPICS effort would ideally excavate multiple 1.5-million-year-old cores in any case. "You cannot trust a single core," says Severinghaus. "We absolutely need different records from different thermal regimes." ■

DRUG DISCOVERY

Weaponized antibodies use new tricks to fight cancer

Next generation of Trojan-horse drugs designed to minimize damage to healthy cells.

BY HEIDI LEDFORD



DENNIS KUNKEL MICROSCOPY/SPL

Breast-cancer cells might be susceptible to drugs that masquerade as antibodies to sidestep defences.

After decades of frustration, efforts to develop antibodies that can ferry drugs into cancer cells — and minimize damage to healthy tissue — are gathering steam. The next generation of these 'weaponized antibody' therapies, called antibody–drug conjugates (ADCs), is working its way through clinical trials.

Researchers will gather to discuss this renaissance on 30 November at the Symposium on Molecular Targets and Cancer Therapeutics in Munich, Germany. The improvements come after the first wave of experimental ADCs failed to deliver on its promise.

"Initially there was a lot of excitement, and then slowly many of them did not work," says Raffit Hassan, a cancer researcher at the US National Cancer Institute in Bethesda, Maryland. Now, he says, there are two new ADCs in phase III clinical trials, and many more in earlier-stage testing.

The concept that underlies these drugs is simple: repurposing an antibody as a vehicle to deliver a toxic drug into a cancer cell. When the antibody in an ADC seeks out and docks onto a tumour cell, the cell takes it up and cleaves the molecular links that bind the drug to the antibody. This frees the drug to kill the cell from within.

But this approach has proved tricky to realize. Sometimes the molecular linkers are too tight, and do not release the drug inside the cell. Sometimes they are too unstable, and release the drug near healthy cells — limiting the dose that can be administered. Even the drugs themselves can be problematic: because most are toxic mainly to rapidly dividing cells, they can leave behind the slowly dividing cells that seed some tumours. And some have had trouble penetrating more than a few cell layers into their target tumours.

Researchers have been chasing ADCs for decades, Hassan says. The US Food and ▶

Drug Administration has approved three, but one was subsequently withdrawn from the market amid concerns that it was not effective and posed safety risks. The other two have met a happier fate: sales of Adcetris (brentuximab vedotin), approved in 2011 to treat lymphoma, and Kadcyla (trastuzumab emtansine), approved in 2013 to treat breast cancer, have been encouraging, says Ryan Million, head of the San Francisco office of the life-sciences and health-care consultancy firm Trinity Partners.

The approvals gave investors confidence in the field and sent researchers into a frenzy to improve their designs. More than 40 ADCs are now in clinical testing. Genentech, the biotechnology firm in South San Francisco, California, that developed Kadcyla, is experimenting with alternative drugs and molecular linkers. "Chemistry efforts have gotten more sophisticated in making decisions about which linker will go with each drug," says Bernard Fine, a group medical director at the firm. The company is now working on nine ADCs.

Researchers are also mining a wealth of data from cancer-sequencing projects in search of new targets for antibodies to latch onto, says Stéphane Depil, medical director of the cancer immunotherapy programme at the Centre Léon Bérard in Lyon, France. Identifying those that are unique, or nearly so, to cancer cells has been a major challenge, he says. But growing interest in harnessing the immune system has led researchers to catalogue unique proteins expressed on the surface of malignant cells.

Some companies are trying to hit familiar targets with entirely new designs. Mersana Therapeutics, a biotechnology firm in Cambridge, Massachusetts, has attached both an antibody and a drug to a biodegradable polymer, rather than linking them to each other. This allows the company to attach 15 molecules of the drug to each polymer, rather than the usual three or four, says chief scientific officer Timothy Lowinger. Mersana is testing its approach in early clinical trials of a drug conjugate that targets HER2, a protein expressed at high levels in some breast-cancer tumours. Kadcyla targets HER2, too, but Lowinger says that Mersana's version can bring in more drug per target, so it could be useful against cancers that express only low levels of HER2.

And at Tarveda Therapeutics, a biotechnology company in Watertown, Massachusetts, researchers have dispensed with the antibody altogether. Instead they are using a short strand of amino acids, the building blocks of proteins, to target cancer cells. The result is a drug that is about 15 times smaller and likely to penetrate deeper into the tumour, says Richard Wooster, Tarveda's president of research and development.

Even with all this activity, the technology has not reached its peak, says Million. "There's still lots to innovate," he says. "But when it works, I think it will work powerfully." ■

Zebrafish embryos star in one peer-reviewed paper investigating the NgAgo gene-editing technique.

BIOTECHNOLOGY

Gene-editing row escalates

Attempts to use a controversial potential rival to the CRISPR–Cas9 technique have now been published.

BY DAVID CYRANOSKI

A heated dispute over gene-editing that began in blogs and social media is now playing out in the scientific literature.

Six months ago, Chinese researchers reported that an enzyme called NgAgo could be used to edit mammalian genes[1] — and that it might be more accurate and more versatile than the popular CRISPR–Cas9 gene-editor. But other scientists complained that they could not replicate the experiment.

Now, a paper published in *Protein & Cell*[2] lists multiple failed replications, and another, published in *Cell Research*[3], suggests that NgAgo may only block, but not edit, genes when injected into zebrafish (*Danio rerio*). *Nature Biotechnology*, which published the first NgAgo paper, has also published a report of three failed attempts to replicate the original experiment[4], and an 'expression of concern' to accompany the original paper.

Nature Biotechnology is editorially independent of *Nature*'s news team and is owned by *Nature*'s publisher, Springer Nature.

Han Chunyu, a biologist at Hebei University of Science and Technology in Shijiazhuang who first reported the NgAgo experiment, says that he stands by his team's original claims and that "the *Nature Biotechnology* paper provides us some clues as to why others are having problems." He says that he hopes to submit a scientific paper explaining why others are having difficulty by the end of the year.

Nature Biotechnology says that it will give Han's team the opportunity to respond to the criticisms in the report by January 2017. "An update will be provided to the community at that time," said a spokesperson.

Gene-editing techniques that precisely disable or modify specific sections of a genome have taken the biomedical world by storm. NgAgo is one of several proposed alternatives to the most popular method, CRISPR–Cas9.

The 20 authors of the *Protein & Cell* paper[2] describe how they attempted without success to use NgAgo to edit a variety of genomes. Eight of the labs then tried the feat again, using genetic materials provided by Han, targeting the same genes and also applying the technique to human cells. They all failed.

CORRECTION

In the story 'Speedy drills start hunt for oldest ice' (*Nature* **540,** 18–19; 2016), the size of the borehole to be drilled by the US RAID was wrong. It will be about 8 cm, and so roughly the same size as the other planned holes. The story should also have noted that as well as Jeffrey Severinghaus, the US project is co-led by John Goodge of the University of Minnesota, Duluth.