SHIPS OF THE FUTURE

As climate change alters the polar seas, nations are upgrading their ability to conduct research in these ice-strewn waters.

NORWAY *Kronprins Haakon*

100 metres

Ice-breaking capability | ~1 metre
Launch date | 2017
Cost | 1.4 billion kroner (US$170m)

Approxiate number of scientists on board

35

CHINA Unnamed

122.5 metres

Ice-breaking capability | 1.5 metres
Launch date | 2019
Cost | Undisclosed

49

UNITED KINGDOM RRS *Sir David Attenborough*

129 metres

Ice-breaking capability | 1 metre
Launch date | 2019
Cost | £200m (US$290m)

60

AUSTRALIA Unnamed

156 metres

Ice-breaking capability | 1.65 metres
Launch date | 2020
Cost | Aus$529m (US$380m)

116

GERMANY Unnamed

Approx. 120 metres

Ice-breaking capability | 1.5 metres
Launch date | 2020
Cost | Unknown

~50

will it be able to push through thicker ice and carry more scientists, but the ship will also be able to explore deeper environments than any other UK research vessel, says Katrin Linse, a deep-sea biologist at the BAS. That ability will allow it to carry out the first direct sampling of the 8.5-kilometre-deep South Sandwich Trench in the southern Atlantic Ocean. "We might find a new ecosystem there that we are not aware of yet," she says. "It's pretty exciting to get a new vessel. That only happens once every 30–40 years." ■

SYNTHETIC BIOLOGY

Enzyme boost for mirror-image life

Polymerase that can copy left-handed DNA marks step forward for looking-glass biochemistry.

BY MARK PEPLOW

It's biochemistry — but not as we know it. Researchers at Tsinghua University in Beijing have created a mirror-image version of a protein that performs two of the most fundamental processes of life: copying DNA and transcribing it into RNA.

The work is a "small step" along the way to making mirror-image life forms, says molecular biologist Jack Szostak of Harvard Medical School in Boston, Massachusetts. "It's a terrific milestone," adds his Harvard colleague George Church, who hopes one day to create an entire mirror-image cell.

Many organic molecules are 'chiral': they can exist in mirror-image forms that cannot be superimposed, like a right-handed and left-handed glove. But life almost always employs one version: cells use left-handed amino acids, and have DNA that twists like a right-handed screw, for instance. In principle, looking-glass versions of these molecules should work together in the same way as normal ones — but they might be resistant to attack by viruses or enzymes that have not evolved in a looking-glass world.

That makes mirror-image biochemistry a potentially lucrative business. One company that hopes so is Noxxon Pharma in Berlin. It uses laborious chemical synthesis to make mirror-image forms of short strands of DNA or RNA called aptamers, which bind to therapeutic targets such as proteins in the body to block their activity. The firm has several mirror-aptamer candidates in human trials for diseases including cancer; the idea is that their efficacy might be improved because they aren't degraded by the body's enzymes. A process to replicate mirror-image DNA could offer a much easier route to making the aptamers, says Sven Klussmann, Noxxon Pharma's chief scientific officer.

THROUGH THE LOOKING-GLASS

Researchers have been making chunks of mirror-DNA for decades, so the Tsinghua team could order much of what it needed for its looking-glass DNA replication attempt from a chemical supplier — a mirror-DNA strand to be copied, mirror-DNA building blocks and a shorter mirror 'primer' strand that could pick up these building blocks in the right order.

The difficult task was to make the mirror-image enzyme that coordinates the copying process, called DNA polymerase. That would need to be synthesized from right-handed amino acids, but commonly used polymerase enzymes have more than 600 amino acids — meaning that they are too big for current synthetic methods.

So the Tsinghua team turned to the smallest known polymerase: African swine fever virus polymerase X, which contains just 174 amino acids. Unfortunately, it is also spectacularly slow — probably because of its small size, says synthetic biologist Ting Zhu, a former graduate student of Szostak's who helped to lead the work. The team made a mirror version of the enzyme and found that, like its natural equivalent, it could extend a mirror-primer consisting of 12 nucleotides (DNA building blocks) to an 18-nucleotide mirror-DNA strand in about 4 hours; and to a 56-nucleotide strand in 36 hours.

When the normal and mirror-image versions of these systems were mixed together in the same test tube, both replication processes worked independently without interference. The mirror-image polymerase could also transcribe mirror-DNA into mirror-RNA — a relatively rare feat for a polymerase — again at a glacial pace. The work is published in *Nature Chemistry* (Z. Wang *et al. Nature Chem.* http://dx.doi.org/10.1038/nchem.2517; 2016).

"For a while mirror-image biochemistry was a non-field. But now it seems very vibrant."

Klussmann says that Noxxon Pharma is interested in pursuing a similar approach with a more efficient enzyme. Indeed, Zhu and his colleagues next hope to build a mirror-image of a more efficient polymerase known as Dpo4, which is built of 352 amino acids.

In their research paper, the Tsinghua researchers also present their work as an effort to investigate why life's chirality is the way it is. This remains mysterious: it may ▶

simply be down to chance, or it could have been triggered by a fundamental asymmetry in nature. But Steven Benner, at the Foundation for Applied Molecular Evolution in Alachua, Florida, says it's unlikely that creating a mirror form of biochemical life could shed light on this question. Almost every physical process behaves identically when viewed in a mirror. The only known exceptions, called 'parity violations', lie in the realm of subatomic physics. Such tiny differences would not show up in these biochemical experiments, says Benner. (He is also interested in making DNA that can avoid unwanted degradation by natural enzymes or viruses, but rather than using mirror-DNA, he has created artificial DNA with non-natural building blocks.)

Church's ultimate goal, to make a mirror-image cell, faces enormous challenges. In nature, RNA is translated into proteins by the ribosome, a complex molecular machine. "Reconstructing a mirror-image of the ribosome would be a daunting task," says Zhu. Instead, Church is trying to mutate a normal ribosome so that it can handle mirror-RNA.

Church says that it is anyone's guess as to which approach might pay off. But he notes that a growing number of researchers are working on looking-glass versions of biochemical processes. "For a while it was a non-field," says Church. "But now it seems very vibrant." ■

BIOTECHNOLOGY

Bankruptcy of nanomedicine firm worries drug developers

Financial troubles of leading biotech firm highlight challenges of making innovative drugs.

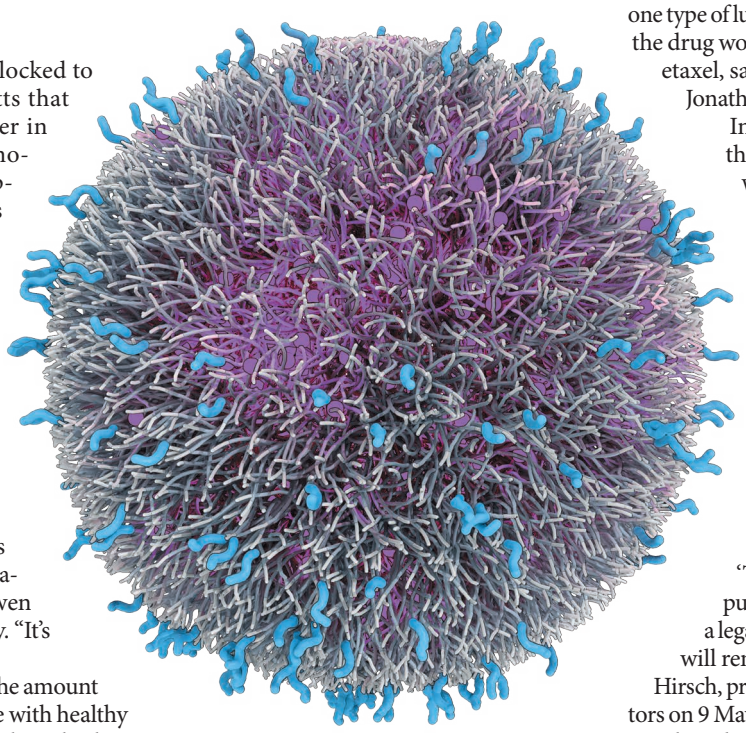
BY HEIDI LEDFORD

Not long ago, investors flocked to a firm in Massachusetts that was hailed as the leader in a wave of next-generation nanotechnology companies developing ways to ferry cancer drugs to tumours. But on 2 May, the company — BIND Therapeutics — declared bankruptcy.

Researchers in the field of nanomedicine are waiting anxiously to see whether the Cambridge-based firm will pull through its financial crisis — and whether its troubles will taint the swiftly evolving field of nanoparticle drug delivery. "It's been a rapid rise and fall," says Eric Schmidt, a biotechnology analyst at the investment bank Cowen and Company in New York City. "It's all unravelled pretty quickly."

Because nanoparticles lessen the amount of contact that cancer drugs have with healthy tissue, they offer a chance to deliver higher doses with fewer side effects. In 1995, the US Food and Drug Administration approved the first such treatment, Doxil, which packages a chemotherapy drug called doxorubicin in a lipid nanoparticle. The particles are too large to escape from normal blood vessels — and so are less toxic to the heart than naked doxorubicin — but they can seep out of the leaky blood vessels often found in tumours.

BIND's nanoparticles were designed to target tumours more precisely than liposome particles can. The company's lead product, BIND-014, involves a polymer particle coated with a molecule that steers the particle to a protein found in many tumours. The particle releases the chemotherapy drug it carries, called docetaxel, inside the tumour.



COURTESY BIND THERAPEUTICS

BIND Therapeutics' nanoparticle is coated in molecules that target it to tumours.

Early tests in animals and small clinical trials showed that the approach was safer than docetaxel alone — and fuelled BIND's US$70.5-million initial public offering in 2013. But later clinical trials disappointed. BIND-014 failed against cervical and head-and-neck cancers. Although it was somewhat effective against one type of lung cancer, it was not clear whether the drug worked any better than regular docetaxel, says BIND's chief scientific officer Jonathan Yingling.

In April, the company announced that it would cut back on its work with BIND-014, and Yingling says that the firm will now explore new targets. It cut the number of employees by 38% and aims to trim its expenses to $6 million per quarter — a dramatic decrease for a company that spent $11 million on research and development alone in the first quarter of 2016.

After one of its creditors demanded that BIND repay a loan ahead of schedule, the company filed for bankruptcy (see 'Troubled times'). It plans to dispute the need for early repayment at a legal hearing on 18 May. "BIND is and will remain open for business," Andrew Hirsch, president of the company, told investors on 9 May.

Schmidt says that BIND remains at the technological forefront of nanoparticle drug delivery, but waited too long to move away from BIND-014. By then, the investor enthusiasm for biotechnology that had driven BIND's initial public offering had cooled. "People are not interested in funding technology right now," Schmidt says. "They're interested in funding later-stage projects. And the one at this company didn't have what it takes."

In the time since BIND-014 was developed, researchers have also realized that differences between tumours — such as size, density and leakiness of the blood vessels that lace through