would cast further doubt on whether the JWST will ever fly, because a House of Representatives committee has already voted, on 13 July, to cancel the telescope.

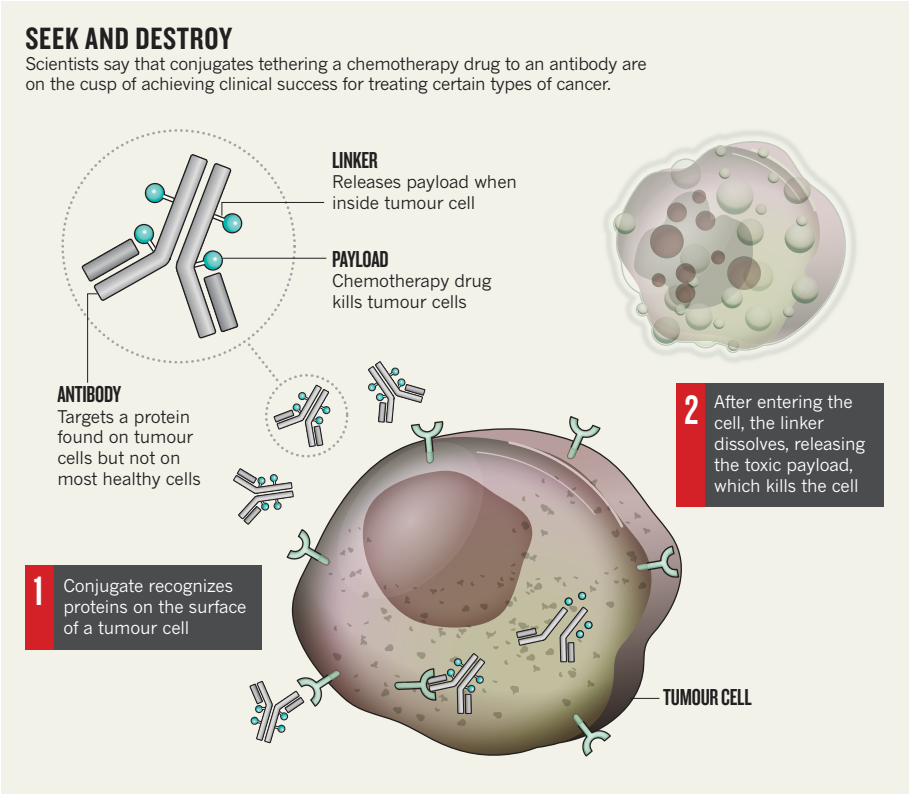
The drama surrounding the JWST is clearly on the mind of Bolden, NASA's highest official. On 2 August, before a meeting of the NASA Advisory Council began, Bolden told an assembly of dozens of advisers that the JWST is now one of the agency's top three priorities.

The first is to continue to support the development of commercial rockets able to carry people to and from the International Space Station in low-Earth orbit, a goal of companies such as Space Exploration Technologies (SpaceX) of Hawthorne, California. Second is the development of a heavy-lift rocket that can take astronauts beyond low-Earth orbit to reach objects such as nearby asteroids. Both of these activities would fall under the aegis of the Human Exploration and Operations Mission Directorate, which was formed on 12 August in a merger of the programme that operated the now-retired space-shuttle fleet and the programme that began the development of the Constellation rockets, part of the now-cancelled project to return to the Moon. That Bolden's third priority is the JWST "makes it clear that he's going to be fighting for it", says Alan Boss, an astronomer at the Carnegie Institution of Science in Washington DC and chair of a NASA astrophysics advisory subcommittee.

Even allowing for cost-sharing within the agency, lawmakers on Capitol Hill would have to cough up more money for NASA than recommended by the House committee if it is to turn all of Bolden's priorities into realities. In September, when Congress returns from recess, it is expected to resume the appropriations process for the 2012 fiscal year. All eyes will be on the Senate and Barbara Mikulski (Democrat, Maryland) to see how strongly she fights for the JWST project, which is being managed in her state.

If the OMB approves NASA's plan — and if lawmakers oblige by appropriating enough money — astronomers should consider themselves lucky. Some observers suggest that if the science division has to cover only half of the JWST's overruns, it could do so without delaying or cancelling any other missions.

But Brett Alexander, president of the Commercial Spaceflight Federation, says that shifting the cuts onto other parts of the agency will definitely hurt. He points out that scientists complained loudly in 2006 when money was redirected from science to support the Constellation rocket-building effort. "Now the science community may be looking for human spaceflight money to cover the science overruns," he says. ■



DRUG DEVELOPMENT

Toxic antibodies blitz tumours

Tightly targeted cancer therapy receives marketing approval.

BY HEIDI LEDFORD

Eventually, Clay Siegall got used to doors slamming in his face. When the cancer researcher decided to create a company that would fight cancer using weaponized antibodies, investors were sceptical. "We contacted 35, then 40, then 45 venture-capital companies," he says. "We got turned down over and over and over."

Siegall and his partners kept trying, and 13 years later the investors who eventually bet on Siegall's company, Seattle Genetics, of Bothell, Washington, are getting their reward. On 19 August, the US Food and Drug Administration (FDA) approved the company's lead therapy, an antibody engineered to deliver a poisonous payload directly into lymphoma cells. The hope is that such antibodies, called antibody–drug conjugates, will sidestep the punishing toxicities of classical chemotherapies, which run loose in the bloodstream and kill healthy cells in addition to their targets.

Tim Illidge, an oncologist at the University of Manchester, UK, says that the approval is a "game-changer" for a promising class of drugs that has struggled to gain a foothold since it was first described in a 1964 *Nature* paper[1] (see 'A long time coming'). "We're essentially in a renaissance of the antibody–drug conjugate," he says.

Unembellished, or 'naked', antibodies are already used to treat cancer because of their unparalleled ability to target proteins found on the surface of tumour cells. Their high profit margins and strong patent protections have pharmaceutical companies clamouring for more. Siegall says that Seattle Genetics toyed with naked antibodies, too. "But by and large," he says, "most naked antibodies just don't have a strong, potent ability to knock out tumour cells."

Enter antibody–drug conjugates, which do have that knock-out punch. Their power comes from their payloads: lethal drugs tethered to the antibody that remain harmless until

the conjugate releases them inside cancer cells (see 'Seek and destroy').

But for decades, developers have struggled to get the crucial elements to work together: the antibody, the drug it carries and the linker that binds the two. Seattle Genetics' conjugate, Adcetris (brentuximab vedotin), seems to have overcome the hurdles; it combines a synthetic poison called vedotin with an antibody that targets CD30, a protein found on many lymphoma cells.

In July, an FDA advisory committee voted unanimously in support of accelerated approval for Adcetris after Seattle Genetics reported that 94% of the 102 people with Hodgkin's lymphoma in a trial of the treatment saw their tumours shrink, and 73% achieved partial or complete remission. "This drug is wildly active," said panellist Mikkael Sekeres, an oncologist at the Cleveland Clinic in Ohio, after the vote.

"It's like a game of whack-a-mole. You knock out one toxicity and another shows up."

The accelerated approval means that the drug can now be prescribed by doctors while Seattle Genetics conducts follow-up clinical studies. Mark Monane, a senior analyst at the investment-banking firm Needham & Company in New York, predicts that the drug will bring in up to US$400 million a year in sales.

Janice Reichert, an analyst at the Tufts Center for the Study of Drug Development in Boston, Massachusetts, expects more approvals to follow. Between 2000 and 2005, only six antibody–drug conjugates entered the clinic for the first time, she says. From 2005 to 2009, 15 more joined their ranks. Now, 25 are currently in cancer clinical trials — more than at any other time. Two have reached late-stage clinical trials: trastuzumab emtansine, a breast-cancer therapy jointly developed by biotechnology firms Genentech, based in South San Francisco, and ImmunoGen in Waltham, Massachusetts; and inotuzumab ozogamicin, a lymphoma therapy developed by Pfizer in New York.

Pitfalls remain. The only other conjugate to ever win accelerated approval from the FDA, a different version of Pfizer's lymphoma therapy, was pulled from the market last year after further tests showed that the drug offered no benefits over standard chemotherapy. Many blame the failure on a linker that fell apart in the bloodstream, boosting toxicity and limiting the dose that could be used. Seattle Genetics had to pull one of its antibodies from clinical trials for similar reasons, says Siegall. As a result, the company developed a linker that is degraded by the enzymes that are most active inside the cell.

ImmunoGen, Seattle Genetics' main competitor, has struggled to find the right drug to couple to its antibodies. For years, the company attempted to use ricin, a toxin produced by castor beans. But ricin triggered a dangerous immune response. ImmunoGen now steers clear of complex proteins and picks small-molecule poisons that are less likely to attract the attention of the immune system.

A lingering problem for the field is a lack of control over how many drug molecules attach to each antibody. More control would help standardize each dose and lessen the potential toxicity of the treatment. A method developed by researchers at Genentech, a subsidiary of Swiss drug firm Roche, seemed to have conquered the problem but has not yet been tested clinically[2]. Unexpected toxicities led the company to shelve the technique for the time being, says Paul Polakis, Genentech's director of cancer targets. "It's like a game of whack-a-mole," he sighs. "You knock out one toxicity and another shows up."

Although antibody engineers still have work to do in optimizing the design, the approval of Adcetris means they have a bellwether to watch. The improving fortunes in the field, which culminated in last week's approval, have finally brought Siegall the investor attention that eluded him for so long. Seattle Genetics has partnered with 11 outside firms, bringing in $150 million in new capital. More than a quarter of that was raised in the past year. "I'm happy to say I no longer have to convince investors that this is a productive field," he says.

All of this leaves those who have followed the technology marvelling at its reversal of fortune. "When I first became interested in the field in the early 1990s, there was a lot of despondency," says Illidge. "And now look at it. Everything has changed." ■

1. DeCarvalho, S., Rand, H. J. & Lewis, A. *Nature* **202,** 255–258 (1964).
2. Junutula, J. R. *et al. Nature Biotechnol.* **26,** 925–932 (2008).

A LONG TIME COMING

For nearly half a century, researchers have been trying to capture the therapeutic potential of antibody–drug conjugates, which combine the tumour-killing power of a drug with the tumour-seeking ability of an antibody.

1964
Researchers create the first antibody–drug conjugates[1].

1981
The Dana Farber Cancer Institute in Boston, Massachusetts, spins out ImmunoGen to focus on conjugates.

1986
US regulators approve the first therapeutic 'naked' antibody.

1998
Seattle Genetics is founded and focuses on conjugates.

2000
US regulators approve Pfizer's Mylotarg (gemtuzumab ozogamicin) for treatment of leukaemia.

2010
Pfizer withdraws Mylotarg after finding no significant benefit to patients.

2011
Regulators approve Seattle Genetics' Adcetris for some forms of lymphoma.

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