Drug Administration has approved three, but one was subsequently withdrawn from the market amid concerns that it was not effective and posed safety risks.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.

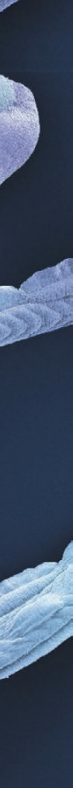
Nature Biotechnology is editorially independent of *Nature*'s news team and is owned by *Nature*'s publisher, Springer Nature.

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.



STEVE GSCHMEISSNER/SPL

The paper urges Han's team to "clarify the uncertainty surrounding NgAgo". One author, Wensheng Wei, a molecular biologist at Peking University, has already made up his mind. "It simply doesn't work, period," he says.

Zhang Xiaoxue, managing editor at *Protein & Cell* in Beijing, says that the journal made an effort to publish the NgAgo paper quickly because of the debate. "In China, it's not just a scientific issue. It's also an ethical and political issue," she says.

The failed replications described in *Nature Biotechnology*[4] were carried out by three more groups; all also used genetic materials provided by Han, targeted the same genes and applied the technique to human cells.

In the *Cell Research* paper[3], researchers report an attempt to use NgAgo to edit a gene in zebrafish embryos that is thought to be related to eye development. Some of the embryos developed either one very small eye and one largely normal eye, or eyes that were fused and formed, according to the paper, on the top of the head "like a cyclops", as if NgAgo had knocked out the gene. But sequencing the genomes of the fish revealed that the gene was still intact.

Lead author Liu Dong, a molecular biologist at Nantong University in China, suggests that the NgAgo molecules clamp onto the genome, but instead of cutting the target gene, they reduce its expression. If he is right, then NgAgo does not make permanent changes that are passed on to the next generation and would therefore not be considered a gene editor.

But Liu offers little insight into the controversy over the original NgAgo experiments, which, he notes, were done in human cells *in vitro*. He adds that the NgAgo protein, which can be easily prepared in the laboratory, could provide a cheap, accessible alternative to current methods of temporarily blocking gene function in zebrafish.

"This is another report confirming that NgAgo does not work as a gene editor."

Critics say that Liu's paper is further evidence against the claims in the original NgAgo paper[1]. "This is another report, now published in a peer-reviewed journal, confirming that NgAgo does not work as a gene editor," says Lluis Montoliu, a geneticist at the Spanish National Centre for Biotechnology in Madrid, who has previously criticized the Han paper.

Han says that he has found a problem that could explain why others are having difficulty replicating his results. "I cannot say right now because the media in China jumps on everything I say," he says. "I need a little bit of time."

One of the few scientists who previously told *Nature* that he had corroborated Han's findings now says that he is using NgAgo, and that he hopes to publish soon. But another who previously noted positive results with NgAgo says now that the "data are confusing" and "we cannot make a conclusion". Neither researcher wanted to be named, for fear of being dragged into the controversy.

The debacle has raised questions about a 224-million-yuan (US$32-million) gene-editing centre that Han's university — the Hebei University of Science and Technology — announced in August that it will build. "Without Han's *Nature Biotechnology* paper and the hype after that, it's impossible for the school to get such huge funding," says Fang Shimin, a former biochemist who has become famous for exposing fraudulent scientists. He was also one of the first to publicize criticism of Han's paper. If Han's work doesn't stand up, "the centre will lose its legitimacy", he says. The university declined requests to discuss the centre. ■

1. Gao, F., Shen, X. Z., Jiang, F., Wu, Y. & Han, C. *Nature Biotechnol.* **34,** 768–773 (2016).
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3. Qi, J. *et al. Cell Res.* http://dx.doi.org/10.1038/cr.2016.134 (2016).
4. Lee, S-H. *et al. Nature Biotechnol.* http://dx.doi.org/10.1038/nbt.3753 (2016).

See http://go.nature.com/2fujd8m for a longer version of this story.