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Gene-silencing technology gets first drug approval after 20-year wait
1 mensagem

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https://www.nature.com/articles/d41586-018-05867-7?utm_source=briefing-dy&utm_medium=email&utm_campaign=briefing&utm_content=20180813

Gene-silencing technology gets first drug approval after 20-year wait

10 August 2018

NEWS

The US Food and Drug Administration's decision breathes new life into RNA-interference therapies.

Heidi Ledford

US regulators have approved the first therapy based on RNA interference (RNAi), a technique that can be used to silence specific genes linked to disease. The drug, patisiran, targets a rare condition that can impair heart and nerve function.

The approval, announced by the US Food and Drug Administration on 10 August, is a landmark for a field that has struggled for nearly two decades to prove its worth in the clinic. Researchers first discovered RNAi 20 years ago[1], sparking hopes of a revolutionary new approach to medicine. Since then, however, a series of setbacks has lessened those expectations.

“This approval is key for the RNAi field,” says James Cardia, head of business development at RXi Pharmaceuticals in Marlborough, Massachusetts, which is developing RNAi treatments. “This is transformational.”

Patisiran works by silencing the gene that underlies a rare disease called hereditary transthyretin amyloidosis. In that illness, mutated forms of the protein transthyretin accumulate in the body, sometimes impairing heart and nerve function.

The drug's approval means that pharmacology textbooks will need to be rewritten, says Ricardo Titze-de-Almeida, who studies RNAi at the University of Brasilia. “We are inaugurating a new pharmacological group,” he says. “We will have many more such drugs in the coming years.”

This was the hope when Alnylam, the company in Cambridge, Massachusetts, that developed patisiran, launched in 2002. Four years later, the Nobel Prize in Physiology or Medicine was

awarded to two RNAi pioneers: Andrew Fire of Stanford University School of Medicine in California and Craig Mello of the University of Massachusetts Medical School in Worcester.

But to make RNAi into medicine, developers would first need to determine how to deliver delicate molecules of RNA safely to their target organs. They needed a way to shield the RNA from degradation in the bloodstream, prevent it from being filtered out by the kidneys, and allow it to exit blood vessels and spread through tissues. “That proved to be a substantially harder problem than we anticipated,” says Douglas Fambrough, chief executive of Dicerna, an RNAi-focused company in Cambridge, Massachusetts.

As researchers grappled with the delivery puzzle, investors began to lose confidence. In 2008, analyst Edward Tenthoff of investment bank Piper Jaffray in New York City advised his clients to stop buying Alnylam stock. “We saw the promise in the technology, but the delivery was lacking,” he says.

By 2010, large pharmaceutical companies were also losing their appetite for RNAi, severing collaborations and ending internal research programmes. “By and large, big pharma left RNAi for dead,” says Fambrough. Safety concerns dealt the field another blow in 2016, when Alnylam abandoned one of its leading RNAi programmes after finding a possible link to patient deaths in a clinical trial.

But gradually, some RNAi companies began to iron out the kinks in their delivery systems, and Tenthoff started to encourage investors to buy stock again. Alnylam experimented with a number of delivery routes and target organs, encasing some of its RNA molecules in fatty nanoparticles orchemically modifying the RNAs to help them survive the perilous journey through the bloodstream.

RNAs protected in this way and injected into the bloodstream tended to accumulate in the kidneys and liver. This led the company to look at transthyretin, which is produced mainly in the liver. In a clinical trial in 225 people with hereditary transthyretin amyloidosis who showed signs of nerve damage, average walking speed significantly improved in those who received the treatment[2]. Walking speed declined in the placebo group.

In the future, Alnylam and others will be able to move beyond the liver, says company co-founder Thomas Tuschl, a biochemist at Rockefeller University in New York City. Quark Pharmaceuticals of Fremont, California is testing RNAi therapies that target proteins in the kidneys and the eye. Alnylam is developing ways to target the brain and spinal cord, and Arrowhead Pharmaceuticals of Pasadena, California, is working on an inhalable RNAi treatment for cystic fibrosis.

“I’ve never been more optimistic about the future of RNAi,” says Fambrough. “All of those tear-your-hair-out days were worth it to get to today.”

Advances in RNA delivery might also benefit researchers who are developing gene-editing therapies based on the popular technique CRISPR–Cas9. That system uses a DNA-cutting protein called Cas9, which is guided to the desired site in the genome by an RNA molecule.

Like RNAi before it, CRISPR–Cas9 has become a common tool in genetics laboratories. But it might still face a difficult and lengthy path to the clinic. Much like ordinary drugs, RNAi therapies

will break down over time; a gene edit, however, is intended to be permanent, which amplifies concerns about safety.

“I hope they can do it more quickly than we did it, but I would not expect it to be so smooth,” says Fambrough. “I wish them the best of luck.”

doi: 10.1038/d41586-018-05867-7

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