

## Antisense technology changed one devastating disease. Why hasn't it transformed others?

by Jason Mast, Max Gelman on November 1st, 2021



The 2016 meeting of the Oligonucleotide Therapeutics Society in Montreal began with a rare mix of promise and elation.

That year, the 27-year-old biotech Ionis showed that a drug, later branded Spinraza, could dramatically alter the course of spinal muscular atrophy, a genetic condition that killed most diagnosed children before age 2. Ionis founder and CEO Stanley Crooke, introduced on stage by a video from past colleagues and SMA patients for a lifetime achievement award, was met with standing applause.

The excitement wasn't just about SMA patients. Spinraza also raised hopes that the long-doubted genetic technology Crooke had championed for decades — strings of DNA known as antisense oligonucleotides — could also offer paths to treat other untreatable neurological conditions.

Ionis already had a few such programs. ALS drugs were in early development. In 2018, Roche and Ionis launched a pivotal trial for Huntington's disease, a devastating neurodegenerative disease.



Louise Vetter

The “trial was a beacon of hope for the HD community,” said Louise Vetter, CEO of the Huntington’s Disease Society of America. “It was the first trial of a disease-modifying therapy that felt real and very close. It was not an in-the-future, it was a now.”

But this year, those hopes faced major setbacks. In March, Roche and Ionis **announced** that the Huntington’s treatment actually appeared to make patients decline faster. A similar drug from Wave Life Sciences **flopped** days later. And weeks ago, Biogen and Ionis **announced** that a treatment for a genetic form of ALS failed to show meaningful differences from placebo in slowing patients’ decline.

The high-profile failures raise a simple question: What happened? Why did the Huntington’s and ALS drugs fail where Spinraza proved such a wild success?

And what does that mean for all the other neurological conditions companies are trying to target with antisense? Two years after Spinraza’s approval, Biogen, which **commercialized** the SMA drug, paid Ionis \$1 billion for a new collaboration. It now has antisense drugs in development with Ionis against Alzheimer’s, Parkinson’s and other forms of ALS. Ionis has a couple fully owned rare nervous system disorder programs. And offshoots from the company are going after degenerative diseases such as muscular dystrophy and Pompe disease.



Frank Bennett

“I’m obviously disappointed,” said Frank Bennett, Ionis CSO and co-inventor of Spinraza. “It’s devastating for the patients. But I think there are a lot of lessons learned and I wouldn’t give up on using antisense for neurological diseases.”

**Anastasia Khvorova, who runs** a therapeutic RNA lab at UMass Medical School, watched the excitement that arose around antisense after Spinraza with some reticence. As transformational as Spinraza was, Khvorova wasn’t certain it would easily translate in other neurological diseases.

“You know,” she said, “I probably knew too much.”

Khvorova pins the Huntington’s and ALS failures in part on the difference between two types of

antisense molecules: RNA-blockers and RNA-degraders.

“It’s two completely different classes of compounds, which have different structures, and on top of it have completely different mechanisms of action,” she said. They are “not the same.”



Anastasia Khvorova

One of the first technologies for genetic therapy ever developed, antisense drugs work by intercepting messenger RNA, the dispatches sent from DNA to the cell’s protein production factories. Then like state censors, they edit the messages before arrival, or trash them altogether. The drugs themselves are made of short strands of nucleotides, the building blocks of DNA and RNA, coded to bind to the precise target.

Broadly speaking, researchers have learned over three decades to do one of two things with these stolen messages: tag them for destruction or block some of the letters, so they contain a slightly altered message. These are two very different tasks, Khvorova said.

Spinraza blocked letters. SMA is caused by mutations in a gene that codes for SMN, a protein nerve cells need to survive. Spinraza binds to RNA from a related gene that usually produces junk, but with a one-letter switch can carry instructions for copious amounts of the crucial protein.

“It just needs to find and bind the [RNA], nothing else,” Khvorova said. Accordingly, Ionis adds a mix of sugars and phosphates that bolt the nucleotides in place, so they remain as stable and immovable as possible.

The Huntington’s and ALS drugs, though, need to destroy RNA. Huntington’s is caused by an unusual genetic defect where three letters in one key gene, called huntingtin, repeat over and over again, producing a toxic protein. And patients with the form of ALS Ionis and Biogen targeted have a mutation that makes a protein toxic. The goal is to eliminate each.

“That’s quite different,” said Adrian Krainer, a professor at Cold Spring Harbor Laboratories and co-inventor of Spinraza.

To destroy RNA, Ionis needed its drug to find its target — the huntingtin gene, for example — and then send a signal to the cell to shred it. Ionis has done this before with at least three different approved therapies, including for an AIDS-related condition, a rare heart disease, and, most recently, amyloidosis, a disease marked by the buildup of toxic protein throughout the body.

Only the amyloidosis drug, though, entered widespread use. And it targets the liver, the easiest spot in the body to pursue.



Adrian Krainer

RNA degradation poses unique biological hurdles: Because the strand has to be recognized by the cell, Ionis can't add much of the sugar-and-phosphate scaffolding it puts on Spinraza to make it stable. That means it's exposed to the cells — “naked on the beach,” Khvorova said — and can be degraded by the various nucleotide-degrading enzymes floating around.

The degradation could give off toxic byproducts, which is one possible explanation for why patients on the Huntington's drug performed worse than placebo. It's also possible Ionis dosed too highly, or that the drug inadvertently eliminated too much of the wild-type huntingtin protein neurons need to survive.

And in both cases, researchers noted, Ionis was trying to slow patients' rapid neurological decline — an inverse and perhaps harder task than helping infants develop for the first time. Few neurodegenerative drugs have ever succeeded.

“There may be some feature of the motor neuron degeneration there that's less responsive to this type of treatment,” said Krainer, referring to the ALS drug. “But I don't think we can conclude that yet from the current result.”

**In ALS, though, investigators think there may be signs of benefit.** The Biogen-Ionis drug, tofersen, tries to degrade the RNA from a gene called SOD1. Some ALS patients have SOD1 mutations that drive the disease and researchers theorized degrading it could slow progression of the disease.



Merit Cudkowitz

“We all expected a very robust clinical finding based on the Phase I and the science,” Massachusetts General ALS director Merit Cudkowitz said.

Tofersen didn't hit the primary in its Phase III study, failing to achieve a significant difference in an ALS functional scale after 28 weeks, though the scale has drawn scrutiny since its introduction in the 1990s. Many observers pointed, however, to the secondary endpoints where tofersen numerically lowered total SOD1 protein and neurofilament levels in the cerebrospinal fluid, a surrogate for cell death.

Most agreed that was enough signal to continue looking at antisense as a way to treat ALS. Cudkowitz said patients whose disease progressed more slowly did “fantastic” in the study, and she's hoping

longer followup will bolster evidence for the drug.

As Biogen brings new antisense ALS drugs forward, they will have to interrogate other outstanding questions about trial design, such as enrolling slow-progressors vs. fast-progressors, determining the correct length and timing of treatment and looking into other genetic mutations to research.

Toby Ferguson, head of Biogen's neuromuscular unit, also noted more could be done to design better trials. A major hurdle is the time it takes to diagnose ALS patients, with most waiting somewhere between nine to 12 months to receive the correct conclusion from doctors.



Toby Ferguson

In a disease that's universally fatal, that can mean precious time wasted both for patients and companies evaluating experimental therapies. Biogen will also re-evaluate how long the trials for antisense or other drugs last, fearing they may have taken patients off placebo too soon to showcase the antisense drug ability.

"I'm cautiously optimistic," Ferguson said. "I don't think we really truly know yet."

Biogen and Ionis are now bringing forward two antisense drugs for other forms of ALS, on top of one program fully-owned by Ionis. And Cudkowicz is taking a glass-half-full approach.

"It's kind of comparable to bone marrow transplants," Cudkowicz said. "The first ones didn't work ... but they kept fine tuning it to be really effective. At that early stage where they're not working as well, they wouldn't give up on that. We have to keep tweaking it for different issues."

**Khvorova thinks it might ultimately take more than tweaks** to tackle the neurological disorders Ionis and others are pursuing. When Crooke founded Ionis, antisense was essentially the only genetic technology available, and it was the first such technology to reach key milestones — the first to be approved as a drug, the first to be effective in the nervous system.

Other genetic technologies followed though, most notably gene therapy and RNAi, a similar technology to antisense that over the years has proved far more effective at degrading RNA, Khvorova said. She noted that Novartis' new RNAi drug for heart disease can be dosed every six months and new technology should extend future drugs to once every 12 months. The Ionis Huntington's drug was dosed every eight weeks.

Tofersen showed some improvement in ALS patients, she said. But there's an RNAi molecule shown to be 70 times more potent than antisense in knocking down SOD1.

"It's a partial failure but it's also a partial success," she said. "The path forward is clear."



Paul Tesar

Not everyone agrees with the forecast. Paul Tesar, a neurologist at Case Western who started focusing on antisense after Spinraza's success, noted that, although there are multiple RNAi drugs now approved that target the liver, no one has even attempted to put RNAi in the nervous system in humans.

Alnylam, Regeneron and Genentech are working toward that goal, including with technology from Khvorova's lab, but the approaches remain unproven. Meanwhile, other antisense strategies have yet to be tested: In Huntington's, small biotechs are developing antisense drugs that only target the mutant huntingtin, leaving the healthy gene unscathed. And Biogen is still waiting on data to see if tofersen can delay the onset of ALS in presymptomatic patients.

"Things are still very early," he said. "We don't yet have answers to all these sorts of questions."



Khvorova, in either case, wasn't writing off antisense entirely. RNAi doesn't work well for blocking RNA, as Spinraza does, leaving antisense as the best option for diseases where you want to change a gene's spelling, such as [muscular dystrophies](#) and a huge number of [ultra-rare diseases](#).

For destroying RNA, she sees it as the beginning of a progression: RNAi could have a better effect on diseases that antisense only has a modest impact on, and gene therapy or CRISPR could have an even larger effect. "I think that future looks really promising," she said.

Vetter, the Huntington's advocate, said she is also cautioning patients to remain optimistic, pointing to the slate of new molecules about to enter the clinic.

"There's enough innovation right now in this space, that we don't have to put all of our eggs in one basket," she said. "I think that's what's allowed the community as a whole to move past the heartbreak of March."

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