

Laboring to breathe and near death as a baby, Cameron Harding, nearly 3, receives a drug that keeps his motor neurons alive, allowing him significant muscle movement.

BIOMEDICINE

Antisense rescues babies from killer disease

Spinal muscular atrophy drug may herald treatments for other genetic brain illnesses

By Meredith Wadman

iomedical researchers tackling genetic diseases dream of tracing a clean, straight line from discovering a mutation to understanding a disease's mechanism to developing a curative drug. The messy complexities of biology have often frustrated that hope. But building on a deep understanding of the basic biology of a disease, they have now taken just such a path to what appears to be an unprecedented advance in treating spinal muscular atrophy (SMA), a progressive, fatal neurological disorder that kills its most severely affected victims as babies or toddlers. The therapy, called nusinersen, is poised to win regulatory approval within weeks or months, and it may well be a harbinger of successes with other grave, inherited neurological disorders, from Huntington disease to subsets of amyotrophic lateral sclerosis (ALS).

"This is a huge win for our field," says molecular neuroscientist J. Paul Taylor of St. Jude Children's Research Hospital in Memphis, Tennessee, who is not involved with the drug or with the companies behind it. "There has never been a disease-altering therapy for a neurodegenerative disease."

As one of a long, but often disappointing, class of drug candidates called antisense, which use snippets of genetic sequence to correct errors in the conversion of RNA into proteins, nusinersen could open the way to similar treatments for other neurodegenerative diseases. "Nusinersen is a game changer," says Loren Eng, the president of the SMA Foundation in New York City and the mother of a 16-year-old with the disease. "It's a drug that treats a disease that has never been treated before. It's also a model for how to make drugs and get them across the finish line early."

SMA, the most common genetic cause of death in childhood, inexorably destroys the motor neurons of the spinal cord and brainstem. These cells allow movement, including swallowing and breathing. About one in 50 adults is an asymptomatic carrier of the recessive genetic defect that causes it, a flaw in the gene *SMNI*—for "survival motor neuron 1." In children who inherit two copies of the defect—between one in 8000 and one in 12,000 infants—the SMN protein is largely missing, which leads to the death of motor neurons. Toddlers with the most severe form of the disease ultimately suffocate when their respiratory muscles give out.

Children with milder forms of SMA can survive into adulthood, but must cope with progressive and often immobilizing weakness. The disease course depends on how many copies they carry of a very slightly different gene, *SMN2*, that produces a modest amount of the SMN protein. Most of the time that protein degrades quickly, because after transcribing *SMN2*, cells splice out a key bit of protein-coding genetic sequence, so-called exon 7, producing a truncated version.

But nusinersen, a snippet of modified nucleic acid akin to RNA, can keep those vital motor neurons alive. Its short sequence complements part of a messenger RNA (mRNA) precursor produced by *SMN2*, binding to the molecule there and altering its processing so that exon 7 is included and the gene's full-length, functional protein is made (see graphic, p. 1360).

The drug's efficacy seems clear from strongly positive, though unpublished, results from two late-stage clinical trials. On 7 November, a trial of the drug in 84 wheelchair-bound children was stopped on the grounds that the treatment's benefits were so obvious that it was unethical to deny the antisense therapy to the 42 untreated children in the control arm. On measures including 33 tests of movement such as sitting, standing, and taking steps, investigators found a "highly statistically significant improvement" in the treated children. In July, a similar trial in 121 infants with the most severe form of the disease, who would otherwise die within several years, was similarly stopped in order to allow the 41 babies in the control group to begin receiving nusinersen. Soon thereafter, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency granted the drug fast-track review status.

Nusinseren clearly saved Cameron Harding of Charleston, South Carolina, who was diagnosed with SMA at 5 weeks old after his parents noticed that their newborn son couldn't move and was struggling to breathe. He began receiving the drug in a clinical trial at 7 weeks old and continues to do so. Late this month he will turn 3 years old. Over that time, he has gone from lying immobile to moving his arms to grasping toys to sitting up unsupported to standing with support and, lately, barreling around in a light-weight wheelchair he propels with his arms. "He absolutely would not be alive without the medication. He wouldn't have lasted 6 months," says Cameron's father. Rob Harding.

Cameron is still improving, he adds. "We were very afraid he would reach a plateau and that was going to be it. But he continues to get stronger."

Other antisense drugs have had far less success over the past 2 decades, with only a handful earning marketing approval. The most recent was the most controversial. In September, Sarepta Therapeutics of Cambridge, Massachusetts, won approval from FDA for eteplirsen, which aims to treat boys with a particular mutation causing another progressive and ultimately fatal inherited condition: Duchenne muscular dystrophy. At the molecular level, eteplirsen does the opposite of nusinersen: It removes an exon that disrupts the reading of an mRNA precursor for a protein, dystrophin, that muscles need. But the resulting protein is truncated and only partially functional. Critics charged that FDA approved the drug only because of pressure from politicians and parents of affected children, overruling its staff advisers and relying on at-best-equivocal trial results.

Although no one expects similar battles over nusinersen given its striking clinical results, it is not a perfect drug. It produced no serious side effects in the trials, but it cannot rescue motor neurons that are already dead, meaning that it cannot restore motor function for older SMA patients. Indeed, the goal is to begin treatment even before babies develop symptoms, and calls for universal newborn screening are expected to follow the drug's approval. "The earlier we treat the better the effect, and the longer we treat the better the effect," says Stanley Crooke, CEO of Ionis Pharmaceuticals, the company in Carlsbad, California, that developed nusinersen and has subsequently licensed it to Biogen in Cambridge.

Eng, who with her husband, Dinakar Singh, has channeled more than \$110 million into SMA research through the foundation the couple launched in 2003, says that the tale of nusinersen demonstrates how "it takes a village" of scientists, physicians, companies, nonprofits, and families to efficiently develop a successful drug. Their foundation, for example, helped fund Adrian Krainer, a biochemist and RNA-splicing expert at the Cold Spring Harbor Laboratory in New York. Eight years after the discovery of the SMN genes in 1995, Krainer set the stage for the development of nusinersen when he engineered a synthetic snippet of genetic code that tweaked the splicing of SMN2's mRNA prescursor, so that the final RNA included exon 7.

A game-changing drug

An RNA-like molecule called nusinersen can treat spinal muscular atrophy (SMA) by boosting production of a key protein.

Exploiting a second gene

In SMA, the SMN1 gene is faulty. A related gene, SMN2, typically makes little functional protein, but nusinersen increases production enough to sustain motor neurons.



Fixing the message

By binding to a messenger RNA (mRNA) precursor, nusinersen boosts the fraction of mRNAs with a key segment, exon 7, needed for a functional protein.



At another point, Eng persuaded Taiwanese researchers to share at reasonable cost a mouse model of SMA with which nusinersen and other drug candidates could be tested. Later, she introduced leaders at Ionis to executives at Biogen. And by the time the drug was ready for all-important phase III trials, the foundation, SMA advocacy and support groups, and physicians had persuaded enough parents of SMA patients to participate in a trial in which their children might not get the actual drug-a sham arm

was considered necessary to prove the drug's value to regulators.

Because antisense drugs do not cross the blood-brain barrier, the drug was injected near the base of the spine into fluid that bathes the brain and spinal cord, where the afflicted motor neurons are located. In the sham arms, babies and children chosen at random simply received needle pricks in their spine. "It was very difficult to see sham injection-controlled trials," Krainer says. But, he adds, the phase III trial results are "the best news one could hope to get."

A paper in The Lancet last week describing an earlier phase II trial of nusinersen demonstrates that such spinal injections reach their targets. Autopsy samples from several infants who died during the trial revealed that the drug had traveled to the targeted brain and spine motor neurons. In samples of the infants' spinal tissue, levels of full-length SMN protein were elevated compared with untreated babies.

To sustain nusinersen's benefits, SMA patients will likely need to receive spinal injections two or three times a year. But that may not keep symptoms that result from the lack of SMN in other tissues and organs from emerging, because the drug does not travel beyond the brain and spinal cord.

Still, the success of nusinersen and its delivery method into neurons has enthused those who work on other inherited neurodegenerative diseases caused by genetic defects that could, in theory, be overcome by antisense drugs that manipulate RNA processing. "There is more excitement now about antisense therapy," says Walter Koroshetz, a Huntington disease expert who is the director of the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland. "If the problem of getting antisense access to the neurons and glia has been solved, then there's potential for a bunch of genetically determined diseases to get effective treatments."

Ionis is already in clinical trials with similarly delivered antisense drugs for Huntington disease and a form of ALS. Its drugs are also being tested in animal models of Rett and Angelman syndromes, rare neurological disorders whose mutations are amenable to an antisense approach.

Jeffrey Rothstein, a neuroscientist at the Johns Hopkins University School of Medicine in Baltimore, Maryland, who was not involved with the trials of nusinersen, sees its success as an object lesson in the importance of understanding the underpinnings of a disease. "It's a powerful story of moving from superb preclinical science to the development of this drug," he says. "This proves that when you get at the initial insult you can really change the course of the disease."

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Editor's Summary

Antisense rescues babies from killer disease Meredith Wadman (December 15, 2016) *Science* **354** (6318), 1359-1360. [doi: 10.1126/science.354.6318.1359]

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