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FEATURES

DARING TO HOPE

Patients thrill to reports of a promising antisense drug against Huntington disease, but no one is sure yet whether it works

By **Meredith Wadman**, *in Vancouver, Canada;*
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The dark shadow of Huntington disease fell squarely over Michelle Dardengo's life on the day in 1986 that her 52-year-old father was found floating in the river in Tahsis, the remote Vancouver Island mill town where she grew up. Richard Varney had left his wedding ring, watch, and wallet on the bathroom counter; ridden his bike to a bridge that spans the rocky river; and jumped. The 4.5-meter drop broke his pelvis. The town doctor happened to be fishing below and pulled Varney out as he floated downstream, saving his life.

But his tailspin continued. The once funny man who read the *Encyclopedia Britannica* for pleasure; the good dancer who loved ABBA, the Three Tenors, and AC/DC; the affable volunteer firefighter—that man was disappearing. He was being replaced by an erratic, raging misanthrope wedded to 40-ounce bottles of Bacardi whose legs would not stay still when he reclined in his La-Z-Boy.

In 1988, Varney was diagnosed with Huntington disease. That explained his transformation but offered little comfort. Huntington is a brutal brain malady caused by a mutant protein that inexorably robs victims of control of their movements and their minds. Patients are plagued by jerky, purposeless movements called chorea. They may become depressed, irritable, and impulsive. They inevitably suffer from progressive dementia. The slow decline typically begins in midlife and lasts 15 to 20 years, as the toxic protein damages and finally kills neurons. For both families and the afflicted, the descent is agonizing, not least because each child of an affected person has a 50% chance of inheriting the fatal disease.

In the United States, about 30,000 people have symptomatic Huntington disease and more than 200,000 carry the mutation that ensures they will develop it. Globally, between three and 10 people in every 100,000 are affected, with those of European extraction at highest risk. In a large study published in the *Journal of Neurology* in June, Danish researchers found that people with Huntington disease were nearly nine times more likely to attempt suicide than the general population.

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For the first 15 years after her father's diagnosis, while scientists discovered the genetic mutation that causes Huntington and embarked on a seemingly endless chase for a remedy, Dardengo avoided the genetic testing that would reveal whether her father's decline was a preview of her future. Already married when her dad was diagnosed, she gave birth to a son and a daughter and had a job she loved, doing software diagnostics for an insurance company. Then in 2003, the year her father died after being institutionalized for more than a decade, she got tested. "It was bothering me," she says. "You have to plan for the future." She was positive for the mutation.

About a decade later, Dardengo noticed that her handwriting was becoming "unmanageable." Her balance declined. She returned from walking her dogs with bloody knees and scraped hands. In April 2015—at 52, the same age that her father had leapt from the bridge—she was forced to leave her job. "Cognitively, I don't think you are a good fit," a new boss told her.

Then an unfamiliar commodity entered her life: hope. Dardengo's physician, Blair Leavitt, a Huntington disease researcher at the University of British Columbia (UBC) here, asked whether she wanted to join a nascent clinical trial of a new medication made by a Carlsbad, California, biotechnology company, Ionis Pharmaceuticals. The drug, the product of 25 years of research, was an antisense molecule—a short stretch of synthetic DNA tailor-made to block production of the Huntington protein.

Michelle Dardengo walks her dog (above) near her home in Coquitlam, Canada. Dardengo's father, shown holding her son Joel in a 1989 photo (left), died of Huntington disease. Joel carries the mutation.

Joining the trial would be risky. Dozens of antisense drugs had entered clinical trials; few had become approved drugs. This particular medicine, injected into the fluid that surrounds the spinal cord, had never been put in humans. Dardengo might receive the active drug or she might get a placebo. In August 2015, she became "patient one."

Three years later, that trial is famous. Its results electrified the Huntington disease community in December 2017 by indicating that the drug, formerly IONIS-

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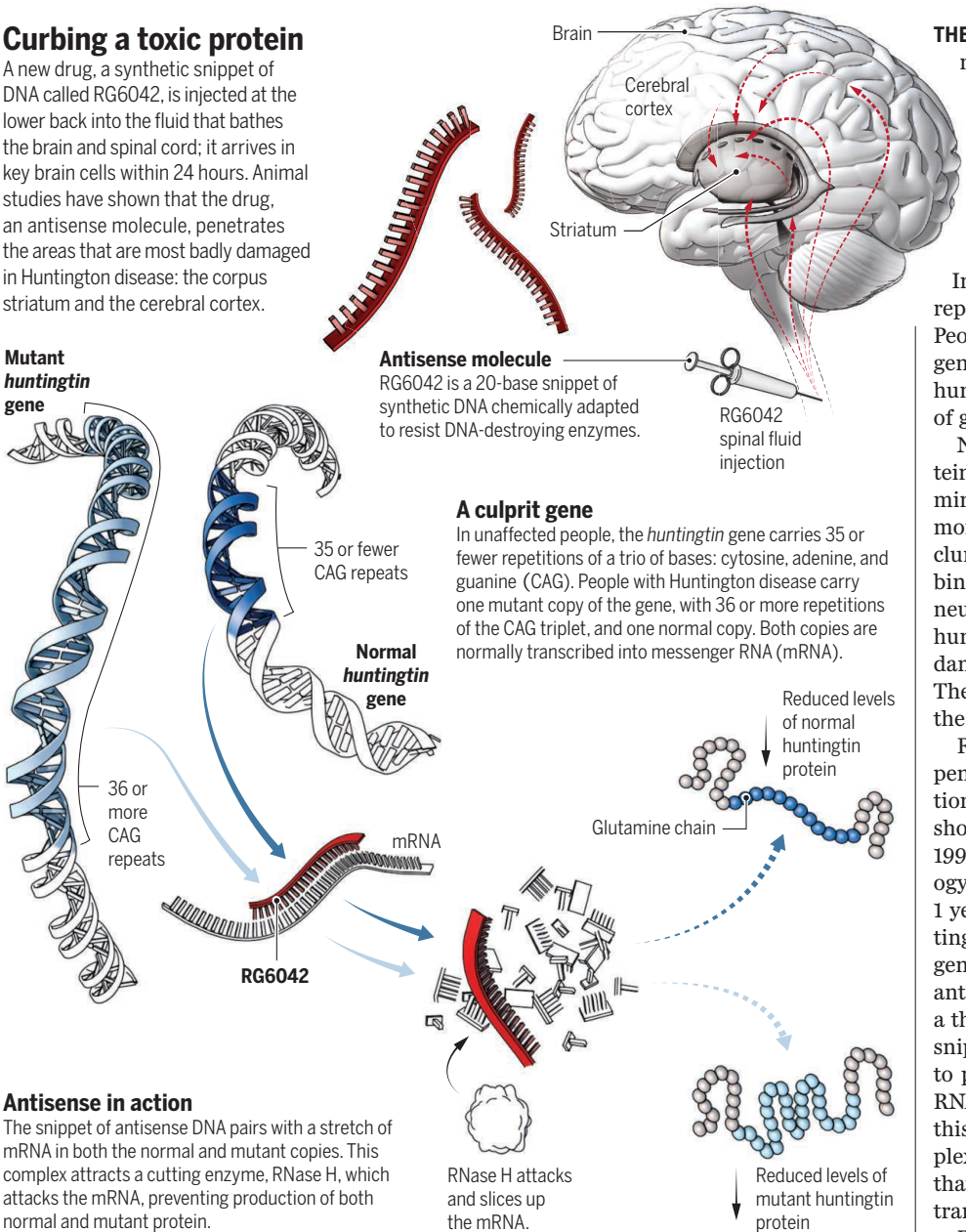
Curbing a toxic protein

A new drug, a synthetic snippet of DNA called RG6042, is injected at the lower back into the fluid that bathes the brain and spinal cord; it arrives in key brain cells within 24 hours. Animal studies have shown that the drug, an antisense molecule, penetrates the areas that are most badly damaged in Huntington disease: the corpus striatum and the cerebral cortex.



HTTRx and now called RG6042, reduces the amount of the culprit protein in the human brain—the first time any medicine has done so. Preliminary data released in April even hint at improvements in a few clinical measures.

The Basel, Switzerland–based pharmaceutical company Roche, which licensed RG6042, is preparing to move it into a pivotal clinical trial, with details to be announced in the next few months. "We had emails and phone calls from patients saying, 'I want to join this [upcoming] trial now. I'm willing to move house to do it,'" recalls Anne Rosser, a neuroscientist at Cardiff University, who oversaw one of nine sites in the first trial.

She and others who work with Huntington patients find themselves scrambling to manage expectations. "One feels for these patients because the clock is ticking for them," Rosser says. But although the drug scored high for safety in the recent trial, whether it slows or stops the disease simply isn't known. "We haven't got evidence of efficacy," she says. That will have to wait for the results of the next trial. And some scientists still worry about the drug's long-term safety.

Given the desperation of patients and their families, Louise Vetter, president and CEO of the Huntington's Disease Society of America in New York City, says her group and others "need to manage back the hope a little bit. And that's really hard."

THE MUTATION that causes Huntington—named after U.S. physician George Huntington, who described the disease in 1872—is located near the tip of the short arm of chromosome 4. Healthy people carry two copies of the *huntingtin* gene, each with up to 35 repetitions of a trio of nucleotides—cytosine, adenine, and guanine (CAG). In the mutated gene, this CAG triplet is repeated 36 or more times, like a stutter. People who inherit a copy of the mutant gene from one parent produce a mutant huntingtin protein with an extra-long chain of glutamine amino acids.

No one is sure just how the mutant protein damages neurons. But chains of glutamine longer than 36 amino acids are much more likely to stick to each other, forming clumps that may disrupt membranes or bind and inactivate other molecules within neurons. Afflicted people produce mutant huntingtin throughout their lives, and the damage mounts until symptoms appear. The more CAG repeats a patient harbors, the sooner the inevitable day comes.

Regardless of how the destruction happens, scientists reasoned, stopping production of the mutant protein at its source should halt downstream damage. Back in 1992, *Science* declared antisense technology one of the 10 hottest areas of the year; 1 year later, the mutation that causes Huntington was published. Because just a single gene was responsible, shutting it down with antisense seemed an obvious approach for a therapy. The idea was that synthetic DNA snippets with a sequence complementary to part of the *huntingtin* gene's messenger RNA (mRNA) would bind to the mRNA. In this case, the resulting DNA-mRNA complex summons a cutting enzyme, RNase H, that degrades the mRNA and prevents its translation into protein (see graphic, left).

But for 25 years the idea wasn't practical. Early antisense oligonucleotides (ASOs) didn't bind mRNA targets efficiently and were quickly degraded by enzymes. Several companies dropped out. By the early 2000s, having chemically improved the ASOs and done animal studies, Ionis began to tailor ASOs to specific neurological diseases, including one to curb spinal muscular atrophy (*Science*, 16 December 2016, p. 1359).

In 2006, Ionis researchers, led by the firm's vice president of research, Frank Bennett, launched a collaboration with neuroscientist Don Cleveland and postdoc Holly Kordasiewicz of the University of California, San Diego, to develop an ASO to attack Huntington disease. (Kordasiewicz has since joined Ionis.) By 2012, they had a 20-letter ASO that reversed symptoms and slowed brain atrophy in mouse models of

GRAPHIC: C. BICKEL/*SCIENCE*

Huntington. In macaques, dogs, and pigs, the researchers injected the ASO into the cerebrospinal fluid (CSF), which bathes the spinal cord and brain. The drug reduced the mutant protein in key brain regions, including the cortex and the corpus striatum, a deeper brain structure that is the disease's first target. And it appeared to be safe.

In early 2015, researchers at several institutions delivered the last tool needed for a human trial: new tests that could detect levels of mutant huntingtin protein in the CSF. Crucially, one group also showed that in mice, reductions of mutant protein in the CSF corresponded to reductions in the brain itself. Now, researchers could collect human CSF and see reflected there how their ASO likely affected levels of the toxic protein in patients' brains.

IN AUGUST 2015, Dardengo lay on her side at UBC Hospital, her face to the wall. She felt Leavitt's needle inject anesthetic in the small of her back. After that, she felt nothing while he withdrew 20 milliliters of her spinal fluid and replaced it with the medication, dissolved in liquid. That was the first of four monthly injections. The trial was double-blind: Neither she nor Leavitt knew whether she was receiving placebo or the lowest of the planned doses of active drug, the only dose given to the first subjects.

Dardengo was unfazed by being patient one. "I never felt afraid," she recalls. "Dr. Leavitt always asked: 'You know that you could die doing this?' I always said: 'Yes, but my kids aren't going to have to worry.'"

She thought she felt better after the last monthly injection, but she saw no improvement in her symptoms. Her balance was still off—she didn't dare wear high heels—and she still got stuck in the middle of sentences. Months earlier, she had quit clipping her cat's claws for fear of injuring the animal. Her husband Marc Dardengo had stopped asking her to run errands for his business because she so often got lost. These things didn't change.

Then in November 2016, she and Marc received news that left them numb. Joel Dardengo, age 27, told his parents he had been tested for the Huntington mutation. He was positive.

His mother's trial was cold comfort for Joel, a realist keenly aware of the pitfalls of science. "You can YouTube the disease and see what the endgame looks like," he says. "It's not the nicest."

Joel told his fiancée that she was free to leave him. She refused. The couple, who want to have children, began to discuss in vitro fertilization, which would allow them to implant only Huntington-free embryos. But Joel, an electronics technician, and his fiancée, a prison guard, see no way to pay for the $30,000 procedure.

Thirteen months later, at 12:01 a.m. on 11 December 2017, Michelle received an email: Ionis had announced the results of the trial in a press release. (A paper is still in the works.) After testing in 46 people, including her, RG6042 appeared to be safe, with minimal side effects. And after four monthly doses, levels of mutant huntingtin in patients' CSF had decreased in a dose-dependent manner: The antisense molecule appeared to be hitting its target.

The results triggered a happy uproar among Huntington families. Michelle and Marc Dardengo uncorked a bottle of chardonnay and toasted the possibility that their children would live Huntington-free lives. Vetter, 5000 kilometers away, got a text message from her scientific director telling her to check her email immediately. She pulled over to the side of New Jersey's Route 23, read the Ionis press release, and wept. At Huntington disease clinics from Baltimore, Maryland, to Bochum, Germany, phones began buzzing, email inboxes overflowing, and appointment requests surging. At University College London, home to the trial's global leader, neurologist Sarah Tabrizi, patient referrals briefly quadrupled.

> ***"I feel so much hope. Things are so different between my dad and me: I've got a life to live."***
> **Michelle Dardengo**

On the same day the results were revealed, Roche announced it had paid $45 million to license the drug from Ionis and would move it into a pivotal clinical trial. That trial will enroll hundreds of patients in Europe, Canada, and the United States for up to 2 years, allowing the company to determine whether RG6042 slows or stops the disease.

Ionis presented more details about the first trial's results at two meetings earlier this year. In March, the company reported that levels of mutant protein in the two highest-dose patient groups had declined on average by 40% and in some cases up to 60%. (In lab animals, smaller reductions had reduced symptoms of the disease.) And in April, Tabrizi reported that aggregated data from all patients showed a statistically significant correlation between the amount of lowering of mutant protein in their spinal fluid and improvement in three of five standard measures used to assess Huntington disease progression. But researchers were quick to temper the resulting excitement with caution. Bennett notes that other clinical measures did not improve significantly. "You can always find some correlations if you look hard enough. … The only way to really validate this is to do additional longer-term studies."

Tabrizi, who like Leavitt consults for Roche and competing companies, agrees. She points out that the first trial wasn't designed to gauge effectiveness. "The big question we have now is: Is the degree of mutant huntingtin lowering in the brain enough to slow the disease's progression?"

At the moment, no one can say whether reduced protein levels will help already damaged brains recover, how long any positive effects might last, or whether dangerous side effects will crop up down the road. Tabrizi says patients should not expect "some Lazarus-like effect."

One scientist not involved with the trial is even more circumspect. "People said in 1993: 'We have the gene—we have the cure,'" recalls Ole Isacson, a neurodegenerative disease expert at the Harvard Stem Cell Institute. In the mid-1990s, he ran a first, failed experiment trying to suppress huntingtin production in mice using an ASO. "And 25 years later, there may be a slight chance. This is not a sure home run."

ALTHOUGH THE FIRST TRIAL appeared to show that RG6042 is safe, some researchers still have concerns because the drug suppresses production of both the normal and mutant forms of the huntingtin protein. Because mutant *huntingtin* genes vary in sequence, a drug targeted to one version of the mutant allele would not work for every patient. It also would be technically more challenging to develop. So Ionis opted for a nonselective ASO that targets a sequence found in all *huntingtin* genes, mutant and normal.

Doing so was a calculated risk. No one knows whether normal huntingtin is essential to brain health in adults. (It is essential to early development: Mice without it perish as embryos.) Bennett notes that RG6042's effects are less drastic than deleting the gene entirely: "We're not knocking out huntingtin [protein], we're reducing it." Leavitt shares his confidence, noting that in Ionis's in-house work, "Nothing from the preclinical animal studies suggested any toxicity."

But 1 year ago, scientists at The University of Tennessee Health Science Center (UTHSC) in Memphis found something different, as they reported in *PLOS Genetics*. They knocked out the huntingtin protein

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in mice at 3, 6, and 9 months of age. At all ages, the mice developed severe motor and behavioral deficits and progressive brain pathology: The animals' thalami—sensory and motor signal relay stations—became calcified, and their brains atrophied.

"We end up sounding like a Cassandra," says Paula Dietrich, a neurobiologist at UTHSC who was the paper's first author. "We bring the bad news, and nobody wants to hear or believe it."

Dietrich concedes that mice findings may not apply to humans. But she notes that *huntingtin* is expressed throughout the brain and cautions that the levels of RG6042 needed to penetrate the deeper structures where Huntington pathology begins could have unwanted effects. "To reach efficacy in the striatum, you may have to expose other regions of the brain to extremely high concentrations," she says.

Another company, Wave Life Sciences of Cambridge, Massachusetts, is developing two antisense drugs aimed at suppressing only the mutant gene, leaving the normal one untouched. Wave's ASOs target two sequence variants, one or both of which occur in 70% of Huntington patients. Both drugs are in initial clinical trials, with results expected next summer, and the firm thinks its approach may be safer than RG6042.

"No one knows the longer-term implications of knocking down the healthy allele," says Chandra Vargeese, Wave's senior vice president and head of research. "The expanded allele is the causative factor. So why not leave the healthy allele intact?"

BY ABOUT 24 HOURS AFTER injection into the CSF, RG6042 has diffused into neurons in the brain, where it remains for 3 to 4 months. Bennett says animal studies tracing the drug's uptake and activity suggest that monthly injections of the highest trial dose might begin to measurably improve symptoms after 6 months—if the drug works.

In January, Michelle Dardengo began to receive monthly injections of 120 milligrams of RG6042—the highest dose dispensed in the first study. Along with 45 other patients from that study, she is taking part in an open-label extension of the trial. It is designed to produce long-term safety data and to chart all 46 patients' disease progression. But for Dardengo, it is a trial of the drug's promise.

In an in-person interview in March, shortly after her third such injection, Dardengo appeared tired. Her speech was sometimes halting and stopped midsentence.

Three months later, in a telephone interview in June, she spoke fluently, in complete sentences. She was still gamely answering questions after 2 hours. "I find that my speaking is a lot better. Like, I can actually finish a sentence," she volunteered.

Dardengo also reports that she and her dogs are walking farther, on rougher trails, than was her habit in January. She added: "My handwriting is becoming quite legible now." In July, Dardengo noted that she has resumed clipping the cat's claws and sent a video of herself doing so with apparently steady hands. Marc Dardengo confirms that his wife's walking stamina and handwriting have improved, and he notes that her violent leg movements while sleeping have virtually disappeared. And he thinks that the deterioration of her memory has stabilized. "Before the start of the [open label] trial, I could see her memory [go downhill] over the course of a year. Since January, [with her] taking this drug, I am not seeing that type of change."

But he cautioned that his wife's verbal fluency is a moving target. "She has easier days with conversation more often than before. But she also has days when the dots aren't connecting."

And Joel Dardengo believes his mother's memory is getting worse. In June, for example, she forgot to buy him a birthday cake, a long-standing tradition. Paying for a pricey meal at a restaurant, she uncharacteristically failed to tip the server.

Trial scientists Tabrizi and Leavitt strongly caution that one patient's experience is an anecdote, not a study. "An *n* of one is just that," Leavitt says, adding: "The placebo effect is very real. We don't want to put out the impression that [the drug] is working. Because we don't know yet." Tabrizi says she and her team are doing their all—by phone, email, and in person—to communicate that to patients.

Today, Michelle Dardengo says her goal is to ride her bicycle in 6 months. To win Leavitt's permission to attempt this, she needs to pass the heel-to-toe walking test administered to suspected drunk drivers without losing her balance, a feat that eludes her today.

She is nonetheless buoyant. "I feel so much hope," she says. "Things are so different between my dad and me: I've got a life to live." For her son, her hopes are even higher: "Joel could definitely be a candidate to potentially never see or experience Huntington."

Joel himself is far more cautious. "I do wish for the best," he says. "At the same time, I do prepare for the worst." ■

Michelle Dardengo, on her way to a hiking trail with her dog, says her confidence behind the wheel has improved since last year.

PHOTO: JOHN LEHMANN

Daring to hope

Meredith Wadman

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