Antisense Therapy Reverses Symptoms in Huntington Model, with Long-term Benefits

Investigators Envision Clinical Trial Within Two Years

BY RICHARD ROBINSON

In contrast, in a June 21 paper in Neuron, investigators reported that the antisense oligonucleotide ("oligo"), a modified form of DNA that caused the destruction of the messenger RNA for both mutant and normal huntingtin, was injected directly into the CSF. Because there are no known cellular receptors for such molecules, they are much more widely circulated before being taken into cells, said the study's senior investigator Don Cleveland, PhD, professor of medicine, neurosciences, and cellular and molecular medicine at the Ludwig Institute for Cancer Research at the University of California, San Diego. Holly Kordasiewicz, PhD, who was formerly in Dr. Cleveland's lab and is now at Isis Pharmaceuticals in Carlsbad, CA, led the study.

"We show that intrathecal delivery can achieve broad distribution, not just in the spinal cord but in almost all brain regions, and reaches the major brain regions that you would want to get to treat Huntington's disease," Dr. Cleveland said.

Mice bearing the mutant human HD gene were continuously infused with the antisense oligo for two weeks, and then the process was stopped. The oligo was not detected in regions of the brain immediately surrounding the injection site.

These levels remained reduced for four weeks after stopping treatment, and returned to normal after an additional four weeks.

Based on these results, Dr. Cleveland said, "it would take a true pessimist to think that we can't deliver the drug in an effective way to parts of the [human] brain that are centrally involved in the disease. And that's pretty good. It's not perfect but it's pretty good." Based on these results, Isis, the company that produces the oligo, is moving ahead with plans for a clinical trial within two years.

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"mitigates the risk of lowering the normal protein because we don't have to suppress it continuously to have a long-term benefit."

The researchers also infused the oligo into the CSF of Rhesus monkeys for 21 days, using technology similar to that used in a recent clinical trial of antisense oligonucleotides for amyotrophic lateral sclerosis. They found that the oligo distributed widely, accumulating in both cortex and the caudate nucleus of the striatum, and reduced levels of huntingtin mRNA by 25 percent to 63 percent, depending on the brain region. These levels remained reduced for four weeks after stopping treatment, and returned to normal after an additional four weeks.

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if you lower it, you have the possibility of recovering function that apparently had been lost. To the extent that holds in humans, that should affect the way we think about neurodegenerative disease. It suggests that at least some aspects of it may be reversible. Almost certainly the deficits we see are the interplay between helpful and maladaptive changes the brain undergoes” to cope with the accumulation of mutant protein.

The exact pathogenic cascade through which mutant huntingtin causes disease remains unclear, said Robert Pacifi ci, PhD, chief scientifi c offi cer of CHDI, a nonprofi t research organization dedicated to Huntington’s disease. “But if there is one therapeutic approach that really skirts these arguments, it is huntingtin lowering.”

Both Dr. Finkbeiner and Dr. Pacifi ci were encouraged and excited about the prospects for a clinical trial. The key question in any clinical trial, Dr. Finkbeiner said, “is are you working on a validated target?” Whatever the downstream mechanisms, it is clear that in HD, the mutant protein is the ultimate validated target, and lowering it should be the initial effi cacy measure in any trial of antisense therapy.

“I think if you show that, I would be very committed to keep doing clinical trials,” even if symptomatic improvement is more diffi cult to demonstrate initially.

It must also be shown that the treatment is safe in humans. “I think all of us feel there is going to be a minimum amount of protein lowering that is going to be necessary to have a therapeutic effect,” Dr. Pacifi ci said, “but also a maximum beyond which you might end up getting del- eterious effects.” due to a reduction in normal huntingtin. The protein is required during development, but its role in the adult brain is unknown, with some researchers suggesting it may be unnecessary.

But the bottom line, he said, is that “we’re very excited about the prospects for antisense treatment in HD. “It’s going to be high risk in terms of its chances for success, but we think it’s well worth trying.”

REFERENCE:

DR. STEVEN FINKBEINER:
“There does seem to be reasonable confidence that you can actually deliver the drug widely throughout the nervous system. The other thing that’s really new is that you can get behavioral benefi ts that last quite a bit longer than the measurable suppression in the Huntington’s gene.”