Silencing of an ALS gene safely delivered to patients in new study

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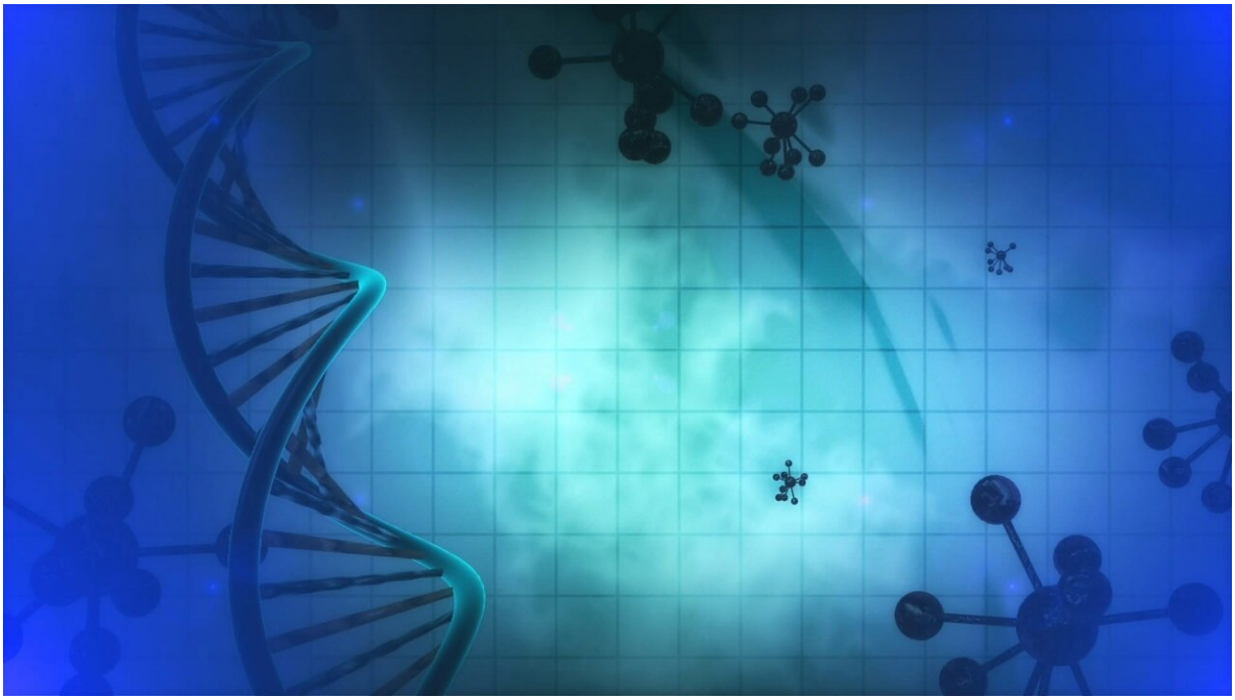

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UMass Medical School and Massachusetts General Hospital are the first to safely treat two research participants with a synthetic microRNA, delivered into the spinal fluid, designed to silence a human disease-causing gene. Details of the treatment, which targeted the mutant SOD1 gene that causes ALS, appear in the *New England Journal of Medicine*.

The study was led by Robert H. Brown Jr., DPhil, MD, the Leo P. and Theresa M. LaChance Chair in Medical Research, professor of neurology and director of the Program in Neurotherapeutics at UMMS; and Christian Mueller, Ph.D., associate professor of pediatrics at UMMS, in collaboration with Merit Cudkowicz, MD, director of the Sean M. Healey & AMG Center for ALS, and chief of neurology at MGH and the Julianne Dorn Professor of Neurology at Harvard Medical School; and James D. Berry, MD, MPH, the Winthrop Family Scholar in ALS Sciences and chief of the MGH Division of ALS and Motor Neuron Diseases at the Sean M. Healey & AMG Center for ALS at MGH.

"The biggest takeaway from this study is that we delivered a new class of silencing gene therapy to patients and suppressed levels of the ALS gene SOD1 quite effectively," said Dr. Mueller. "The next step for the program will be to test the clinical efficacy of the second generation of this clinical candidate in a placebo controlled trial."

While the first patient in the study experienced an inflammatory response to the treatment delivery vehicle and an associated focal pain syndrome, the use of immunosuppressants in the second patient mitigated this problem. The immunosuppressants, which will only be required at the time of injection, blunt the body's immune system while the viral capsids from the delivery vector are being cleared from the body.

"The insights we have gained from this important collaboration help us understand the therapy's potential effect," said Dr. Berry. "This early work is helping to pave a path forward for broader testing of an exciting and potentially powerful method to target ALS caused by SOD1 mutations."

ALS, also known as Lou Gehrig's disease, is a progressive,

neurodegenerative disorder of the motor neurons. An estimated 6,000 people in the Unites States are diagnosed with the disease each year. As motor neurons die, there is progressive paralysis and then death from respiratory failure. The average survival time in ALS is three to five years. In 1993, a team of researchers led by Dr. Brown discovered the first gene linked to familial ALS, a protein anti-oxidant known as superoxide dismutase or SOD1. Only 10 percent of ALS cases are familial, while roughly 90 percent are sporadic in nature—meaning there is no identifiable familial risk or family history.

Toxic mutations in the SOD1 gene, such as those targeted in the trial described in this publication, account for 20 percent of inherited cases of ALS. A potential therapy for these cases is to suppress the activity of mutant genes and thereby reduce levels of the toxic protein. At least in animal models, this approach slows or even reverses motor neuron death. One approach to targeting these genes uses microRNAs.

MicroRNAs are part of the natural RNA silencing machinery found in plants and animals. These small RNAs bind and destabilize a gene's RNA template, so the cell cannot transform the RNA into proteins. Using this cell machinery, scientists believe they can effectively "turn off" toxic genes and proteins that cause disease.

More than 180 different mutations to the SOD1 gene are linked to ALS. The Mueller lab identified commonalities in the DNA sequences of these various mutations, permitting the team to develop using RNA sequences that target almost all of the different SOD1 mutations. "Otherwise, each unique mutation sequence would require its own drug to silence," said Mueller. "This approach allows us to target the vast majority of the patients with an SOD1 mutation using a single drug."

When infused into the spinal fluid, the adeno-associated virus was able to deliver its anti-SOD1 microRNA throughout the length of the spinal

cord. Once delivered, the microRNA reduced SOD1 protein production in the spinal cord tissue.

"We are encouraged and gratified by these early results," said Brown, "as we have pursued SOD1 gene suppression since 1993. In the current study there appears to be silencing of the SOD1 gene and a suggestion of clinical benefit. Equally important, we learned how to manage the potential side effects of the drug through immunosuppression. This helps us move to a larger study in which efficacy can be evaluated."

In an accompanying editorial in the *New England Journal of Medicine*, Orla Hardiman, MD, clinical professor of neurology at Trinity College, Dublin and head of academic clinical medicine at the Trinity College Institute of Neurosciences; and Leonard H. van den Berg, MD, Ph.D., professor of neurology and chair in experimental neurology of motor neuron diseases at the University Medical Center Utrecht in the Netherlands, wrote, "These advances signal a new beginning for ALS therapeutics in which some forms of the disease may become treatable. By starting with subgroups with specific genomic features, investigators are providing new hope for patients at genetic risk for this devastating fatal disease."

More information: Orla Hardiman et al. The Beginning of Genomic Therapies for ALS, *New England Journal of Medicine* (2020). DOI: 10.1056/NEJMe2012930

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