Potential New Therapy Silences SOD1 Gene in Non-Human Primates

In a promising new study by Drs. Robert Brown and Christian Mueller at the University of Massachusetts Medical School report that a type of viral gene therapy using synthetic microRNAs (miRNAs) targeting the ALS SOD1 gene is safe and effective in nonhuman primate macaques (monkeys). The ALS Association provided $1.7 million in funding for this study, which demonstrated an efficient reduction of the SOD1 protein without side effects. This paves the way forward for further development of this potential therapy.

Familial (inherited) ALS accounts for 10 percent of ALS cases. Of that percentage, 20 percent of cases are caused by mutations in the SOD1 gene, the first gene discovered to cause ALS in 1993, by co-author Dr. Robert Brown. Over the years, numerous studies have shown that mutant SOD1 is toxic to motor neurons, the cells that die in ALS, via multiple identified mechanisms. In addition, misfolding of toxic of SOD1 proteins have been identified in sporadic (non-inherited) cases of ALS.

With this in mind, researchers have targeted SOD1 for potential ALS therapies. For example, studies in a SOD1 mouse model demonstrated that silencing (decreasing) SOD1 delayed disease onset, increased survival time, and reduced muscle loss and motor and respiratory issues.

In this study published in high impact journal *Science Translational Medicine*, Mueller, Brown, and team administered miRNA to the central nervous system (CNS) in macaques, via spinal cord delivery. MicroRNAs are a part of the inherent gene silencing pathways found in both plants and animals. They are designed to specifically bind to target sequences found on messenger RNAs (the instruction book to make protein) to prevent toxic proteins from being made in the first place. This technique can effectively "turn off" toxic genes and proteins, which in this case is SOD1.
The miRNAs were delivered via an adeno-associated virus (AAV), which was previously shown to be safe in non-human primates and requires a one-time spinal cord injection. AAV delivery allows effective and widespread delivery of the microRNA into the spinal cord and motor neurons. Once administered, researchers found as much as a 93 percent reduction of SOD1 proteins. Importantly, this AAV-based therapy did not result in any side effects.

Together, this promising study shows that AAV carrying miRNA targeting SOD1 protein can safely and effectively reduce SOD1 protein in the CNS of nonhuman primates via spinal cord injection. Data presented here demonstrate that this therapy has potential to treat people harboring the mutant SOD1 gene. Since misfolding of SOD1 is also observed in sporadic ALS cases, this therapy could also have potential in this population.

This points to the need to take this therapy into human clinical trials. The U.S. Food and Drug Administration (FDA) recently approved an investigational drug application (IND #17179) to begin a pilot phase I clinical trial in humans.

"We are excited to see that Dr. Brown's work is providing such promising results in non-human primates and we are proud to support this work," said Neil Thakur, Executive Vice President of Mission Strategy at The ALS Association. "We are cautiously optimistic that this AAV therapy will have a positive impact on people with ALS in future clinical trials."

The ALS Association awarded $1,675,000 in grants to Dr. Robert Brown and ALS ONE for this work and will continue to update the community with further progress.

By Florie Borel, Gwladys Gernoux, Huaming Sun, Rachel Stock, Meghan Blackwood, Robert H. Brown, Jr., Christian Mueller

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