

Health & Physiology

Gene therapy and ALS: one step closer to the clinic

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ABSTRACT

Amyotrophic lateral sclerosis is a devastating, invariably fatal neurodegenerative disorder. Now researchers demonstrate that a novel gene therapy treatment that silences the toxic gene is safe in monkeys. This breakthrough treatment could soon be in the clinic



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[Amyotrophic lateral sclerosis](#) (ALS) is a devastating disease that on average kills in only 3 to 5 years after diagnosis, and for which there is still no cure today. ALS patients have progressive muscle weakness, leading to gradual paralysis and difficulties breathing which will usually require ventilation. The only two approved treatments are riluzole, a pill which increases median survival by 2 to 3 months, and edavarone, an injectable which in at least one study increased median survival by 7 to 8 months. It is generally estimated that there are about 450,000 people living with ALS worldwide, including 30,000 in the United States and 30,000 in Europe. In the last few years, fundraising efforts spearheaded by patients have led to a surge in research to better understand this disease and to create more effective treatments.

Many genes can cause ALS, and this study focused on one named SOD1 (superoxide dismutase 1). This gene is responsible for about 1 in 5 cases of familial ALS (meaning patients who have a family history of the disease), and because it was the very first ALS gene to be discovered in 1993, many tools are available for researchers such as a transgenic mouse model, which is a ALS mouse in which the human SOD1 gene was introduced. In 2012, our group of gene therapy researchers at the University of Massachusetts Medical School created a gene therapy treatment that silences SOD1 and teamed up with Bob Brown, the doctor who discovered the SOD1 gene. In 2016, we reported that mice treated with gene therapy were doing much better than their non-treated siblings: they were getting paralyzed

later, had more muscle strength, were able to breathe better, and survived longer. The next step was then to test the treatment in monkeys, because they are closer to humans in terms of size of brain and spinal cord, the two organs where motor neurons are located. Motor neurons are the cells that are most affected by ALS, and whose death causes ALS symptoms.

In this study, we injected the gene therapy directly into the [cerebrospinal fluid](#) (CSF), the liquid that bathes our spinal cord and our brain. The injection was done in a very similar fashion to that for a spinal epidural tap used for anesthesia during child birth. After 3 months, the monkeys were euthanized, and samples were harvested and analyzed, including the brain and different levels of the spinal cord. The goal of this study was to find answers to multiple questions in order to evaluate if this treatment may be suited for clinical testing. First, is the gene therapy going to the right cells in the spinal cord and in the brain in a large animal like a monkey? Second, is the gene therapy silencing the toxic SOD1 gene in these cells as it should? Last but not least, is it safe?

The results showed that the gene therapy was indeed going to the motor neurons in the spinal cord and in the brain. In addition, the whole length of the spinal cord was treated, which is important because it is a rather long organ in monkeys and in humans.

Having established that, we used a laser to cut out only the motor neurons from the spinal cord tissue, and we checked if SOD1 was silenced in these cells. The gene was indeed silenced in motor neurons, and the silencing was strong and actually increased over time. Finally, we took a close look at safety. Upon first glance, the monkeys tolerated well both the injection procedure and the 3 months follow-up, with no sign of any adverse event. In additional safety experiments, we also showed that there was no reason to expect off-target effects, meaning that the gene therapy did not silence genes other than SOD1, and as far as we can tell from our analysis it behaved like it was supposed to.

This study shows that in monkeys, the gene therapy treatment is safe and effective. One limitation is that immune responses cannot be accurately predicted in animals.

Overall, this study supports cautious optimism that this gene therapy treatment may offer meaningful therapy for patients with ALS caused by SOD1. Some recent research has suggested that SOD1 is also involved in sporadic ALS, meaning when people do not have a family history of the disease. If that proves true, this gene therapy treatment may be applicable to these patients as well.