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AMYOTROPHIC LATERAL SCLEROSIS:

“Transgenic Mouse Models of FUS/TLS-Mediated Amyotrophic Lateral Sclerosis”

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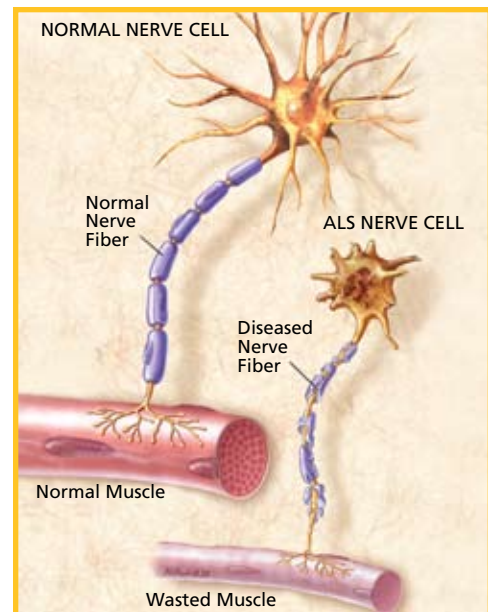
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GRANT DESCRIPTION

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease, is a devastating neurodegenerative condition that kills nerve cells in the brain and spinal cord that control the muscles, leading to progressive weakness and death within 3-5 years. Currently, no treatment can slow the progression of the disease, thus raising the urgency for developing new animal models of ALS that can be used to identify novel therapeutic targets. The major goal of this project is to establish and characterize mouse models of ALS based on transgenic expression of a newly discovered ALS gene, FUS/TLS. Mutant forms of FUS/TLS have been linked to inherited forms of ALS, but even the normal function of this nucleic acid binding protein in nerve cells is not well understood. We propose to use three parallel but complementary approaches to produce mice that express normal or mutant FUS/TLS. For some of the mice, regulation of the gene will be under normal control, while for others, the disease gene can be turned on or off experimentally in different cell types or at different ages.

SCIENCE AND HEALTH IMPLICATIONS

These animals will provide the research community with tools to study the pathological mechanisms and to develop new therapeutic strategies for ALS. The approaches we will use that enable precise control of transgene expression in space and time are likely to produce one or more animal models of mutant FUS/TLS expression with an age-dependent paralytic phenotype and neurodegeneration resembling ALS. Such models will enable us to determine whether the FUS/TLS mutations trigger dominant gain-of-function, loss-of-function, or dominant-negative mechanism(s) in specific cell types to cause ALS. Moreover, these insights will enable the identification of novel targets for ALS treatments, including FUS/TLS itself or interacting molecules, and will accelerate rapid preclinical testing of appropriate therapeutic strategies for ALS.



ALS attacks nerve cells in the brain and spinal cord that control the muscles of the body. When the damaged nerve cells can no longer stimulate the muscles, they weaken and waste away. As a result, the brain and spinal cord lose their ability to initiate and control movement.

The Society for Neuroscience (SfN) is the world’s largest organization of scientists and physicians devoted to advancing understanding of the brain and nervous system. Since its inception in 1969, the Society has grown from 500 members to more than 40,000.