B6-hSOD1 G93A, hSOD1

Strain Name: C57BL/6JGpt-Tg(hSOD1 G93A,hSOD1)61/Gpt
Strain Type: Transgene
Strain Number: T055223
Background: C57BL/6JGpt

Description

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease which characterizes degeneration of the nerve cells in the brain and spinal cord. There are about 5,000 people diagnosed with ALS each year, and their average life expectancy is almost 3-5 years after diagnosis. The major clinical features of ALS patients are losing the ability of the movement, speak, and swallow, which causes paralysis, and eventually cannot breathe [1, 2]. ALS seriously threatens the health of people, but still don't have effective treatment strategies. Only three drugs (Riluzole, Edaravone and Relyvrio) are approved by FDA for ALS, but have less effects on disease progression [3, 4].

The causes of ALS are complex, which could be the genetic or environmental effects. About 10% of ALS cases are familial and almost 90% are sporadic. At least 30 genes have been implicated in ALS, which include SOD1, TARDBP, FUS, and C9ORF72[2, 5]. SOD1 (superoxide dismutase 1) was the first identified ALS gene, which represents in 20% familial and 2% sporadic ALS, more than 150 mutations in SOD1 gene were found [1]. The expression of mutant SOD1 protein induces protein misfolding and aggregation, which leads to the neuron toxic and causes neuron degeneration [4, 6, 7]. The first ALS mouse model was generated by transgene which carried the human SOD1 G93A mutation [8]. The SOD1 G93A mouse model develops the ALS-like phenotypes, and widely used for ALS studies and therapeutic strategies development.

Until now, huge demands are still required for development the disease-modifying therapies for ALS disease. To meet the research and market demands, the B6-hSOD1 G93A, hSOD1 mouse strain was generated at GemPharmatech using transgenic strategy, which co-expressed the human wild type and G93A mutated SOD1. The B6-hSOD1 G93A, hSOD1 mice develop progressive motor ability decrease, which represents ALS-like phenotypes. B6-hSOD1 G93A, hSOD1 mouse model can be used for neurodegenerative disease area research, especially ALS disease, it can be used to explore the disease mechanisms and development of disease-modifying therapies for ALS disease.

Strategy

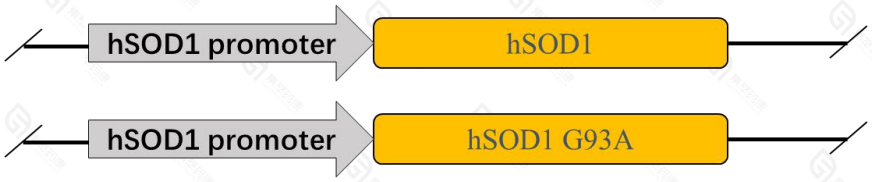

Fig.1 Schematic diagram of B6-hSOD1 G93A, hSOD1 model strategy.

Applications

1. Efficacy evaluation of ALS drugs
2. Mechanism research of ALS disease
3. Neuro-inflammation regulations in ALS disease

Data support

1. Validation of the B6-hSOD1 G93A, hSOD1 mouse model

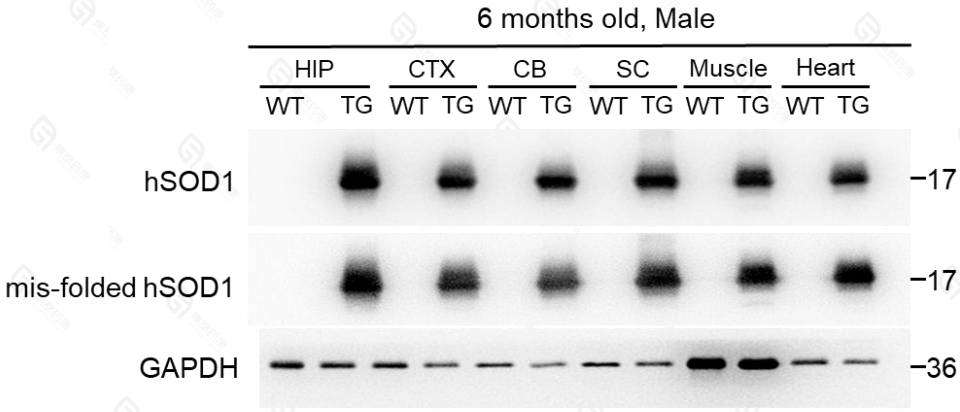

Fig 2. Detection of human SOD1 expression.

human SOD1 (hSOD1) and misfolded human SOD1 protein was detected in central nervous system, muscle and heart from 6-month-old wild-type and B6-hSOD1 G93A, hSOD1 male mice by Western blot. Female mice were similar.

HIP: Hippocampus, CTX: Cortex, CB: Cerebellum, SC: Spinal cord.

2. Muscle atrophy in B6-hSOD1 G93A, hSOD1 mice

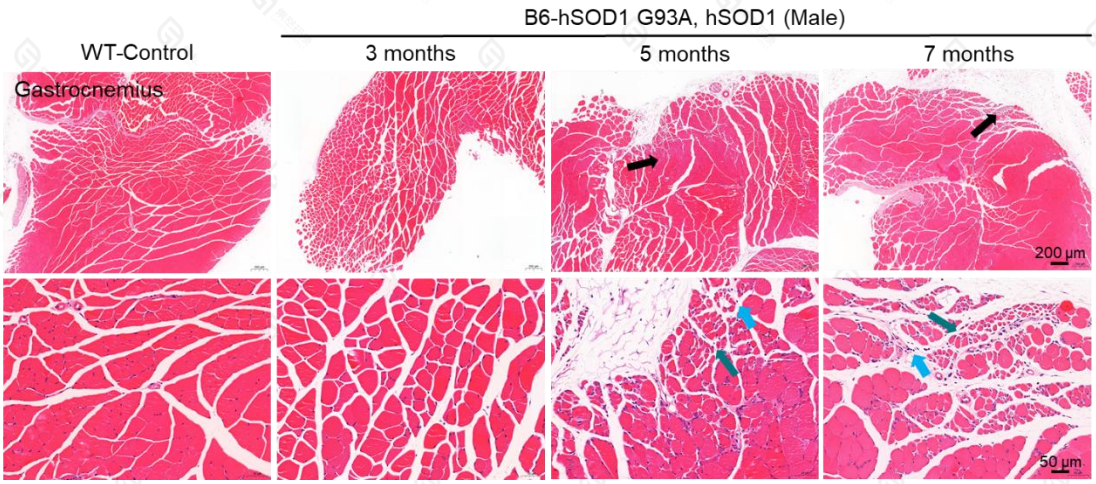

Fig 3. Muscle atrophy

Representative images of the hind-limb muscles of 3-, 5- and 7-month-old wild type and B6-hSOD1 G93A, hSOD1 male mice. The black arrow point to muscle fiber necrosis, the green arrow point to muscle cells atrophy, and the blue arrow point to inflammatory cell infiltration. Scale, 200 μm, 50 μm.

3. Motor neuron loss in B6-hSOD1 G93A, hSOD1 mice

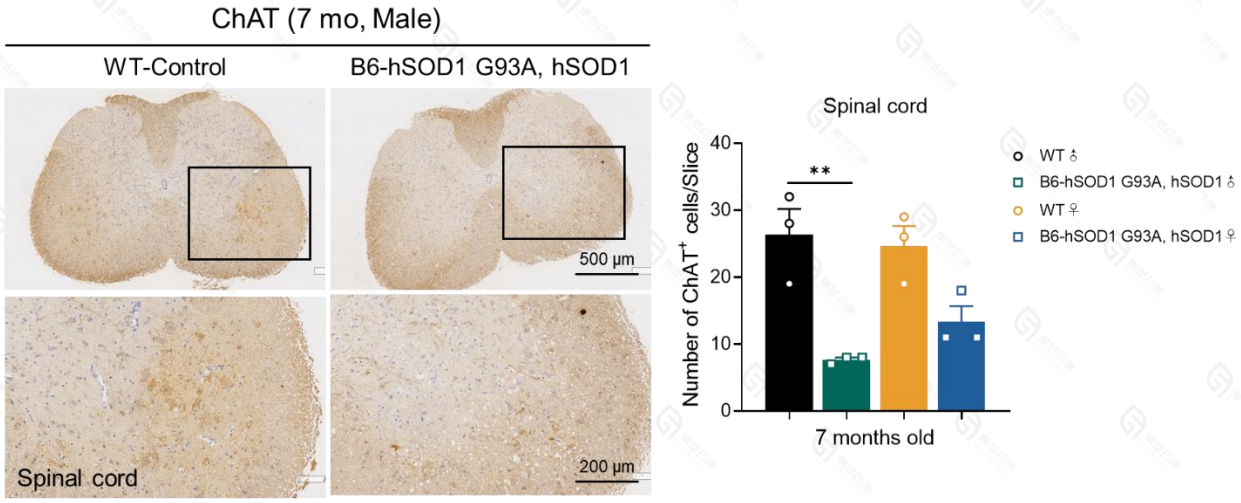

Fig 4. Motor neuron loss.

Representative images of the ChAT⁺ neuron in lumbar spinal cord of 7-month-old wild type and B6-hSOD1 G93A, hSOD1 male mice. Scale, 500 μm, 200 μm.

All data represent as MEAN ± SEM. **p < 0.01, two-way ANOVA, Tukey's post hoc analysis.

4. Glial activation in B6-hSOD1 G93A, hSOD1 mice

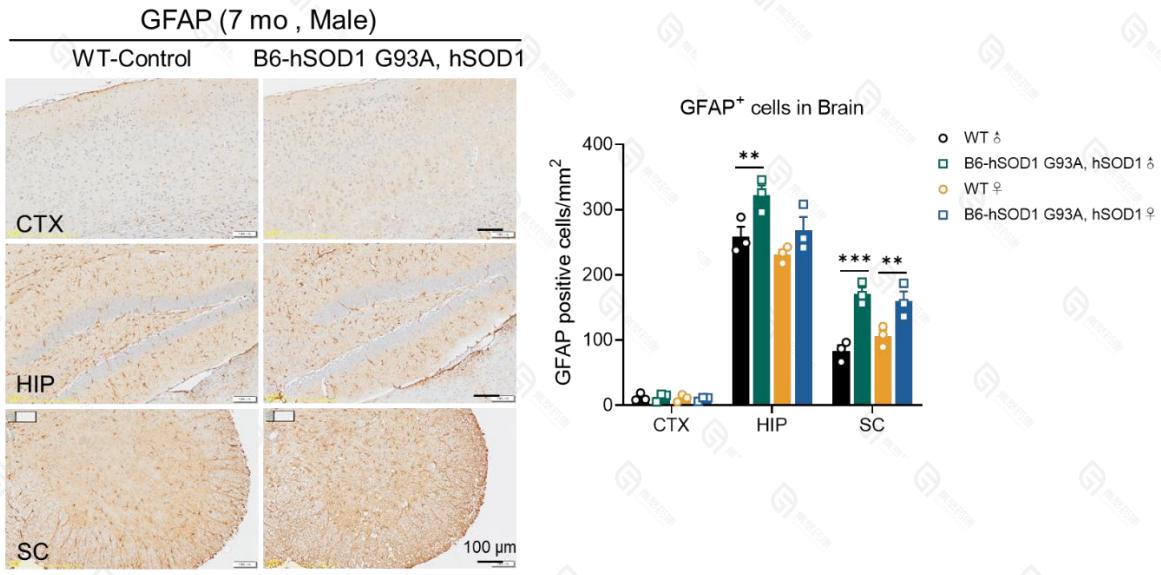

Fig 5. Astrocyte activation.

Representative images of the GFAP⁺ astrocytes in lumbar spinal cord of 7-month-old wild type and B6-hSOD1 G93A, hSOD1 male mice. Scale, 100 µm. CTX: Cortex, HIP: Hippocampus, SC: Spinal cord. All data represent as MEAN ± SEM. **p < 0.01, ***p < 0.001, two-way ANOVA, Tukey's post hoc analysis.

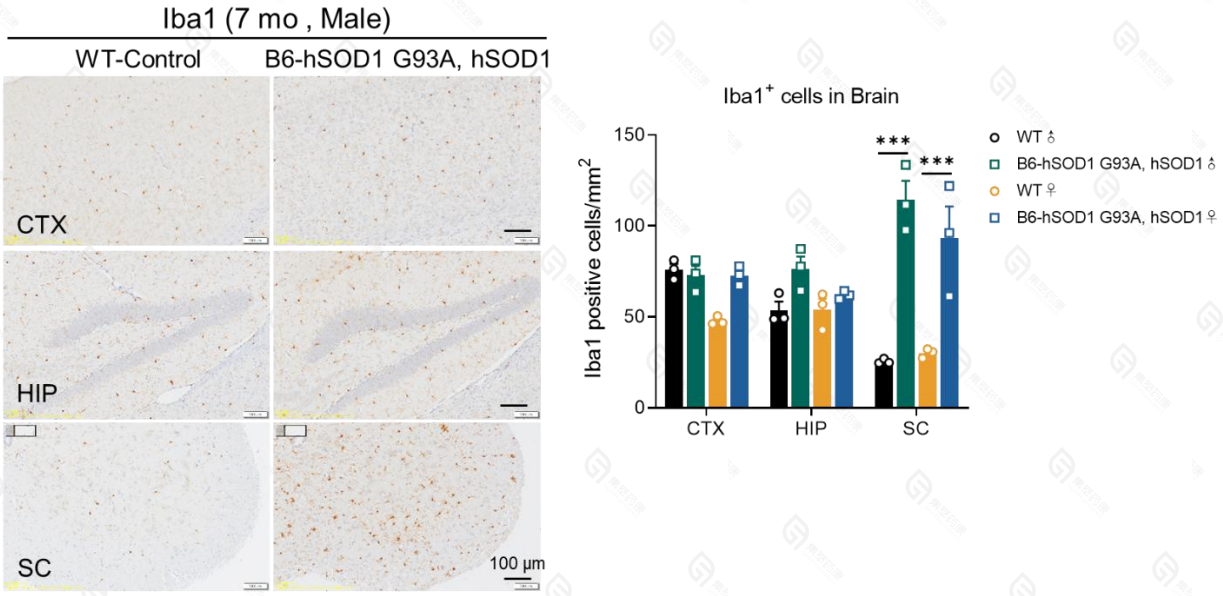

Fig 6. Microglia activation.

Representative images of the Iba1⁺ microglia in lumbar spinal cord of 7-month-old wild type and B6-hSOD1 G93A, hSOD1 male mice. Scale, 100 µm. CTX: Cortex, HIP: Hippocampus, SC: Spinal cord. All data represent as MEAN ± SEM. ***p < 0.001, two-way ANOVA, Tukey's post hoc analysis.

5. Body weight changes and survival curve in B6-hSOD1 G93A, hSOD1 mice

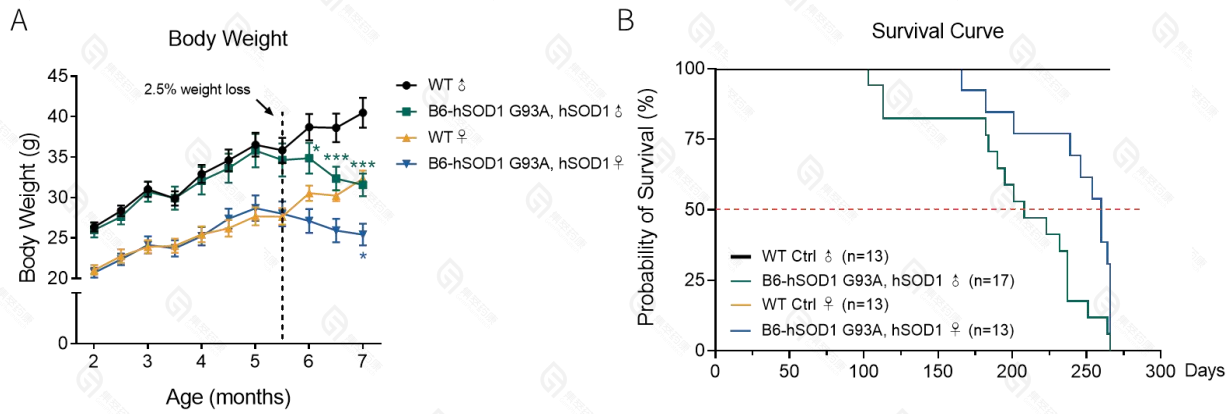

Fig 7. Body weight changes and survival curve.

Weight changes and survival curve in B6-hSOD1 G93A, hSOD1 mice aged 2 to 7 months. The male mice began to die at the age of 3.5 months, and the median survival time reached at the age of 7-month-old. Female mice began to die at 5.5 months of age, and the median survival time was reached at 8-months-old. (A) N=10 each group. All data represent as MEAN ± SEM. *p < 0.05, ***p < 0.001, two-way ANOVA, Tukey's post hoc analysis. (B) N>10 each group.

6. Behavioral changes in B6-hSOD1 G93A, hSOD1 mice

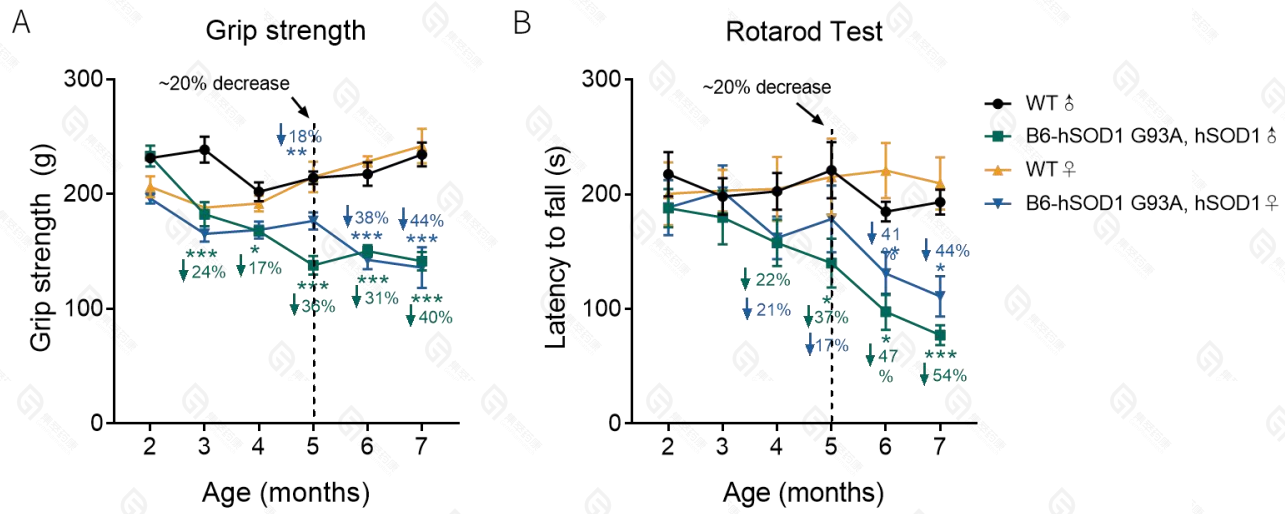

Fig 8. Motor function changes.

(A) Grip strength in B6-hSOD1 G93A, hSOD1 mice. The limbs grip strength at 2- to 7-month-old of wild type and B6-hSOD1 G93A, hSOD1 in grip strength test. (B) Rotarod test in B6-hSOD1 G93A, hSOD1 mice. The latency (seconds fall in the rotarod) of 2- to 7-month-old of wild type and B6-hSOD1 G93A, hSOD1 mice in the rotarod test.

N=10 each group. All data represent as MEAN ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001, two-way ANOVA, Tukey's post hoc analysis.

7. RNA profiling reveals the immune responses are highly activated in B6-hSOD1 G93A, hSOD1 mice after disease onset

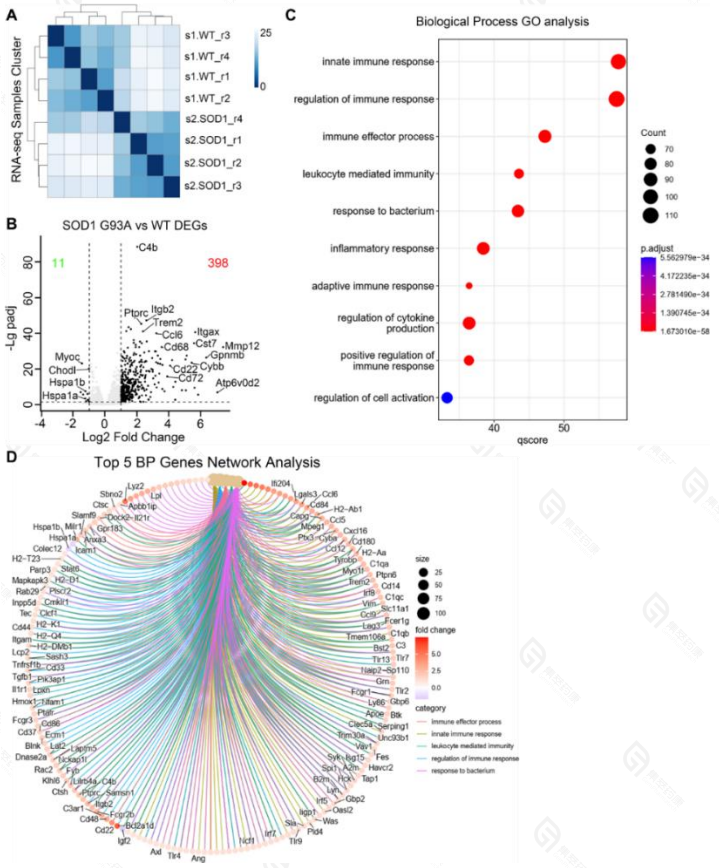

Fig 9. Transcriptomic profiling in B6-hSOD1 G93A, hSOD1 male mice.

(A) The RNA-seq samples cluster of spinal cord in 6-month-old wild type control mice and B6-hSOD1 G93A, hSOD1 male mice. (B) The volcano plot shown the differential expressed genes (DEGs) compare the B6-hSOD1 G93A, hSOD1 mice to wild type control. The number in the figures label the DEG numbers, red represents up-regulated genes and green for down-regulated genes. The DEGs defined as |log2 FC| ≥ 1 & padj ≤ 0.05. (C) The dot plot represents the enriched biologic process GO analysis for the DEGs. (D) The network plot for the top 5 enrichment biologic process related genes.

8. The timeline of disease progression in B6-hSOD1 G93A, hSOD1 mice

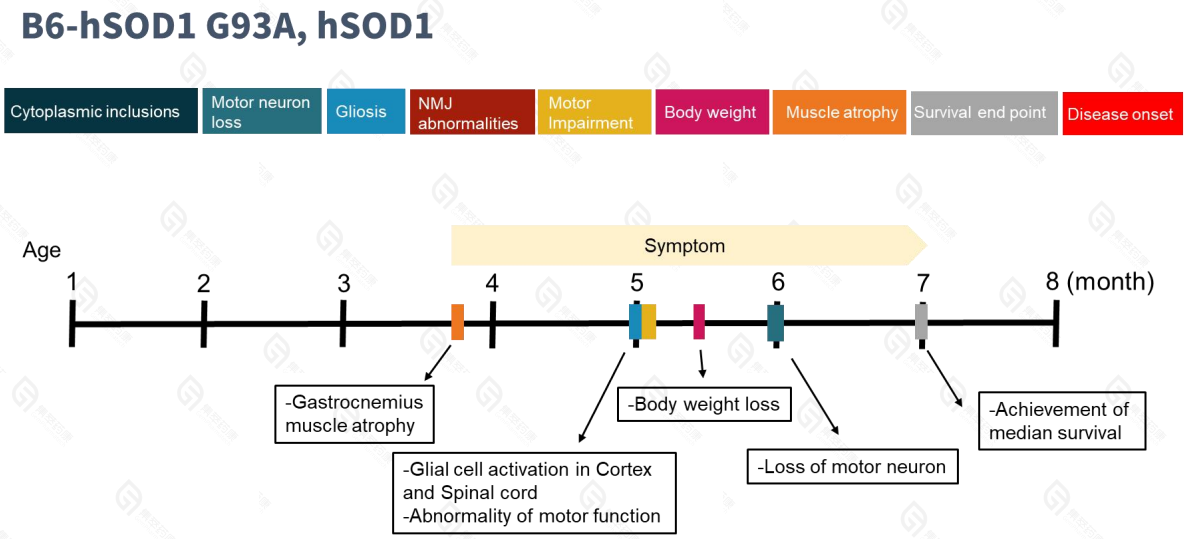

Fig 10. The timeline (month) of disease progression in B6-hSOD1 G93A, hSOD1 mice.

References

1. Taylor, J.P., R.H. Brown, Jr., and D.W. Cleveland, Decoding ALS: from genes to mechanism. Nature, 2016. 539(7628): p. 197-206.
2. Brown, R.H. and A. Al-Chalabi, Amyotrophic Lateral Sclerosis. N Engl J Med, 2017. 377(2): p. 162-172.
3. Jaiswal, M.K., Riluzole and edaravone: A tale of two amyotrophic lateral sclerosis drugs. Med Res Rev, 2019. 39(2): p. 733-748.
4. Chio, A., L. Mazzini, and G. Mora, Disease-modifying therapies in amyotrophic lateral sclerosis. Neuropharmacology, 2020. 167: p. 107986.
5. Kim, G., et al., ALS Genetics: Gains, Losses, and Implications for Future Therapies. Neuron, 2020. 108(5): p. 822-842.
6. Al-Chalabi, A., L.H. van den Berg, and J. Veldink, Gene discovery in amyotrophic lateral sclerosis: implications for clinical management. Nat Rev Neurol, 2017. 13(2): p. 96-104.
7. Abati, E., et al., Silence superoxide dismutase 1 (SOD1): a promising therapeutic target for amyotrophic lateral sclerosis (ALS). Expert Opin Ther Targets, 2020. 24(4): p. 295-310.
8. Gurney, M.E., et al., Motor neuron degeneration in mice that express a human Cu, Zn superoxide dismutase mutation. Science, 1994. 264(5166): p. 1772-5.