**Gene Therapy and its Impact on ALS**

Author: Melia Harp
Major: Biology- Allied Health
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

**Key Words:**

ALS, gene therapy, neurodegenerative

**Abstract**

ALS, also known as amyotrophic lateral sclerosis, is a disease that damages brain cells and can cause a loss of function in the muscles (2). This disease is lethal and currently does not have a cure, but modern science and medicine might be able to change that with the help of gene therapy (2). Gene therapy works by producing proteins called oligonucleotides that can attempt to help save the dying cells (2). Gene therapy is a fairly new field that is being tested. One of the genes directly involved with ALS and gene therapy is the gene C9orf72 (3). This gene either has a loss of function or becomes toxic (3). Although there is a long way to go, the progress that has recently been made in gene therapy is exciting and could change the future of treatment for not only ALS but many diseases like cancer and other neurodegenerative diseases.

**Introduction**

ALS even though it is rare, affects tens of thousands of people in America alone (1). This disease is also known as Lou Gehrig’s disease and is responsible for the destruction of neurons (2). These nerve cells often impact basic movement like moving your mouth to eat and chew or moving your legs to simply walk (1). Over time a person with ALS loses control of their movements (1). Once this disease begins, it progressively gets worse and there is no way to stop it. Motor neuron diseases are responsible for the death and destruction of neurons that stretch from muscles over the body to the spinal cord and brain (1). These motor neurons help send messages between the muscles and the brain (1). Scientists and doctors do not know exactly why some people get it and others don’t, but they do think it could be caused by genetics and environmental factors (1). One of the environmental factors is traumatic experiences. For example, athletes and veterans are much more likely to develop ALS because of their traumatic experiences that they might endure (1). ALS mainly occurs in adults and causes the patient diagnosed with it to be paralyzed and for them to have an early death (1). Some of the early symptoms of ALS are involuntary muscle movements, cramps, weak muscles or stiffness, having a hard time chewing food or being able to swallow (1). There are ways to make the patient more comfortable during this process and ways to help slow the disease to help the patient live a little longer but there is not a cure.

**Recent Progress**

 People who are diagnosed with ALS have thousands of G4C2 repeats on the C9orf72 gene (2). There are multiple studies being done that test gene therapy. One of the approaches that have been done to study how gene therapy impacts ALS was done by running tests on mice that had the same C9orf72 human gene (3). These mice did begin to have neuro-degenerative diseases which helped confirm the origin and pathway of ALS (3). This therapy focused on this specific gene and was responsible for minimizing the repeats which turn into RNA foci (3). Focusing on this strand not only lowered the number of repeats but was also able to salvage some of the nerve cells (3). Another study that was done to observe gene therapy and its effect on ALS and the one that is the basis of this paper is therapy using AAV or adeno-associated virus (3). This approach uses an artificial miRNA that is made to focus on the C9orf72 gene (3). The transcripts for miRNA are constantly being made which can increase the amount of time that the therapy would be effective. In order to find out if the amount of C9org72 genes were lowered one hundred and twelve mice were used to test whether the AAV gene therapy would be successful or not.

**Discussion**

Various types of nerve cells were used to see if the C9orf72 was reduced (3). This was observed by looking at the cytoplasm and nucleus (3). This study found that the miC that focused on the C9orf72 did lower the RNA foci in the mouse brain (3). They found that in the cells that were given the adeno-associated virus that about 90% of the miC was found in the cytoplasm while the other 10% were found in the nucleus (3). Of these there were a 30% decrease in the C9orf72 gene in the nucleus and 40% decrease in the gene in the cytoplasm (3). The information gathered in this study suggest that silencing the gene C9orf72 could be a path leading to treatment for this disease. (3). Before these studies had been done ALS was thought to be strictly a disease of the motor neurons but it was found that ALS effects more cell types than just motor neurons (3). Some of these other cell types include glial cells (3). One of the downsides to gene therapy is that sometimes it only works for a certain type of ALS or ALS that is caused by one specific thing but the findings in these studies are very promising in helping those diagnosed with ALS in the future.

**References**

1. “Amyotrophic Lateral Sclerosis (ALS) Fact Sheet.” National Institute of Neurological Disorders and Stroke. U.S. Department of Health and Human Services. Accessed February 12, 2021. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Amyotrophic-Lateral-Sclerosis-ALS-Fact-Sheet.
2. Cappella, Marisa; Ciotti, Chiara; Cohen-Tannoudji, Mathilde; Biferi, Maria G. 2019. "Gene Therapy for ALS—A Perspective" *Int. J. Mol. Sci.* 20, no. 18: 4388. <https://doi.org/10.3390/ijms20184388>
3. Martier, Raygene, Jolanda M. Liefhebber, Ana García-Osta, Jana Miniarikova, Mar Cuadrado-Tejedor, Maria Espelosin, Susana Ursua, et al. “Targeting RNA-Mediated Toxicity in C9orf72 ALS and/or FTD by RNAi-Based Gene Therapy.” *Molecular Therapy - Nucleic Acids* 16 (2019): 26–37. <https://pubmed.ncbi.nlm.nih.gov/30825670/>