Gene Therapy for Upper Airway and Respiratory Insufficiency in an ALS Mouse Model

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Gene Therapy for Upper Airway and Respiratory Insufficiency in an ALS Mouse Model

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Research Abstract

Project Summary/Abstract Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease that initially manifests with either bulbar or spinal (limb) symptoms. Bulbar involvement leads to speech and swallowing impairment and recurrent aspiration

pneumonia. Death due to respiratory failure occurs within 2-3 years for patients with bulbar onset ALS and 3-5 years for limb onset cases. To date, no treatment exists for this relentless and fatal disease. The only FDA approved drug for ALS is Riluzole – a glutamate release inhibitor which minimally increases life by 3-5 months. As diaphragm and respiratory muscle weakness progress, targeted respiratory therapy with non-invasive ventilatory support improves survival. Therefore, the goal of this proposal is to use gene therapy to target the respiratory system (upper airway, diaphragm and intercostals) in a popular ALS mouse model – the SOD1G93A mouse and assess if this improves breathing and survival. This application proposes to study the impact of respiratory directed gene therapy on spontaneous breathing, pulmonary mechanics, and respiratory efferent nerve output. Adeno- associated virus (AAV) gene therapy coupled with microRNA that silences SOD1 (miRSOD1) will be delivered through retrograde transduction to the entire motor unit (muscle, neuromuscular junction, nerve and motor neurons). In addition, this proposal aims to study the impact of respiratory targeted and systemic gene therapy on pulmonary physiology and neurophysiology outcome measures as well as behavioral testing and survival. Thus, the fundamental hypothesis driving this proposal is that AAV- miRSOD1 gene therapy targeting the upper airway and respiratory system will enhance breathing in the ALS SOD1G93A murine model; and when coupled with systemic delivery of AAV, will improve respiratory function, mobility and prolong survival. Two specific aims are proposed: Aim 1 will test the hypothesis that an intralingual and intrathoracic injection of AAV-miRSOD1 will effectively transduce the entire hypoglossal and phrenic motor units and stimulate respiratory drive. Aim 2 will test the hypothesis that systemic AAV-miRSOD1 delivery coupled with respiratory targeted therapy will halt degeneration, improve survival and enhance respiratory function. Project Relevance: This work is innovative because it will use gene therapy to target respiratory insufficiency (the main cause of death in ALS patients) in an ALS mouse model. The impact of this therapy will be assessed using translational pulmonary outcome measures with the ultimate goal of translating this therapy to the clinic. AAV gene therapy is now in clinical trials and if successful, this therapy will provide a therapeutic option for respiratory failure in the patients with mutations in the SOD1 gene.

Further information available at:

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