Stem Cell-Derived Astrocyte Precursor Transplants in Amyotrophic Lateral Sclerosis

Grant Award Details

Stem Cell-Derived Astrocyte Precursor Transplants in Amyotrophic Lateral Sclerosis

Grant Type: Disease Team Research I

Grant Number: DR1-01471

Investigator:

Name: Lawrence Goldstein
Institution: University of California, San Diego
Type: PI

,

Name: Samuel Pfaff
Institution: Salk Institute for Biological Studies
Type: Co-PI

,

Name: Martin Marsala
Institution: University of California, San Diego
Type: Co-PI

Disease Focus: Amyotrophic Lateral Sclerosis, Neurological Disorders

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $5,694,308

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Stem Cell-Derived Astrocyte Precursor Transplants in Amyotrophic Lateral Sclerosis

Public Abstract: Amyotrophic lateral sclerosis (ALS), a lethal disease lacking effective treatments, is characterized by the loss of upper and lower motor neurons. 5-10% of ALS is familial, but the majority of ALS cases are sporadic with unknown causes. The lifetime risk is approximately 1 in 2000. This corresponds to ~30,000 affected individuals in the United States and ~5000 in the Collaborative Funding Partner country. There is currently only one FDA-approved compound, Rilutek, that extends lifespan by a maximum of three months. Although the causes of ALS are unknown and the presentation of the disease highly variable, common to all forms of ALS is the significant loss of motor neurons leading to muscle weakness, paralysis, respiratory failure and ultimately death. It is likely that many pathways are affected in the disease and focusing on a single pathway may have limited impact on survival. In addition, as ALS is diagnosed at a time that significant cell loss has occurred, an attempt to spare further cell loss would have significant impact on survival. Several findings support the approach of glial (cells surrounding the motor neurons) transplants. Despite the relative selectivity of motor neuron cell death in ALS, published studies demonstrate that glial transporters critical for the appropriate balance of glutamate surrounding the motor neurons are affected both in animal models and in tissue from sporadic and familial ALS. The significance of non-neuronal cells in the disease process has been well characterized using SOD1 mouse models representing many of the key aspects of the human disease. In addition, transplantation using glial-restricted precursors (GRPs) that differentiate into astrocytes in SOD1 mutant rats has been shown to increase survival. Motor neurons have a process, the axon, up to a meter in length which connects the cell body to its target, the muscle. The ability to appropriately rewire and ensure functional connections after motor neuron replacement remains a daunting task with no evidence to date that this will be possible in humans. Therefore, we will focus on the development of an ALS therapy based on hES-derived astrocyte precursor cell transplants to prevent the progression of ALS.

Our proposed project will develop clinical grade stem-cell derived astrocyte precursor transplants for therapy in a prospective Phase I clinical trial. We will: 1) generate astrocyte precursors from three different sources of human embryonic stem cell (hESC) lines; 2) identify the hESC line and glial progenitor combination that has the best characteristics of minimal toxicity, best efficiency in generating astrocytes, and reducing disease phenotypes in vivo in a rat model of ALS; 3) manufacture the appropriate cells in a GMP facility required by the FDA; 4) work with our established clinical team to design a Phase I safety trial; and 5) submit an application for an invesitgational new drug (IND) within the next four years.

Statement of Benefit to California: Amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's Disease) is a common and devastating adult motor neuron disease that afflicts many Californians. In the absence of a cure, or an effective treatment, the cost of caring for patients with ALS is substantial, and the consequences on friends and family members similarly takes a devastating toll. Our goal is to develop a safe and effective cell transplant therapy for ALS by starting with human embryonic stem cells. If successful, this advance will hopefully diminish the cost of caring for the many Californians with ALS, extend their useful lives, and improve their quality of life. In addition, the development of this type of therapeutic approach in California will serve as an important proof of principle and stimulate the formation of businesses that seek to develop these types of therapies in California with consequent economic benefit.

Source URL: https://www.cirm.ca.gov/our-progress/awards/stem-cell-derived-astrocyte-precursor-transplants-amyotrophic-lateral-sclerosis