# Development of a Relevant Pre-Clinical Animal Model as a Tool to Evaluate Human Stem Cell-Derived Replacement Therapies for Motor Neuron Injuries and Degenerative Diseases

## Grant Award Details

Development of a Relevant Pre-Clinical Animal Model as a Tool to Evaluate Human Stem Cell-Derived Replacement Therapies for Motor Neuron Injuries and Degenerative Diseases

**Grant Type:** Tools and Technologies III

**Grant Number:** RT3-07616

**Project Objective:** Development of a novel and clinically relevant non-human primate model to study transplantation of human stem cell-derived motor neurons into the primate spinal cord after a lumbosacral ventral root avulsion injury and root repair. The injury model mimics many features of motor neuron death associated with, such as ALS in adults and SMA in the pediatric population. These studies in rhesus macaques will address key bottleneck issues and allow for:

- Long-term studies of the survival and engraftment of transplanted human cells in the primate spinal cord over extended periods of time (for instance 3-6 months)
- Studies of axonal regeneration and elongation by human stem cell-derived motor neurons in surgically repaired ventral roots and peripheral nerves over long distances and axonal growth periods that mimic those required for reinnervation of proximal muscle targets in humans
- Development of human outcome measures suitable for repeat measures and long-term studies, including treadmill locomotion, urodynamics, electromyography (EMG) of pelvic floor muscles, pain behavioral and sensory threshold studies, and magnetic resonance imaging (MRI) of the spinal cord, to determine patterns of recovery of motor, sensory, and autonomic function and to monitor for potential adverse effects, including spasticity and pain
- Studies of human cell transplantation in a model with human-like biology, including key features of the spinal cord anatomy and immune responses.

**Investigator:**

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| **Name:** | Leif Havton |
| **Institution:** | University of California, Los Angeles |
| **Type:** | PI |

**Disease Focus:** Amyotrophic Lateral Sclerosis, Neurological Disorders, Spinal Cord Injury, Spinal Muscular Atrophy

**Human Stem Cell Use:** Embryonic Stem Cell

**Cell Line Generation:** Embryonic Stem Cell

**Award Value:** $1,308,711

**Status:** Closed

## Progress Reports

**Reporting Period:** Year 1

**View Report**

**Reporting Period:** Year 3

**View Report**

**Reporting Period:** NCE Year 4

**View Report**

## Grant Application Details

**Application Title:** Development of a Relevant Pre-Clinical Animal Model as a Tool to Evaluate Human Stem Cell-Derived Replacement Therapies for Motor Neuron Injuries and Degenerative Diseases

**Public Abstract:** Motor neurons degenerate and die as a consequence of many conditions, including trauma to the spinal cord and its nerve roots and degenerative diseases such as amyotrophic lateral sclerosis and spinal muscular atrophy. Paralysis and in many cases death may result from a loss of motor neurons. No effective treatments are available for these patients. Most cellular therapy studies for motor neuron disorders are done in rodents. However, because of the dramatic differences between the rodent and human spinal cord, translation of these studies to humans is difficult. In particular, the development of new stem cell based treatments is limited by the lack of large animal models to test promising candidate therapies.
This bottleneck will be addressed by developing a new research tool in which human embryonic stem cell-derived motor neurons are transplanted into the spinal cord of rhesus macaques after injury and surgical repair of motor nerve roots. This injury and repair model mimic many features of motor neuron degeneration in humans. Microscopic studies will determine survival and tissue integration of transplanted human cells in the primate spinal cord tissues. Evaluations of walking, muscle and bladder function, sensation and magnetic resonance imaging (MRI) will test for possible benefits and potential adverse effects. This new research tool will be available for future pre-clinical testing of additional stem cell-based therapies that target motor neuron loss.

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| **Statement of Benefit to California:** | Paralysis resulting from motor neuron loss after cauda equina and conus medullaris forms of spinal cord injury and from neurodegenerative conditions, such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), are devastating and affects thousands of patients and their families in California (CA). These conditions also create a significant financial burden on the state of CA. No effective treatments are available for these underserved patients. Development of a clinically relevant research tool is proposed to evaluate emerging stem cell-based motor neuron replacement therapies in translational studies. No such models are presently available to the global research community. As a result, the proposed research tool, which will remain based in CA, may attract interest across the United States and abroad, potentially being able to tap into a global translational research market of stem cell-based therapies and contribute to a positive revenue flow to CA.<br>Future benefits to people in CA include: 1) Development and translation of a new CA-based research tool to facilitate and expedite clinical realization of emerging stem cell-based therapies for devastating neurological conditions affecting motor neurons; 2) Reduction of health care costs and care giver costs for chronic motor neuron conditions with paralysis; 3) Potential for revenue from intellectual properties related to new cellular treatments entering clinical trials and human use. |

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