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**Human stem cell derived oligodendrocytes for treatment of stroke and MS**

**Grant Award Details**

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Human stem cell derived oligodendrocytes for treatment of stroke and MS

**Grant Type:** Comprehensive Grant

**Grant Number:** RC1-00135

**Investigator:**

**Name:** Samuel Pleasure  
**Institution:** University of California, San Francisco  
**Type:** PI

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**Disease Focus:** Immune Disease, Multiple Sclerosis, Neurological Disorders, Stroke

**Human Stem Cell Use:** Adult Stem Cell, Embryonic Stem Cell

**Award Value:** \$2,459,235

**Status:** Closed

**Progress Reports**

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**Reporting Period:** Year 2

**View Report**

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**Reporting Period:** Year 3

**View Report**

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**Reporting Period:** Year 4

**View Report**

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**Reporting Period:** Year 5 NCE

**View Report**

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## Grant Application Details

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**Application Title:** Human stem cell derived oligodendrocytes for treatment of stroke and MS

**Public Abstract:** Strokes that affect the nerves cells, i.e., "gray matter", consistently receive the most attention. However, the kind of strokes that affecting the "wiring" of the brain, i.e., "white matter", cause nearly as much disability. The most severe disability is caused when the stroke is in the wiring (axons) that connect the brain and spinal cord; as many as 150,000 patients are disabled per year in the US from this type of stroke. Although oligodendrocytes ("oligos") are the white matter cells that produce the lipid rich axonal insulator called myelin) are preferentially damaged during these events, stem cell-derived oligos have not been tested for their efficacy in preclinical (animal) trials. These same white matter tracts (located underneath the gray matter, called subcortical) are also the primary sites of injury in MS, where multifocal inflammatory attack is responsible for stripping the insulating myelin sheaths from axons resulting in axonal dysfunction and degeneration. Attempts to treat MS-like lesions in animals using undifferentiated stem cell transplants are promising, but most evidence suggests that these approaches work by changing the inflammation response (immunomodulation) rather than myelin regeneration. While immunomodulation is unlikely to be sufficient to treat the disease completely, MS may not be amenable to localized oligo transplantation since it is such a multifocal process. This has led to new emphasis on approaches designed to maximize the response of endogenous oligo precursors that may be able to regenerate myelin if stimulated. We hypothesize that by exploiting novel features of oligo differentiation in vitro (that we have discovered and that are described in our preliminary data) that we will be able to improve our ability to generate oligo lineage cells from human embryonic stem cells and neural stem cells for transplantation, and also to develop approaches to maximize oligo development from endogenous precursors at the site of injury in the brain. This proposal will build on our recent successes in driving oligo precursor production from multipotential mouse neural stem cells by expressing regulatory transcription factors, and apply this approach to human embryonic and neural stem cells to produce cells that will be tested for their ability to ameliorate brain damage in rodent models of human stroke. Furthermore, we hope to develop approaches that may facilitate endogenous recruitment of oligo precursors to produce mature oligos, which may prove a viable regenerative approach to treat a variety of white matter diseases including MS and stroke.

**Statement of Benefit to California:** Diseases associated with disruption of oligodendrocyte function and integrity (such as subcortical ischemic stroke and multiple sclerosis) are major causes of morbidity and mortality. Stroke is the third leading cause of death and the leading cause of permanent disability in the United States, costing over \$50 billion dollars annually, as approximately 150,000 chronic stroke patients survive the acute event and are left with permanent, severe motor and/or sensory deficits. While much less common, multiple sclerosis (MS) is the primary non-traumatic cause of neurologic disability in young adults. Most patients are diagnosed in their 20s-40s and live for many decades after diagnosis with increasing needs for expensive services, medications and ultimately long-term care. Existing strategies for stem cell based therapies include both strategies to replace lost cells and to augment regeneration after injury, but most of these efforts have emphasized the role of undifferentiated stem cells in treatment despite the realization that the main nexus of injury in both diseases is frequently a differentiated cell type – the oligodendrocyte. This project will use new insights into the development of oligodendrocytes from the laboratories of the investigators to find ways to improve production of oligodendrocytes from human ES cells and human neural stem cells, test whether these cells can improve the clinical outcome in rodent models of stroke and MS after transplantation and search for new molecular treatments that would augment the regeneration of oligodendrocytes from resident brain stem cells after injury. This is the first step to translating the basic fundamental understanding of oligodendrocyte development into viable therapies for important human diseases that are major burdens on the citizens of California.