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**Embryonic-Derived Neural Stem Cells for Treatment of Motor Sequelae following Sub-cortical Stroke**

**Grant Award Details**

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Embryonic-Derived Neural Stem Cells for Treatment of Motor Sequelae following Sub-cortical Stroke

**Grant Type:** Disease Team Research I

**Grant Number:** DR1-01480

**Project Objective:** Original Grant application:  
To develop NSC as an allogeneic cellular therapy product candidate for treatment of motor deficit following subcortical ischemic stroke. Activities under this award include characterizing and manufacturing the cells; conducting IND-enabling pharmacology and toxicology studies, and filing an IND for a Phase 1 first-in-human trial.  
In the Phase 1 trial, NSCs will be directly injected into the subcortical peri-infarct tissue adjacent to the stroke cavity. The initial concept in the application was treatment of acute stroke; based on work by other teams and the PI with a different therapeutic candidate, the team is now focusing on chronic stroke which may have a more favorable risk / benefit profile.  
BJS: Revised project goal consistent with wind down in March 2015 -  
CIRM worked with the team to revise the goal of the project as follows. 1) Demonstration of safety in GLP toxicology for the therapeutic candidate and 2) IND filing are no longer milestones for DR1-01480, and may be the subject of future application(s). The final goal will be to have completed, by March 31, 2015 or before the following (in reference to Milestones from NGA Amendment Feb 2013):  
\*GMP manufacturing process development and product release assays established (complete)  
\*In vivo efficacy/POC, dosing and timing demonstrated for therapeutic candidate (complete)  
\*Non-GLP pilot safety demonstrated for therapeutic candidate (complete)  
\*FDA agreement on planned GLP tox study protocol (to be completed)  
\*Manufacture and release of clinical (cGMP) lots (complete)

**Investigator:****Name:** Gary Steinberg**Institution:** Stanford University**Type:** PI**Name:** Stanley Carmichael**Institution:** University of California, Los Angeles**Type:** Co-PI**Name:** Johannes Boltze**Institution:** Fraunhofer-Institute for Cell Therapy and Immunology**Type:** Partner-PI**Disease Focus:** Neurological Disorders, Stroke**Collaborative Funder:** Germany**Human Stem Cell Use:** Embryonic Stem Cell**Cell Line Generation:** Embryonic Stem Cell**Award Value:** \$17,244,851**Status:** Closed**Progress Reports****Reporting Period:** Year 1**View Report****Reporting Period:** Year 2**View Report****Reporting Period:** Year 3**View Report**

**Reporting Period:** Year 4

**View Report**

**Reporting Period:** Year 5 (NCE)

**View Report**

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## Grant Application Details

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**Application Title:** Embryonic-Derived Neural Stem Cells for Treatment of Motor Sequelae following Sub-cortical Stroke

**Public Abstract:** A stroke kills brain cells by interrupting blood flow. The most common "ischemic stroke" is due to blockage in blood flow from a clot or narrowing in an artery. Brain cells deprived of oxygen can die within minutes. The loss of physical and mental functions after stroke is often permanent and includes loss of movement, or motor, control. Stroke is the number one cause of disability, the second leading cause of dementia, and the third leading cause of death in adults. Lack of movement or motor control leads to job loss and withdrawal from pre-stroke community interactions in most patients and institutionalization in up to one-third of stroke victims. The most effective treatment for stroke, thrombolytics or "clot-busters", can be administered only within 4.5 hours of the onset of stroke. This narrow time window severely limits the number of stroke victims that may benefit from this treatment. This proposal develops a new therapy for stroke based on embryonic stem cells. Because our (and others') laboratory research has shown that stem cells can augment the brain's natural repair processes after stroke, these cells widen the stroke treatment opportunity by targeting the restorative or recovery phase (weeks or months after stroke instead of several hours).

Embryonic stem cells can grow in a culture dish, but have the ability to produce any tissue in the body. We have developed a technique that allows us to restrict the potential of embryonic stem cells to producing cell types that are found in the brain, making them "neural stem cells". These are more appropriate for treating stroke and may have lower potential for forming tumors. When these neural stem cells are transplanted into the brains of mice or rats one week after a stroke, the animals are able to regain strength in their limbs. Based on these findings, we propose in this grant to further develop these neural stem cells into a clinical development program for stroke in humans at the end of this grant period.

This proposal develops a multidisciplinary team that will rigorously test the effectiveness of stem cell delivery in several models of stroke, while simultaneously developing processes for the precise manufacture, testing and regulatory approval of a stem cell therapy intended for human use. Each step in this process consists of definite milestones that must be achieved, and provides measurable assessment of progress toward therapy development. To accomplish this task, the team consists of stroke physician/scientists, pharmacologists, toxicologists, experts in FDA regulatory approval and key collaborations with biotechnology firms active in this area. This California-based team has a track record of close interactions and brings prior stroke clinical trial and basic science experience to the proposed translation of a stem cell therapy for stroke.

**Statement of Benefit to California:**

The State of California has made a historic investment in harnessing the potential of stem cells for regenerative therapy. While initially focused on developing new stem cell technologies, CIRM has recognized that translational progress from laboratory to clinic must also be fostered, for this is ultimately how Californians will benefit from their investment. Our focus on developing a neuro-restorative therapy for treatment of motor sequelae following sub-cortical stroke contains several benefits to California. The foremost benefit will be the development of a novel form of therapy for a major medical burden: The estimated economic burden for stroke exceeds \$56.8 billion per year in the US, with 55% of this amount supporting chronic care of stroke survivors (1). While the stroke incidence markedly increases in the next half-century, death rates from stroke have declined. These statistics translate into an expected large increase in disabled stroke survivors (1) that will have a significant impact on many aspects of life for the average Californian. Stroke is the third greatest cause of death, and a leading cause of disability, among Californians. Compared to the nation, California has slightly above average rates for stroke (2). Treatments that improve repair and recovery in stroke will reduce this clinical burden.

The team that has been recruited for this grant is made of uniquely qualified members, some of whom were involved in the development, manufacturing and regulatory aspects of the first clinical trial for safety of neural stem cells for stroke. Thus not only is the proposed work addressing a need that affects most Californians, it will result in the ability to initiate clinical studies of stem cells for stroke recovery from a consortium of academic and biotechnology groups in California.

1. Carmichael, ST. (2008) Themes and strategies for studying the biology of stroke recovery in the poststroke epoch. *Stroke* 39(4):1380-8.

2. Reynen DJ, Kamigaki AS, Pheatt N, Chaput LA. The Burden of Cardiovascular Disease in California: A Report of the California Heart Disease and Stroke Prevention Program. Sacramento, CA: California Department of Public Health, 2007.

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