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**Genetic manipulation of human embryonic stem cells and its application in studying CNS development and repair**

**Grant Award Details**

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Genetic manipulation of human embryonic stem cells and its application in studying CNS development and repair

**Grant Type:** SEED Grant

**Grant Number:** RS1-00333

**Investigator:**

<b>Name:</b>	Binhai Zheng
<b>Institution:</b>	University of California, San Diego
<b>Type:</b>	PI

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

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

**Award Value:** \$600,441

**Status:** Closed

**Progress Reports**

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**Reporting Period:** Year 2

**View Report**

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**Reporting Period:** NCE

**View Report**

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**Grant Application Details**

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**Application Title:** Genetic manipulation of human embryonic stem cells and its application in studying CNS development and repair

**Public Abstract:**

The advent of human embryonic stem cells (hESCs) has offered enormous potential for regenerative medicine and for basic understanding of human biology. On the one hand, hESCs can be turned into many different cell types in culture dish, and specific cell types derived from hESCs offer an almost infinite source for cellular replacement therapies. This is the primary reason for which hESCs have received much attention from the general public. On the other hand, scientists can study the properties of hESCs and their derivatives, and determine the effect of genes and molecules on such properties either in culture dish or with transplantation studies in live animals. This second aspect of hESC research would not only significantly enhance our understanding of the function of human genes, but will greatly augment our ability to apply hESCs in transplantation therapies and regenerative medicine. To attain the full potential of hESCs, genetic manipulation of hESCs is essential. In this proposal, we will establish the methods to genetically manipulate an increasingly used, non-federally approved hESC line, the HUES-9, and assess the feasibility to use genetically modified HUES-9 cells in cell transplantation studies to assess the integration of hESCs into the mouse central nervous system. We propose to achieve both homologous recombination (i.e. gene targeting) and transgene expression (with bacterial artificial chromosome), which have complementary utilities in assaying gene function in addition to the opportunity to label hESCs or their derivatives with fluorescent markers. Specifically, with genetic engineering of hESCs we will be able to 1) label hESCs and specific cell types derived from hESCs so that they can be readily followed in culture dish and in animals that have received cellular transplants; 2) disturb an endogenous gene or add more copies of a gene so that the effect of a gene of interest can be assessed (for this purpose, a gene involved in the development of a major motor tract, the corticospinal tract, will be studied). We will then transplant genetically engineered hESCs and their derivatives into the embryonic and adult mouse CNS to assess how well these cells integrate into the mouse CNS, and whether such transplanted animals can serve as valid models to study the effect of genes on hESC function in live animals. In transplantation studies involving adult mouse recipients, injured mouse CNS will be used in addition to intact CNS in order to evaluate the potential of hESCs to integrate into injured CNS, which has direct implications on the therapeutic potential of these cells. In summary, our proposal will establish the methods and tools to genetically manipulate HUES-9 cells, explore a paradigm to study human genes and cells in a context of neural development and cellular therapies, and will pave the way for future studies of genes and pathways in basic biology and regenerative medicine with hESCs.

**Statement of Benefit to California:**

The disability, loss of earning power, and loss of personal freedom associated with spinal cord injury is devastating for the injured individual, and creates a financial burden of an estimated \$400,000,000 annually for the state of California. Research is the only solution as currently there are no cures for spinal cord injury. My lab studies the underlying mechanisms for axon regeneration failure after spinal cord injury using mouse genetics and animal models of spinal cord injury. The current proposal aims to genetically manipulate human embryonic stem cells, study their potential to integrate into immature and mature central nervous system and analyze the effect of genes on such integration. Achieving genetic modification of hESCs will expedite studies with hESCs to cure a variety of human diseases and injuries including spinal cord injury. Our studies will pave the way for discoveries that might lead to novel treatment strategies for spinal cord injury and other neurological conditions. Effective treatments promoting functional repair will significantly increase personal independence for people with spinal cord injury, increase earning capacity and financial independence, and thus decrease the financial burden for the State of California. More importantly, treatments that enhance functional recovery will improve the quality of life for those who are directly or indirectly affected by spinal cord injuries.

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