WNT signaling and the control of cell fate decisions in human pluripotent stem cells.

Grant Award Details

WNT signaling and the control of cell fate decisions in human pluripotent stem cells.

Grant Type: Basic Biology I

Grant Number: RB1-01406

Project Objective: The overall objective is to elucidate the role of Wnt in human pluripotent stem cell biology, i.e. self-renewal, differentiation, reprogramming, interactions with extracellular matrix, etc.

Investigator:

Name:	Karl Willert
Institution:	University of California, San Diego
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,329,298

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

Grant Application Details

Application Title: WNT signaling and the control of cell fate decisions in human pluripotent stem cells.

Public Abstract: With their ability to develop into virtually all mature cell types, human pluripotent stem cells (hPSC) represent a unique and powerful research tool to study the fundamental mechanisms regulating human development. In addition, hPSC provide the “raw material” for the development of cell-based therapies of presently incurable diseases, such as cancer, cardiovascular disease, and neurodegenerative disorders. However, our understanding of the basic mechanisms underlying stem cell biology is incomplete, and the processes by which individual cells organize each other to give rise to the complexity of multicellular life remain mysterious.

At the heart of embryonic development lies an intricate process of cell communication. Individual cells within the developing organism produce and release signals, known as growth factors, that instruct neighboring cells to assume specific behaviors and properties. Unique combinations of such growth factors regulate a multitude of developmental processes, including the growth and differentiation of hPSC.

Wnt proteins represent a major class of growth factors with potent effects on stem cells and developmental processes. However, despite nearly 30 years of research on these proteins with over 1,500 publications in 2008 alone, the mechanisms by which Wnt proteins elicit specific cellular responses and regulate stem cell biology remain poorly understood.

Two major shortcomings have impeded progress in the study of Wnt proteins. First, Wnt proteins long resisted biochemical characterization so that their manipulation in biological systems was difficult and even impossible. Second, Wnt proteins do not act alone but rather exert their activities in combination with thousands of biological molecules. Present day technologies are insufficient in to re-creating these complex cellular microenvironments in which Wnts act.

We have developed powerful technologies that allow us to systematically dissect the role of Wnt signaling in regulating the behavior of hPSC. By developing the means to isolate Wnt proteins we are now able to examine their effects on stem cell growth and differentiation. In addition, we established a novel technology platform with which we can interrogate the effect of thousands of combinations of Wnt proteins and other biological molecules on hPSC.

This combination of technological advances and expertise puts us in an ideal position to define the role of Wnts in developmental processes. By identifying the mechanisms by which Wnt proteins act we will contribute valuable tools and protocols for the manipulation and specific differentiation of hPSC into mature cell types that can be utilized in cell replacement therapies.

Statement of Benefit to California:	The rise in life expectancy to over 80 years will likely lead to an increase in the number of people suffering from age-related diseases, such as cancer, heart disease and neurodegenerative disorders. Current medical treatments can control, but not cure, such diseases. Recent advances in the study of human pluripotent stem cells (hPSC) have provided the opportunity to develop novel cell replacement therapies for the treatment of many such diseases. Development of novel cell based therapies will also overcome the inadequacy of conventional drug-based treatments. Several scientific obstacles need to be overcome before the full potential of hPSC-based therapies can be realized. First, sufficiently large numbers of clinical grade hPSC that can be thoroughly tested and characterized need to be derived. Second, robust protocols for the directed differentiation of hPSC into functionally mature cell types suitable for transplantation need to be developed. To address these challenges we propose a set of experiments that will significantly expand our understanding of basic biology of hPSC. To this end we will examine the role of a major class of stem cell factors, called Wnt proteins, in regulating hPSC growth and differentiation. In addition, we will expand on a technology that allows us to interrogate the effect of thousands of combinations, including Wnt proteins, on hPSC behavior. These experiments will enable the development of cost-effective protocols for the large-scale production of undifferentiated hPSC and functionally mature cell types. Our technology, which we will make freely available, will additionally benefit many other lines of scientific inquiry, such as defining growth conditions of rare adult stem cell populations and modeling the cellular basis of diseases. Thus, our proposed research is fundamental to applications of hPSC in regenerative medicine and has broad benefits to researchers with a wide spectrum of scientific interests. This research will not only benefit the health of Californians, but also the California economy by developing new reagents, protocols and technologies that will be adopted by existing companies as well as seed and complement novel business ideas. The outcome of this project will contribute to the development of a biotechnology platform that can provide great benefits to the advancement of California biotechnology. The patents, royalties and licensing fees that result from the advances in the proposed research will provide California tax revenues. Thus, the current proposed research provides not only the essential foundation for the scientific advances in regenerative medicine to improve health and quality of life, but also potential technology advancement and financial profit for the people in California.