Role of Mitochondria in Self-Renewal Versus Differentiation of Human Embryonic Stem Cells

Grant Award Details

Role of Mitochondria in Self-Renewal Versus Differentiation of Human Embryonic Stem Cells

Grant Type: SEED Grant

Grant Number: RS1-00313

Project Objective: Explore a hypothesis that mitochondria both reflect and influence hESC decisions to self-renew versus differentiate

Investigator:

Name:	Michael Teitell
Institution:	University of California, Los Angeles
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $543,274

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Role of Mitochondria in Self-Renewal Versus Differentiation of Human Embryonic Stem Cells

Public Abstract:

Human embryonic stem cells (hESCs) hold great potential for treating multiple human dread diseases, including but not limited to cancer, diabetes, obesity, Alzheimer disease, and certain types of heart failure. However, a growing appreciation exists for the notion that not all hESCs have identical capabilities in correcting or ameliorating disease and not all hESCs will be valuable as potential therapeutic cell sources. Because hESCs contain genetic information like all human cells, some hESCs will have genetic mutations or alterations that will make them more or less desirable for therapy. The heritable information contained with hESCs comes from DNA in the cell nucleus and also from DNA within maternally inherited mitochondria. In fact, it is the functional capabilities of mitochondria in hESCs that this proposal addresses because over 400 mutations in mitochondrial DNA result in disease and many more disorders associated with mitochondrial dysfunction, often unidentified at the molecular level, arise from mutations in nuclear DNA.

It is potentially dangerous that so little is known about the functional capabilities and role for mitochondria in hESCs and in the major decisions that hESCs make, such as whether to self-renew and make more stem cells or to differentiate into any one of the known human lineages, including muscle, skin, brain, and other cell types. We anticipate the day when stem cell therapies to combat disease or provide replacements for worn out components will be a main part of individualized medical treatment. We believe it is therefore critical to choose the best stem cell starting materials for such therapeutic applications. This view, combined with a desire to understand how mitochondria, as the main source for a cell's energy and building block generation, functions in stem cell decisions, propels us to provide 3 integrated areas of specific investigation into stem cell mitochondria and their role(s) in decision making. Our studies will evaluate basic mitochondrial functions and structures in a variety of hESCs to gain an appreciation for variability in distinct hESCs (Aim 1). We will alter mitochondrial function in hESCs with genetic and environmental insults to gain an appreciation for the global effects on hESC function and as a way to help select appropriate stem cells for future therapeutic applications (Aim 2). We will force hESCs with normal or altered mitochondria to differentiate into germ cells, blood cells, skin cells, or brain cells with expert collaborators in each lineage type to evaluate how the state of mitochondrial function will dictate the ability for hESCs to provide multiple, distinct replacement lineages for use (Aim 3).

In sum, we expect our studies will reveal the critical role for mitochondria In stem cell biology and this new knowledge and our analytical approach will help provide essential information for choosing optimum stem cells for future therapeutic applications.

Statement of Benefit to California:

Our proposal will benefit California by adding new knowledge on the functional capabilities of human embryonic stem cells (hESCs) and their lineage differentiated derivatives, which will support the California peoples' and taxpayers' commitments to individualized medical treatments of the near future. It will help us select the best possible stem cells for study and therapy development in our major academic centers and will provide information to many of California's biotechnology and pharmaceutical companies in the burgeoning stem cell industry, whose success will propel hiring and increased economic prosperity for the state. Our work will provide additional information to patient advocates, ethicists, and even (eventually) medical geneticists to help select the optimal course for developing and modifying stem cell usage policies and infrastructure within California. This proposal will provide information for patients and their physicians, that may, at some future time, impact the selection of particular stem cell attributes for specific types of therapeutic applications. In sum, the added knowledge provided by a detailed analysis of mitochondrial capabilities in hESCs will have tangible health and economic impact on California, its academic institutions and biotechnology/pharmaceutical companies, and the rest of the nation as California and its people move forward with personalized medicine during the 21st century.