Antibody tools to deplete or isolate teratogenic, cardiac, and blood stem cells from hESCs

Grant Award Details

Antibody tools to deplete or isolate teratogenic, cardiac, and blood stem cells from hESCs

Grant Type: Tools and Technologies II

Grant Number: RT2-02060

Project Objective: To improve methods to purify tissue-specific stem cells from mixed cultures using a 'cell signature' of surface markers so they can be used safely and effectively for therapy.

Investigator:

Name:	Irving Weissman
Institution:	Stanford University
Type:	PI

Disease Focus: Blood Disorders, Heart Disease, Liver Disease, Metabolic Disorders

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Award Value: $1,463,814

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Antibody tools to deplete or isolate teratogenic, cardiac, and blood stem cells from hESCs

Public Abstract: Purity is as important for cell-based therapies as it is for treatments based on small-molecule drugs or biologics. Pluripotent stem cells possess two properties: they are capable of self regeneration and they can differentiate to all different tissue types (i.e. muscle, brain, heart, etc.). Despite the promise of pluripotent stem cells as a tool for regenerative medicine, these cells cannot be directly transplanted into patients. In their undifferentiated state they harbor the potential to develop into tumors. Thus, tissue-specific stem cells as they exist in the body or as derived from pluripotent cells are the true targets of stem cell-based therapeutic research, and the cell types most likely to be used clinically. Existing protocols for the generation of these target cells involve large scale differentiation cultures of pluripotent cells that often produce a mixture of different cell types, only a small fraction of which may possess therapeutic potential. Furthermore, there remains the real danger that a small number of these cells remains undifferentiated and retains tumor-forming potential. The ideal pluripotent stem cell-based therapeutic would be a pure population of tissue specific stem cells, devoid of impurities such as undifferentiated or aberrantly-differentiated cells.

We propose to develop antibody-based tools and protocols to purify therapeutic stem cells from heterogeneous cultures. We offer two general strategies to achieve this goal. The first is to develop antibodies and protocols to identify undifferentiated tumor-forming cells and remove them from cultures. The second strategy is to develop antibodies that can identify and isolate heart stem cells, and blood-forming stem cells capable of engraftment from cultures of pluripotent stem cells. The biological underpinning of our approach is that each cell type can be identified by a signature surface marker expression profile.

Antibodies that are specific to cell surface markers can be used to identify and isolate stem cells using flow cytometry. We can detect and isolate rare tissue stem cells by using combinations of antibodies that correspond to the surface marker signature for the given tissue stem cell. We can then functionally characterize the potential of these cells for use in regenerative medicine.

Our proposal aims to speed the clinical application of therapies derived from pluripotent cell products by reducing the risk of transplanting the wrong cell type - whether it is a tumor-causing residual pluripotent cell or a cell that is not native to the site of transplant - into patients. Antibodies, which exhibit exquisitely high sensitivity and specificity to target cellular populations, are the cornerstone of our proposal. The antibodies (and other technologies and reagents) identified and generated as a result of our experiments will greatly increase the safety of pluripotent stem cell-derived cellular therapies.

Statement of Benefit to California:	Starting with human embryonic stem cells (hESC), which are capable of generating all cell types in the body, we aim to identify and isolate two tissue-specific stem cells – those that can make the heart and the blood – and remove cells that could cause tumors. Heart disease remains the leading cause of mortality and morbidity in the West. In California, 70,000 people die annually from cardiovascular diseases, and the cost exceeded $48 billion in 2006. Despite major advancement in treatments for patients with heart failure, which is mainly due to cellular loss upon myocardial injury, the mortality rate remains high. Similarly, diseases of the blood-forming system, e.g. leukemias, remain a major health problem in our state. hESC and induced pluripotent stem cells (collectively, pluripotent stem cells, or PSC) could provide an attractive therapeutic option to treat patients with damaged or defective organs. PCS can differentiate into, and may represent a major source of regenerating, cells for these organs. However, the major issues that delay the clinical translation of PSC derivatives include lack of purification technologies for heart- or blood-specific stem cells from PSC cultures and persistence of pluripotent cells that develop into teratomas. We propose to develop reagents that can prospectively identify and isolate heart and blood stem cells, and to test their functional benefit upon engraftment in mice. We will develop reagents to identify and remove residual PSC, which give rise to teratomas. These reagents will enable us to purify patient-specific stem cells, which lack cancer-initiating potential, to replenish defective or damaged tissue. The reagents generated in these studies can be patented forming an intellectual property portfolio shared by the state and the institutions where the research is carried out. The funds generated from the licensing of these technologies will provide revenue for the state, will help increase hiring of faculty and staff (many of whom will bring in other, out-of-state funds to support their research) and could be used to ameliorate the costs of clinical trials – the final step in translation of basic science research to clinical use. Only California businesses are likely to be able to license these reagents and to develop them into diagnostic and therapeutic entities; such businesses are at the heart of the CIRM strategy to enhance the California economy. Most importantly, this research will set the platform for future stem cell-based therapies. Because tissue stem cells are capable of lifelong self-renewal, stem cell therapies have the potential to be a single, curative treatment. Such therapies will address chronic diseases with no cure that cause considerable disability, leading to substantial medical expense. We expect that California hospitals and health care entities will be first in line for trials and therapies. Thus, California will benefit economically and it will help advance novel medical care.

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