Regulation of Stem Cell Fate in Bioengineered Arrays of Hydrogel Microwells

Grant Award Details

Regulation of Stem Cell Fate in Bioengineered Arrays of Hydrogel Microwells

Grant Type: Tools and Technologies I

Grant Number: RT1-01001

Project Objective: To characterize the in vitro behavior of muscle stem cells in response to biophysical cues towards developing culture methods for their maintenance and expansion

Investigator:

Name:	Helen Blau
Institution:	Stanford University
Type:	PI

Disease Focus: Aging, Skeletal/Smooth Muscle disorders, Trauma

Human Stem Cell Use: Adult Stem Cell

Award Value: $949,608

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Regulation of Stem Cell Fate in Bioengineered Arrays of Hydrogel Microwells

Public Abstract:

Stem cell biology, since its inception 30 years ago, has been hindered by our limited ability to observe and direct the decisions of individual stem cells. In the case of adult tissue-specific stem cells, such as those from blood, muscle or pancreas, the numbers available for clinical use are extremely limited, as in tissue culture the cells either have limited viability, do not divide, or rapidly specialize and lose their stem cell properties and potential to contribute to tissue regeneration. To overcome this hurdle, over the past three years we have been developing and optimizing a novel technology that employs arrays of bioengineered hydrogel microwells to study the fate of single stem cells dynamically by timelapse microscopy. This technology has several distinct advantages: (1) The hydrogel material is hydrated and substantially softer than standard tissue culture plastic, which substantially increases stem cell viability; (2) The arrays consist of wells containing hundreds of microwells so that single stem cells can be monitored simultaneously, which is critical since the stem population is inherently diverse; (3) Finally, the hydrogels we developed can be chemically modified so that the stem cells are exposed to molecules found in the tissue – soluble or tethered. We have found that the viability of human fetal pancreatic progenitors is increased 1,000-fold when grown on our hydrogels, which could impact the development of a treatment for diabetes. We have also found that exposure of blood stem cells to specific proteins causes them to self-renew in culture, a step toward overcoming a major roadblock to their use in the treatment of hematologic malignancies. Finally, studies of human embryonic stem cells (hES) could benefit from this platform, as conditions improve. In the current grant, we propose to apply this technology to study factors that increase the function of young and old murine muscle stem cells. In addition, we propose to develop protocols for the isolation and characterization of human muscle stem cells, which will further help the translation of our findings to the clinic. A second novel technology with broad utility is presented here, non-invasive bioluminescence imaging, which we have developed in order to monitor muscle stem cell function in vivo. It entails a method for following stem cell numbers dynamically and quantitatively in mice using bioluminescence imaging. This method will allow the pattern of tissue formation to be monitored in real time without sacrificing the mice and will generate a more accurate picture of tissue regeneration following cell transplants. Together these technologies should advance the use of muscle stem cells for the treatment of age-related muscle wasting. In addition, these technologies should advance and benefit the entire stem cell field.

Statement of Benefit to California:

The state of California is the front-runner in stem cell research, having gathered not only private investments, as demonstrated by the numerous biotechnology companies that are developing innovative tools, but also extensive public funds via Prop 71, that allows the state, through CIRM to sponsor stem cell research in public and private institutions. In order to preserve the leadership position and encourage research on stem cells, the CIRM is calling for research proposals that could lead to significant breakthroughs or the development of technologies useful for studying stem cells in order to improve human health. We propose here to develop a platform that will establish a “gold standard” for monitoring and manipulating stem cells in culture. Adult stem cells are present in many tissues, but their regenerative potential is not currently fully realized. Although isolation of these cells is performed routinely, their expansion has been hindered by the lack of tools and knowledge of the factors capable of inducing their division without loss of their stem cell properties. Here we describe a highly innovative and powerful bioengineered platform capable of enhancing stem cell function in culture. We apply it here to muscle stem cells for the treatment of muscle wasting, which is a common problem in the aging population, detected by a progressive loss of muscle mass and decline in muscle function. A better understanding of muscle stem cell biology is greatly needed to effectively treat these disorders and our technological platform is focused on defining the conditions and factors required for expansion of muscle stem cells. This technology will contribute substantially to all types of stem cell research, including human embryonic stem cells and induced pluripotent stem cells.
