Mechanisms of Stem Cell Fate Decisions

Grant Award Details

Mechanisms of Stem Cell Fate Decisions

Grant Type: New Faculty I

Grant Number: RN1-00540

Project Objective: -Determine the role of the tyrosine kinase receptor Flk2 in cell fate decisions of hematopoietic stem and progenitor cells.
-Assess cell fate decisions during in vivo hematopoietic differentiation using novel lineage tracing models.
-test models of intercellular relationships of hematopoietic stem and progenitor populations using computational biology of global datasets.

Investigator:

Name:	Camilla Forsberg
Institution:	University of California, Santa Cruz
Type:	PI

Award Value: $2,201,759

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Grant Application Details

Application Title: Mechanisms of Stem Cell Fate Decisions

Public Abstract: Stem cells can mature into a diverse range of specialized cell types, providing exciting possibilities for regeneration of different tissue types. Many disorders can conceivably be treated by transplanting stem cells to replace the defective cells. However, several disorders affect a specific cell type, while other cells and tissues in the same patient are functioning normally. Examples of such cell type-specific cases are Parkinson's disease, diabetes and anemia. A fundamental challenge in using stem cells to treat disease is to be able to steer their maturation into the specific cell type needed. Maturation into the wrong cell type may cause problems due to uncontrolled growth or immune rejection. For example, a blood stem cell transplant intended to treat anemia would be optimally efficient and safe if the transplanted cells could be directed to generate red blood cells without also producing T cells. Another major limitation of transplantation therapy is the shortage of cells for clinical use. This too could be alleviated by efficient generation of the desired cell type.

This proposal investigates the regulation of stem cell maturation into specific functional cell types. We are using blood cell development as a model system. Bone marrow transplantations, containing blood stem cells, have been used clinically for many years and are among few routinely performed cell-based therapies. The cumulative experience from years of clinical use together with decades of research on blood stem cell maturation makes this a strong model system for understanding both basic stem cell biology and clinical stem cell applications.

The many years of research on blood cell maturation has allowed the generation of a basic road map, complete with intersections indicating a choice in maturation pathway. As stem cells mature, choices are made along the way to become, for example, a T cell or a red blood cell. Scientists have identified signposts at these intersections that help mark some of the choices. These signposts are useful both as diagnostic tools to determine where cell maturation went wrong, and as targets for drugs when trying to promote one choice over another. Currently, we do not know when and how these choices are made under normal conditions and what goes wrong in various disorders. Our ability to direct or redirect cell fates upon transplantation or in cancer is therefore absent or inefficient. The goal of this proposal is to better define the intersections and signposts in blood cell development. We will generate new tools and methods to study stem cell maturation, and attempt to identify maturation stages and targets that will be useful to diagnose and treat blood-related disorders and increase the efficiency and safety of stem cell transplantation.

Statement of Benefit to California:	Bone marrow and blood stem cell transplantation is a potentially curative treatment for patients with a variety of blood-related disorders, including leukemia, lymphoma, anemias and auto-immune diseases, as well as non-blood disorders such as enzyme deficiencies. Survival and quality of life of patients with these disorders have been improving steadily since bone marrow transplantations, containing blood stem cells, came into clinical use in the 1970's. Now among the few routinely performed cell-based therapies, bone marrow transplantation thus serves as an important paradigm for clinical application of other types of stem cells. Although routinely used to treat a variety of diseases, the pretreatment preparing the patient for transplant is grueling and the risk of life threatening complications are unacceptably high. The research in this proposal is intended to understand how blood stem cells mature into different cell types. The goal is to be able to detect, prevent and treat blood-related disorders and to improve the efficiency and safety specifically of blood stem cell transplantation. With increased safety of transplantation regimens, this type of treatment will become available to a greater number of patients and lead to higher survival rates and fewer complications. Stem cell transplantation may also eventually be used to treat non-life-threatening, but burdensome, disorders. In addition, this research will contribute to the California education and health care systems by training undergraduate, graduate and postdoctoral students into highly skilled stem cell biologists.