Genetic dissection of mesodermal commitment to the hematopoietic fates.

Grant Award Details

Genetic dissection of mesodermal commitment to the hematopoietic fates.

Grant Type: New Faculty I

Grant Number: RN1-00575

Project Objective: The goal of this project is, using the zebrafish embryo as a model, to identify the cellular and molecular mechanisms by which definitive HSC first become specified during embryogenesis.

Investigator:

Name:	David Traver
Institution:	University of California, San Diego
Type:	PI

Award Value: $2,150,620

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: Genetic dissection of mesodermal commitment to the hematopoietic fates.

Public Abstract: Genetic dissection of mesodermal commitment to hematopoietic fates.

Hematopoietic cell transplantation is the gold standard for cell-based therapy and is routinely used to treat a wide variety of blood disorders and cancer. A major limitation exists, however, in finding donors whose immune systems are compatible with those of the patients requiring transplantation. The recent creation of human embryonic stem cell (hESC) lines holds great promise for new cell-based therapies. ES cells can generate all cell types in the body and can be stored indefinitely. Large banks of genetically diverse or genetically engineered hESC cells could thus be used to match donor and host immune systems. For hematopoietic cell transplantation, ESCs must be coaxed to differentiate into hematopoietic stem cells (HSCs). This is currently not possible, due in large part to a lack of understanding of the molecular cues required to generate HSCs during development.

In the vertebrate embryo, two waves of blood cell production occur. The first generates only erythroid cells and the second HSCs. Understanding the development of these two waves is important since ES cells have been shown to normally generate only the first. In this application, we will determine the genetic factors necessary to create HSCs from mesoderm by leveraging the unique advantages of the zebrafish system. Zebrafish embryos are transparent, and we have recently created transgenic animals that possess fluorescent HSCs. We will therefore combine genetic analyses with the direct imaging of HSC behavior in living embryos to provide an unprecedented view of HSC development. Many of the genetic pathways used to pattern the early embryo are later used to specify and maintain HSCs. These include pathways controlled by the Notch and Wnt factors. We will focus our efforts on these pathways using in vivo developmental and genetic approaches. Zebrafish possess the same blood cell types as humans, and findings in one system can be readily translated to the other. Understanding the development of HSCs in the vertebrate embryo, and how we can ultimately recapitulate this process in vitro using hESCs, is critical in improving human health since HSCs are the cells responsible for the therapeutic benefits of hematopoietic cell transplantation.

Statement of Benefit to California: The therapeutic use of stem cells began decades ago following the advent of bone marrow transplantation (BMT). BMT has routinely been used to cure blood cell disorders, leukemia, and immune deficiencies. BMT is often limited, however, by an inability to find donors that are genetically matched to patients requiring transplantation. The recent creation of human embryonic stem cell (hESC) lines holds great promise for new cell-based therapies, including BMTs. ESCs can generate all cell types in the body and can be stored indefinitely. Large banks of genetically diverse or genetically engineered hESCs could thus be used to match donor and host immune systems. For use in BMTs, however, ESCs must be coaxed to differentiate into hematopoietic stem cells (HSCs), the rare cell type within bone marrow responsible for the long-term, curative effects of BMT. This is currently not possible, due in large part to a lack of understanding of the molecular cues required to generate HSCs during development.

The goal of our proposed experiments is to provide a better understanding of the molecules required to generate HSCs in the vertebrate embryo. The results from our powerful in vivo system can easily be translated to the in vitro system of hESCs. Insight into the molecular factors needed to drive mesodermal commitment to HSCs in vivo will be used to provide similar factors at similar timepoints during in vitro culture of hESCs to generate HSCs. Once realized, it will be possible to create genetically characterized banks of diverse hESCs that can be selected based on patient genotypes to generate HSC-based therapies. Our research will thus lead to great improvements in stem cell therapies to better meet the needs of patients in California.