# Mechanisms of Hematopoietic stem cell Specification and Self-Renewal

## Grant Award Details

Mechanisms of Hematopoietic stem cell Specification and Self-Renewal

**Grant Type:** New Faculty I

**Grant Number:** RN1-00557

**Project Objective:** The goal of this grant was to define mechanisms that govern blood stem cell specification and self-renewal.

**Investigator:**

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| **Name:** | Hanna Mikkola |
| **Institution:** | University of California, Los Angeles |
| **Type:** | PI |

**Disease Focus:** Anemia, Blood Cancer, Blood Disorders, Cancer

**Human Stem Cell Use:** Adult Stem Cell, Embryonic Stem Cell

**Award Value:** $2,286,900

**Status:** Closed

## Progress Reports

**Reporting Period:** Year 2

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**Reporting Period:** Year 3

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**Reporting Period:** Year 4

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**Reporting Period:** Year 5

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## Grant Application Details

**Application Title:** Mechanisms of Hematopoietic stem cell Specification and Self-Renewal

**Public Abstract:** During an individual's lifetime, blood-forming cells in the bone marrow called hematopoietic stem cells (HSCs) supply all the red and white blood cells needed to sustain life. These blood stem cells are unique because they can make an identical copy of themselves (self-renew). Disorders of the blood system can be terminal, but such diseases may be cured when patients are treated with a bone marrow transplant. Unfortunately, bone marrow is in short supply due to limited availability of donors, and it is not yet possible to expand HSCs outside of the human body; HSCs that are removed from their native environment, or niche, rapidly lose their ability to self-renew and thus cannot sustain hematopoiesis in a transplant recipient. Furthermore, attempts to make blood stem cells from embryonic stem cells (ESCs) have also proved unsuccessful to date because these "tailored HSCs" are defective in self-renewal as well. These problems suggest that our understanding of the biology of HSCs is not sufficient to foster their maintenance or generation. To address this issue, we propose to study hematopoietic stem cells in the context of mammalian development; the entire complement of a person's HSCs is made in a very short time window during the first trimester of pregnancy. By increasing our understanding of how HSCs are made and acquire self-renewal in vivo, we hope to develop better methods of generating HSCs in vitro and learn to provide the missing cues to coax them into becoming fully functional, self-renewing hematopoietic stem cells. Specifically, we plan to investigate how the fate decision that delineates blood cells from their embryonic precursor, called specification, is maintained at the molecular level. Second, we are interested in what cell type human HSCs descend from so as to understand what precursor to look for when attempting to differentiate ESCs into blood stem cells. Finally, we plan to apply molecular analyses to the property of self-renewal by looking at cell populations that cover a spectrum with regards to self-renewal: HSCs, cultured HSCs (not self-renewing), HSC precursors (not self-renewing), and ESCs differentiated to non-self-renewing HSCs. These comparisons will help define the molecular regulation of self-renewal, and place ESC-derived progenitors on the spectrum of self-renewal. Through these studies, we hope to better understand blood stem cells as they are made and maintained during human development with the ultimate goal to provide wider access to stem cell-based therapies.

**Statement of Benefit to California:** Funding of research to understand hematopoietic stem cell (HSC) biology offers rewards beyond the pursuit of knowledge. HSCs are responsible for providing all of the blood cells in the body, including both red cells that carry oxygen and white cells that mediate immunity. Inherited disorders affecting HSCs and their progeny are responsible for diseases such as sickle cell anemia, Severe Combined Immunity Disorder (SCID), and leukemia; these devastating ailments change the lives of thousands of people in California every year, and currently most are incurable without a bone marrow or cord blood transplant. Due to the limited availability of donors, other alternatives, such as differentiating embryonic stem cells (ESCs) into HSCs, are being explored. One critical fault of ESC-derived progenitors is their inability to "self-renew", i.e. produce more of themselves, thus eliminating their usefulness for transplantation. However, a deeper understanding of the developmental and molecular processes that create functional HSCs that can self-renew may ultimately make the goal of deriving HSCs from ESCs attainable. Research into the mechanisms of self-renewal may also improve treatments of cancers such as leukemia, as these diseases are a function of over-proliferation of cells caused by uncontrolled self-renewal; targeting genes or proteins involved in abnormal self-renewal programs may provide more specific cancer fighting drugs, and would likely foster collaborations with biotechnology companies. Furthermore, as all stem cells in the body have the ability to self-renew, a clear understanding of self-renewal mechanisms will benefit all stem cell research, and could have a positive effect in a wide range of biomedical specialties.

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