Role of Innate Immunity in hematopoietic stem cell-mediated allograft tolerance

Grant Award Details

Role of Innate Immunity in hematopoietic stem cell-mediated allograft tolerance

Grant Type: Transplantation Immunology
Grant Number: RM1-01709
Project Objective: This proposal aims to test the hypothesis that signals mediated through pattern recognition receptors (PRRs) impair the development of HSC-mediated mixed hematopoietic chimerism and impair HSC-induced tolerance to solid organ transplants.

Investigator:

<table>
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<tr>
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<tr>
<td>Institution</td>
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<td>Type</td>
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Disease Focus: Blood Disorders
Human Stem Cell Use: Adult Stem Cell
Award Value: $1,705,554
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
The research proposed in this project has very high potential to identify new medications to boost the natural ability of stem cells to prevent rejection of transplanted organs. This is a very important goal, because patients that receive a life-saving transplanted organ must take toxic medications that increase their risk for cancer and serious infections.

Experimental clinical trials have recently shown that stem cells given to patients at the same time as they receive their transplanted organ can engraft in the patient and prevent rejection of the transplanted organ, without the need to take immunosuppressive medications. The problem though is that the stem cells don't last forever; they are eventually rejected by the patient's own immune system.

A promising target to prevent rejection of stem cells in patients is a group of primitive molecules that are receptors on stem cells, as well as many other cells in the body. These primitive receptors are called innate immune receptors and they provide the trigger for activation of a cascade of mechanisms that lead to rejection of the stem cells. If the trigger is not pulled, then the stem cells will not be rejected.

Therefore, our proposal focuses on how to block activation of the rejection cascade so that stem cells are able to engraft in the patient and prevent rejection of transplanted organs, without the life-long use of toxic medications.

We have extensive experience studying innate immune receptors and transplantation and therefore are poised to make significant advances in our understanding of how stem cells are rejected by signals that depend on innate immune receptors. Furthermore, once we identify which innate immune receptors are relevant, targeted rationale blockade of these receptors can be proposed.

The proposed research will benefit the State of California and its residents by providing important knowledge about new ways to prevent rejection of transplanted organs. Currently, patients with transplanted organs must take life-long toxic medications to prevent rejection of their organs. This proposal will help develop ways to avoid the use of these toxic medications, while allowing life-saving organ transplants to survive in their new host. The use of stem cells in recipients of solid organ transplants is the first new breakthrough in decades for transplantation and therefore it is very important to try to optimize the use of stem cells to allow the survival of transplanted organs without toxic immunosuppressive medications.