California Institute for Regenerative Medicine

In Utero Embryonic Stem Cell Transplantation to Treat Congenital Anomalies

**Reporting Period: Year 1**

Our group works on developing methods for successful transplantation of blood stem cells to treat fetuses with genetic disorders such as sickle cell disease or thalassemia. In this grant, we are using novel stem cells that will differentiate into blood-forming cells and other techniques to improve the "engraftment" of these cells. This year, we focused on using a new technique that creates "space" in the bone marrow of the recipient using an antibody (ACK2) to deplete the host's blood stem cells. In a mouse model, we showed that this antibody is very effective in improving the engraftment of transplanted blood stem cells. In fact, the treatment is more effective in the fetal environment than the adult. These findings were recently published and we are planning to use this strategy in the monkey model as a step toward clinical applications. We are also working on transplanting human blood stem cells into immunodeficient mouse fetuses to understand whether different sources of stem cells vary in their ability to make blood cells in this setting.

**Reporting Period: Year 2**

The goal of our grant is to optimize the strategy of in utero transplantation of hematopoietic stem cells, with the ultimate goal of treating fetuses with congenital stem cell disorders. Our project includes transplantation of HSC into both mice and non-human primates. This year, we have continued our work with in utero transplantation of human HSCs into the fetuses of an immunodeficient mouse strain. We have observed engraftment of the cells and differentiation into multiple blood lineages, including T cells, B cells, and regulatory T cells. We are working with other HSC types, such as those derived from iPS cells, to determine whether they can engraft in these mice as well. We are also testing different routes of administration of these cells, including into the placenta, which is a site of hematopoesis. These experiments are designed with the goal of translating these discoveries to treat fetuses with genetic disorders such as thalassemia or sickle cell disease.

**Reporting Period: Year 3**

Our group works on developing methods for successful transplantation of blood stem cells to treat fetuses with genetic disorders such as sickle cell disease or thalassemia. In this grant, we are using novel stem cells that will differentiate into blood-forming cells and other techniques to improve the "engraftment" of these cells. Our strategies involve using antibodies to deplete stem cell from the fetal host to create "space" in the bone marrow for the engraftment of the newly transplanted cells. A second strategy involves co-transplanting regulatory T cells, which may prevent an immune response against the transplanted cells. The clinical applications of our work would involve performing stem cell transplant in fetuses with inherited blood stem cell disorders so that they can be born healthy.

**Reporting Period: Year 4**

Our group works on developing methods for successful transplantation of blood stem cells to treat fetuses with genetic disorders such as sickle cell disease or thalassemia. In this grant, we are using novel stem cells that will differentiate into blood-forming cells and other techniques to improve the engraftment of these cells. Our strategies involve using antibodies to deplete stem cell from the fetal host to create "space" in the bone marrow for the engraftment of the newly transplanted cells. A second strategy involves co-transplanting regulatory T cells, which may prevent an immune response against the transplanted cells. In this reporting period, we have made progress in implementing a strategy that involves harvesting bone marrow cells from the mother and transplanting large numbers of these cells, along with Tcells to promote engraftment into the fetus in a large animal model. We have determined that this strategy is safe and feasible. Experiments to determine levels of engraftment and the differentiation profiles of the engrafted cells are under way.
This grant has enabled us to study important parameters related to transplantation of blood stem cells in fetuses in animal models. Based on these data, we have started a phase 1 clinical trial of in utero stem cell transplantation in patients with a blood disorder named alpha thalassemia major.

In Utero Embryonic Stem Cell Transplantation to Treat Congenital Anomalies

Grant Type: New Faculty Physician Scientist
Grant Number: RN3-06532
Project Objective: To achieve donor-specific tolerance to stem cell-derived / differentiated hematopoietic cells by in utero transplantation into the host fetus recipient. The Aims relate to derivation of the proper cell for transplantation, modulation of the host hematopoietic niche to allow engraftment and differentiation of the hematopoietic stem cells and to do so in the proper animal model.

Investigator:

<table>
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<tr>
<th>Name</th>
<th>Tippi MacKenzie</th>
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<tbody>
<tr>
<td>Institution</td>
<td>University of California, San Francisco</td>
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<td>Type</td>
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Disease Focus: Blood Disorders, Pediatrics

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $2,661,742

Status: Active

Application Title: In Utero Embryonic Stem Cell Transplantation to Treat Congenital Anomalies
Public Abstract:

Many fetuses with congenital blood stem cell disorders such as sickle cell disease or thalassemia are prenatally diagnosed early enough in pregnancy to be treated with stem cell transplantation. The main benefit to treating these diseases before birth is that the immature fetal immune system may accept transplanted cells without needing to use immunosuppressant drugs to prevent rejection. Moreover, transplanting stem cells into the fetus—in which many stem cell types are actively multiplying and migrating—can promote similar growth and differentiation of the transplanted cells. Although this strategy works well in animal models, when applied clinically, the number of surviving cells in the blood ("engraftment") has been too low to achieve a reliable cure.

Our lab studies ways to improve engraftment, with the long-term goal of applying these strategies to treat fetuses with congenital blood disorders. In this application, we will use novel embryonic stem cells that may be better suited to differentiate into blood cells in the fetal environment. We will also test various approaches to improve the survival advantage of these stem cells in fetal organs that make blood cells. Finally, we will study the fetal immune system to determine how fetuses become tolerant to the transplanted cells. The experiments in this proposal will give us important information to design clinical trials to treat fetuses with common, currently incurable stem cell disorders.

Statement of Benefit to California:

The long-term goal of our project is to develop safe and effective ways to perform prenatal stem cell transplantation to treat fetuses with congenital blood disorders, such as thalassemia and hemoglobin disorders. These diseases affect many California citizens. For example, hemoglobin disorders are so common that they are routinely screened for at birth (and prenatal screening is performed if there is a family history). Thalassemias are found more commonly in persons of Mediterranean or Asian descent and are therefore prevalent in our state’s population. Prenatal screening is routinely offered, especially to patients with a family history or those with an ethnic predisposition. Fetal stem cell transplantation would also benefit children with sickle cell disease, 2000 of which are born each year in the United States, and inborn errors of metabolism, which occur in 1 in 4000 births. Thus, once we develop reliable techniques to treat these disorders before birth, there will be an enormous potential to make a difference.

Fetal surgery was pioneered in California and is performed only in select centers across the country. Therefore, once we have developed safe and effective therapies for fetuses with stem cell disorders, we also expect increased referrals of such patients to California. The convergence of our expertise in fetal therapies with those in stem cell biology carries great promise for finally realizing the promise of fetal stem cell transplantation.

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