Project Summary

John Hansen Research Grant 2020

Project Title: Defining the role and targets of T cell DNA methylation in control of graft-versus-host disease and the graft-versus-tumor effect after allogeneic hematopoietic stem cell transplantation

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Blood and marrow transplantation (BMT) remains the only curative option for many pediatric and adult patients with cancer of the blood and lymphoid systems (including aggressive leukemia, lymphoma, and multiple myeloma), and some solid tumors. However, successful outcomes can be limited either by cancer relapse, or by the development of graft-versus-host disease (GVHD). GVHD is a complication wherein the new, donor, immune system (the “graft”) attacks the patient (the “host”) causing targeted multi-organ injury and dysfunction, which can be fatal. Such graft-versus-host effects can be beneficial when residual cancer cells are targeted, in a process known as the graft-versus-tumor (GVT) effect. Unfortunately, significant gaps remain in our ability to treat GVHD while permitting continued GVT activity.

It is well known that T lymphocytes, a type of white blood cell, play a major role in the development of both GVHD and GVT activity. We also know that one way that our body controls the function of T cells and the immune system is through changes in DNA and gene expression called epigenetic modifications. A process known as DNA methylation is one form of epigenetic regulation. In this project, we will use mice that have been genetically engineered so that they are unable to control their T cells via DNA methylation. These mice will serve as donors in BMT experiments, in which we will study the severity of GVHD and potency of GVT activity present in groups of mice that receive the genetically modified T cells as compared to mice that receive “normal” T cells. These experiments will allow us to directly examine the effects that T cell DNA methylation has on GVHD and GVT activity. This line of investigation will identify new pathways that can be targeted in order to improve outcomes for patients who require blood and marrow transplantation as a curative option for their underlying disease.