THE HARTWELL FOUNDATION

2012 Individual Biomedical Research Award

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Novel Molecular Regulators of Hematopoietic Stem Cell Specification: Expanding Access to Life-Saving Transplant Therapy

Hematopoietic stem cells (HSC) are specialized cells derived from bone marrow that are responsible for maintaining and replenishing all the different cell types of the blood. About 3000 children require HSC transplants each year in the United States to treat hematologic blood-related diseases and represent the only curative therapy for many blood disorders. Most of those children will be transplanted with either their own saved cells, or cells from a related donor (like a sibling or parent). Unfortunately, every year in the U.S. hundreds of children are unable to take advantage of HSC critical life-saving therapy. In about 15% of cases, children requiring transplants will have no choice but to accept a transplant from an unrelated donor who will not be a perfect match and thus, will be required to take immunosuppressive therapy. These children who receive cells from imperfectly matched donors are at high risk for transplant rejection and fatal graft-versus-host disease, as well as infections due to immunosuppression. Alternative sources of perfectly matched HSC could however, eliminate the need for donors and vastly expand access to this critical therapy. To avoid rejection, Shannon proposes that the ideal source of HSC could be pluripotent stem cells (PSC) derived from the patient's own skin cells, which will generate cells perfectly matched to the patient because they are the patient's own cells. Under the right culture conditions, PSC can generate any cell type in cell culture, indefinitely. This is in contrast to HSC, which can generate the many different types of blood cells but not cells of other tissue types. The problem is how to coax PSC to produce HSC. Shannon's suggests that nature has already optimized the generation of HSC and the key is to recapitulate the natural process. In effect, she seeks to coax HSC from PSC by advantageously promoting certain existing genes and molecular pathways active at the precise moment of HSC fetal development. To achieve this aim, she will use a novel experimental platform to identify the genes critical for HSC production in mouse embryos and induced PSC. If Shannon is successful, expanding access to an inexhaustible source of HSC will mean every child in need of a bone marrow transplant will have ready access to alternative life-saving therapy without the risk of rejection or the requirement for immunosuppression.