THE HARTWELL FOUNDATION

2024 Nominee Individual Biomedical Research Award

Hojun Li, MD, Ph.D.

Assistant Professor
Department of Pediatrics

University of California, San Diego

Epigenetic Engineering to Treat Inherited Bone Marrow Failure

Inherited bone marrow failure syndromes are a devastating group of childhood diseases caused by mutations in genes affecting the ability to properly produce blood cells. This group of disorders affects approximately two hundred live births per year in the United States. Affected children require chronic red blood cell transfusions to address anemia, platelet transfusions to address bleeding risk, and frequent use of intense antibiotic regimens to treat repeated infections. Despite these supportive care measures, mortality remains high and those children that do survive have an inferior quality of life due to frequent complications. Bone marrow transplantation is the only cure for bone marrow failure, but it carries a significant risk of death related to toxicities from the transplant procedure. Thus, there is a major unmet need for improved pediatric bone marrow failure therapies. Currently, the only bone marrow failure syndrome with an effective drug treatment is Diamond-Blackfan Anemia, where steroids improve red blood cell counts in 80% of patients. Unfortunately, chronic steroid usage leads to numerous toxicities, including immune suppression, high blood pressure, kidney disease, diabetes, cataracts, and bone fractures, illustrating a need for less toxic therapeutics. Recent advances identified the mechanism by which steroids increase red blood cell production: slowing down the speed of the developmental process for cell formation, which allows blood producing cells in the bone marrow to undergo a greater number of cell divisions and increase the total amount of cells eventually made. These findings argue for new bone marrow failure treatment strategies that will slow down the developmental process of forming blood cells to increase overall cell production. Because the speed of developmental processes is governed by the speed of turning on genes important for blood cell maturation, *slowing down the turning on* of maturation genes is a promising therapeutic approach to treat inherited bone marrow failure. A new class of drugs that prevent DNA from unwinding and exposing genes to be turned on has recently been developed to treat abnormally elevated levels of gene activation in many cancers. These drugs have been well tolerated in clinical trials with little to no side effects. Given that DNA unwinding can turn on gene expression by altering DNA accessibility, I hypothesize that this new class of drugs will work in an analogous manner as steroids for improving blood cell production. My research goal is to definitively test if this novel class of drugs improves blood cell production in a variety of bone marrow failure subtypes. If my hypothesis is correct and I am successful in implementation, it will be possible to launch a clinical trial testing such drugs in pediatric bone marrow failure patients, which will transform the lives of affected children by establishing a new long-term treatment strategy using a minimally toxic drug.