Targeted Gene Editing in the Treatment of X-Linked Hyper-IgM Syndrome

Grant Award Details

Targeted Gene Editing in the Treatment of X-Linked Hyper-IgM Syndrome

Grant Type: Quest - Discovery Stage Research Projects

Grant Number: DISC2-10124

Project Objective: To develop a gene-corrected HSC therapy for X-linked Hyper IgM Syndrome; will optimize and compare TALEN and CRISPR based approaches to select candidate for translation.

Investigator:

Name:	Caroline Kuo
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Blood Disorders

Human Stem Cell Use: Adult Stem Cell

Award Value: $1,512,333

Status: Active

Grant Application Details

Application Title: Targeted Gene Editing in the Treatment of X-Linked Hyper-IgM Syndrome

Public Abstract:

Research Objective

We are seeking to develop site-specific hematopoietic stem cell gene therapy with autologous transplant as a definitive treatment option for X-linked Hyper-IgM Syndrome.

Impact

These studies would bring stem cell gene therapy for X-HIGM closer to the clinic, as there are currently no options for those without an HLA match or with infections too severe for allogeneic HSCT.

Major Proposed Activities

- Identify the optimal CRISPR gRNA, Cas9 variant, and cDNA donor template targeting the CD40L gene.
- Compare TALENs and CRISPR/Cas9 targeting the CD40L gene in terms of their activity, specificity, and ability to allow homology-directed repair in CD34+ PBSC through short term cultures in vitro.
- Evaluate methods to maximize gene editing and maintain HSC survival and pluripotency.
- Evaluate the efficacy of optimized genome-editing reagents in hematopoietic stem cells long term in vitro in the artificial thymic organoid system and in vivo in NSG mice.
- Assess gene editing of the CD40L gene of X-HIGM patient derived CD34+ cells using the optimal gene editing platform and reagents determined in Milestones 1-4.

Statement of Benefit to California:

Safe, definitive therapies for X-HIGM represent an unmet medical need. Allogeneic stem cell transplant is frequently complicated by graft-versus-host disease and worsening of pre-existing infections. Successful demonstration that stem cell gene therapy can safely and effectively cure X-HIGM will shift the paradigm by which patients will be treated, led by California's position as a leader in the field of gene therapy. This will result in improved patient care in the state and around the world.
