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June 13, 2022

The Independent Citizen's Oversight Committee (ICOC)
California Institute for Regenerative Medicine (CIRM)
1999 Harrison Street, Suite 1650
Oakland, CA 94612

Application: DISC2-13415
Project Title: Defining the Optimal Gene Therapy Approach of Human Hematopoietic Stem Cells for the Treatment of Dedicator of Cytokinesis 8 (DOCK8) Deficiency
PI Name: Caroline Y. Kuo, M.D.

Dear Members of the Board,

We thank the Grants Working Group (GWG) for their critical review of our research proposal, which received a median/mean score of 85, with 14 out of 14 reviewers recommending funding. We would like to take this opportunity to emphasize important aspects of our proposal and ask for the ICOC's consideration to fund this project at the upcoming June 2022 Board Meeting.

Unmet Medical Need

Our proposed research program is directly in line with the CIRM mission to accelerate stem cell treatments to patients with unmet medical needs. ***DOCK8 Deficiency syndrome (DIDS) is a deadly immunodeficiency*** with an estimated incidence of about 1 in 1,000,000 persons that results in severe, recurrent infections of the skin, lung, liver, and GI tract, some of which are akin to those with life-threatening immune suppression seen in diseases such as AIDS, cancer, and severe combined immunodeficiency (SCID). ***Currently, the only potentially curative treatment is donor bone marrow/hematopoietic stem cell (HSC) transplantation; however for DOCK8 deficiency, this procedure is associated with a particularly high incidence of graft-versus-host disease, worsening of pre-existing infections, and death***. In addition, many patients do not have HLA-matched bone marrow donors or are already too ill to undergo high intensity conditioning regimens with chemotherapeutic agents. ***Even with available therapies, outcomes for patients with DIDS is poor, with >95% mortality by 40 years of age and a median survival of 10-20 years***. Therefore, gene editing of an affected individual's own HSC (patient is her/his own donor) can circumvent many of these complications and provide the potential for cure for a patient population in desperate need of new therapies. **As the GWG observed, *"…the likelihood that autologous HSC grafts (corrected for DOCK8) will work is high. This approach would also likely eliminate risk of graft versus host disease."***

Feasibility

As a clinician-scientist, I have dedicated my clinical practice and research to the care and treatment of both pediatric and adult patients with primary immune deficiencies. Though DIDS is a rare disease, it is

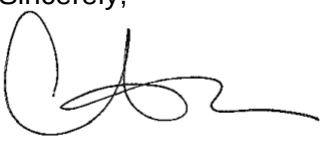
important to note, UCLA is home to Southern California's only Jeffrey Modell Foundation Diagnostic Center, which consists of 35 diagnostic and research centers worldwide dedicated to individuals with primary immunodeficiency disease. For this reason, ***UCLA has been a major referral center for patients with DIDS and other rare diseases.*** In addition, I have been working with the DOCK8 Foundation formed in 2021 with the mission to aid and assist people with DOCK8 deficiency by creating community, developing a registry of DOCK8 patients, and funding experimental medical research to progress treatment and cures for DOCK8. The research proposed in this application will be shared with patients through this foundation to spread awareness regarding potential new therapies for this disease. Through the DOCK8 Foundation, patients can connect with me for clinical consultation or to participate in my research.

Potential to Change the Medical Paradigm & Save Lives

In all, this project has the potential to change the paradigm by which DIDS patients are treated. Rather than pursuing definitive therapy through allogeneic HSCT only when complications have already ensued, DIDS patients may one day have the opportunity to change their disease course without ever having experienced clinical manifestations or complications. There is a clear unmet medical need for better curative therapies for patients with DOCK8 Deficiency. ***This work will not only serve this group of vulnerable patients without many treatment options but provide a foundation by which other immune and blood diseases may be cured in the future.***

We are happy to discuss this further and will be present at the next Application Review Subcommittee Meeting on June 23, 2022.

Sincerely,



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