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October 08, 2019

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

Application: TRAN1-11536
Project Title: *Ex Vivo* Gene Editing of Human Hematopoietic Stem Cells for the Treatment of X-Linked Hyper IgM Syndrome
PI Name: Caroline Y. Kuo, M.D.

Dear Members of the Board,

Thank you for the opportunity to respond to the July 2019 ICOC Application Review Subcommittee Meeting. We also thank the Grants Working Group for their critical review of ***our research proposal,*** which ***received a median/mean score of 92. This was the highest score from this most recent round of TRAN applications, with 15 out of 15 reviewers recommending funding***. While we understand that it was a programmatic decision of the ICOC Application Review Subcommittee to focus on embryonic stem cell and fetal tissue research projects during its recent meeting, 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 October 2019 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. ***X-linked Hyper IgM Syndrome (XHIM) is a deadly immunodeficiency*** with an estimated incidence of 1 in 500,000 persons that results in invasive infections of the liver, GI tract, and lungs, 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 allogeneic bone marrow transplantation; however for XHIM, 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, the survival probability for patients is only 30% at 30 years of age***. Therefore, gene editing of an XHIM patient's own hematopoietic stem cells can circumvent many of these complications and provide the potential for cure for a patient population in desperate need of new therapies.

Technology with Broad Applicability

Under an ongoing CIRM Discovery Stage Award (DISC2-10124), we have defined a set of gene editing reagents that achieve site-specific integration of an entire corrective DNA copy of the *CD40LG* gene, overriding any one of almost 200 different reported disease-causing mutations patients with XHIM may

have. This approach is, therefore, applicable to any individual affected by XHIM regardless of their mutation. Perhaps even more important is the potentially broad applicability of this work, as this project is developing a platform from which other monogenic diseases may be cured by stem cell gene therapy, using site-specific gene insertion. ***The approach we have pioneered of site-specific cDNA insertion for regulated gene expression is applicable to many other disorders including sickle cell disease, Beta thalassemia, other primary immunodeficiencies, Fanconi anemia, Lysosomal Storage Diseases, leukodystrophies, etc***.

Immediate Feasibility: FDA Meeting and Advancing CIRM Clinical Success with ADA-SCID

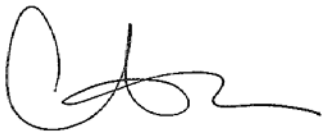
Another important consideration is the feasibility of this project. In February 2019, we completed an INTERACT meeting with the FDA, and the milestones defined in our proposal specifically address guidance from this interaction to bring gene editing of human hematopoietic stem cells for XHIM to the pre-IND stage of development within approximately 2 years. The team of scientists working on the earlier stage DISC grant have already begun to naturally transition to the translational stage project. PI Dr. Caroline Kuo has led the development of this gene editing strategy and is expert in application of CRISPR for gene editing in hematopoietic stem cells. In addition, Dr. Donald Kohn, who is part of a CIRM-funded parallel study on gene editing for sickle cell disease and a Co-Investigator in this research program, will share expertise in both gene editing as well as translating stem cell research into clinical trials. Dr. Kohn's experience in bringing stem cell gene therapy for Adenosine Deaminase Deficiency (ADA) SCID to successfully treating more than 50 babies with this deadly immune deficiency and successfully treating patients with X-linked Chronic Granulomatous Disease (XCGD) will undoubtedly foster the progression of this project to the clinic.

Potential to Change the Medical Paradigm & Save Lives

In all, this project has the potential to change the paradigm by which XHIM patients are treated. Rather than pursuing definitive therapy through allogeneic HSCT only when complications have already ensued, XHIM 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 X-linked Hyper IgM Syndrome. ***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 Board Meeting on October 31, 2019.

Sincerely,



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