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**Written comments to the ICOC Application Review Subcommittee****DISC2-09526 GENE EDITING FOR FOXP3 IN HUMAN HSC**

I would like to thank the reviewers for their recognition of the scientific merits and unanimous agreement for funding of this proposal, submitted within the Quest 2016 Call for applications. The described use of gene editing offers hope for an otherwise lethal childhood disease, Immunodysregulation Polyendocrinopathy Enteropathy X-linked or IPEX, making this an ideal translational study that fully meets the mission of CIRM to use highly innovative technologies applied to human hematopoietic stem cells to develop unique treatment options for patients who cannot be otherwise cured.

We have devoted years of past clinical and research experience to the study of IPEX Syndrome, caused by mutation of a single gene, FOXP3. Although it is a rare disease, IPEX is a prototype of a series of diseases with autoimmunity of genetic origin that overall severely affect children at a very early age. This expertise has given us a unique path forward in developing a definitive cure for this devastating genetic disease. Additionally, we have global access to recruit IPEX patients, thus minimizing the limitations of targeting a rare disease population. Importantly, increased awareness of the disease has led to increased diagnosis, a trend we sadly expect to continue.

In this project we will perform the preclinical studies required for the development of a **cure** for IPEX patients using a highly efficient genome editing approach to repair the patients' own hematopoietic stem cells (HSC). We are confident that our combined expertise in gene editing and human T regulatory cells as well as genetic diseases with immune dysregulation, in particular IPEX syndrome, will assure the success of our therapeutic approach.

This achievement will address a strong unmet medical need by providing a long-term cure for an otherwise lethal childhood disease, with current limited therapeutic options. In addition, it will be the first-in-human demonstration of the curative potential of edited HSCs. Because the FOXP3 gene expression is highly regulated, only a very specific editing technology, such as CRISPR/Cas9, could restore the function within specific types of T lymphocytes. Our standard protocols will allow us to assess and preserve the safety of the approach, including detailed analysis of off-target effects. The success of this work will be seminal in the subsequent adoption of this approach toward targeted gene repair for treatment of other blood monogenic diseases.

In conclusion, restoration of normal FOXP3 gene function via the proposed technology is ideal to restore the normal biology of the cells that is disrupted by mutations leading to a defective immune system causing severe and lethal autoimmunity. Importantly, our work will lay the foundation to cure IPEX and other similar monogenic immune diseases and will significantly contribute to maintain California's lead position in Stem Cell Research.



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