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Department of Pediatrics
Stem Cell Transplantation and Regenerative Medicine

To the CIRM Board of Governors, in support of the CLIN1 application 11591.

October 23, 2019

Dear ICOC,

We first would like to thank the scientific reviewers who unanimously supported the significance of our proposal as a "vital" replacement therapy and approved our investigational new drug (IND)-enabling studies.

We are grateful for the opportunity to advocate for the work we are ready to perform to bring our novel cell therapy product to the clinic, which consists of regulatory T (Treg) cells as a "living drug" for patients, who are genetically incapable of producing functional Treg cells. Because of their deficiency, these patients are affected at birth with IPEX (Immunedysregulation Polyendocrinopathy Enteropathy X-linked) syndrome, a severe life threatening autoimmune disease with very limited therapeutic options.

Treg cells are critical to the maintenance of immune system health. IPEX is the "experiment of nature" demonstrating how important Treg cells are to prevent autoimmune diseases, such as type 1 diabetes, acute refractory enteritis, severe dermatitis or alopecia, autoimmune hemolytic anemia, thyroiditis, hepatitis, or nephritis. IPEX patients may have all these symptoms because of a single gene defect. However, each of these manifestations are well known among the general population since millions of people are affected with autoimmunity and immune dysregulation without having IPEX. Without treatment, IPEX is rapidly fatal. The only current curative treatment is allogeneic stem cell transplantation (allo-HSCT) from a normal donor which is not available for every patient and can have unsatisfactory outcomes. These facts make IPEX patients, in addition to representing an urgent unmet medical need, ideal candidates for Treg cell therapy.

The clinical use of gene-modified T cells has recently been demonstrated as a safe therapy for cancer. We have developed instead, a gene-transfer strategy to produce Treg-like cells to treat autoimmunity, by expressing the correct version of the IPEX disease-causing gene, *FOXP3,* in conventional T cells. We call our cell therapy product $CD4^{LVFOXP3}$. With this technology we have successfully converted T cells from healthy donors and multiple IPEX patients into functioning Treg cells. The genetically engineered IPEX $CD4^{LVFOXP3}$ T cells have identical cellular markers and suppressive function to naturally occurring Treg cells from healthy donors. Among the favorable features of $CD4^{LVFOXP3}$ T cell product are: i) ease of generation, ii) stable FOXP3 expression leading to functional stability, and iii) co-expression of a second "marker" gene that allows us to track the cells *in vivo* once they are administered to patients. Importantly, the production of $CD4^{LVFOXP3}$ for the treatment of IPEX patients will use the patient's own T cells with no risk of rejection or graft-versus-host disease (GVHD). With the infusion of $CD4^{LVFOXP3}$ we aim to reduce or avoid pharmacological immunosuppression, stabilizing the condition of the patients as a bridge to allo-HSCT, or possibly even to replace allo-HSCT.

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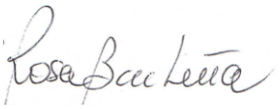
Our proposal details the IND-enabling studies of $CD4^{LVFOXP3}$ T cells for the treatment of Treg-deficient IPEX patients that we plan to begin at the end of the funding period. Longer term, we envisage that the best definitive therapy for IPEX will consist of the administration of gene edited autologous HSCs, an area we are actively pursuing in pre-clinical research. We believe that there is a strong rationale for a Treg-like cell replacement therapy with the $CD4^{LVFOXP3}$ T cells to bring immediate benefit to IPEX patients while long-term definitive therapies are developed. Further, the use of the $CD4^{LVFOXP3}$ T cells, that functionally replace defective autologous Treg cells, would not prevent IPEX patients from undergoing gene-edited HSC therapy in the future.

In finishing, the safe use of the $CD4^{LVFOXP3}$ in IPEX patients should enable the broadening of their use to additional autoimmune mediated diseases including but are not limited to inflammatory bowel disease (IBD), atopic dermatitis, newly diagnosed type 1 diabetes and steroid refractory acute GVHD. A Phase I/II trial of $CD4^{LVFOXP3}$ in IPEX patients will demonstrate their safety, *in vivo* survival, and impact on disease manifestations, and will lead to their evaluation in the treatment of more common autoimmune diseases.

We thank you for your consideration and look forward to the opportunity to further discussions with you at your next meeting scheduled for October 31.



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