CLINICAL

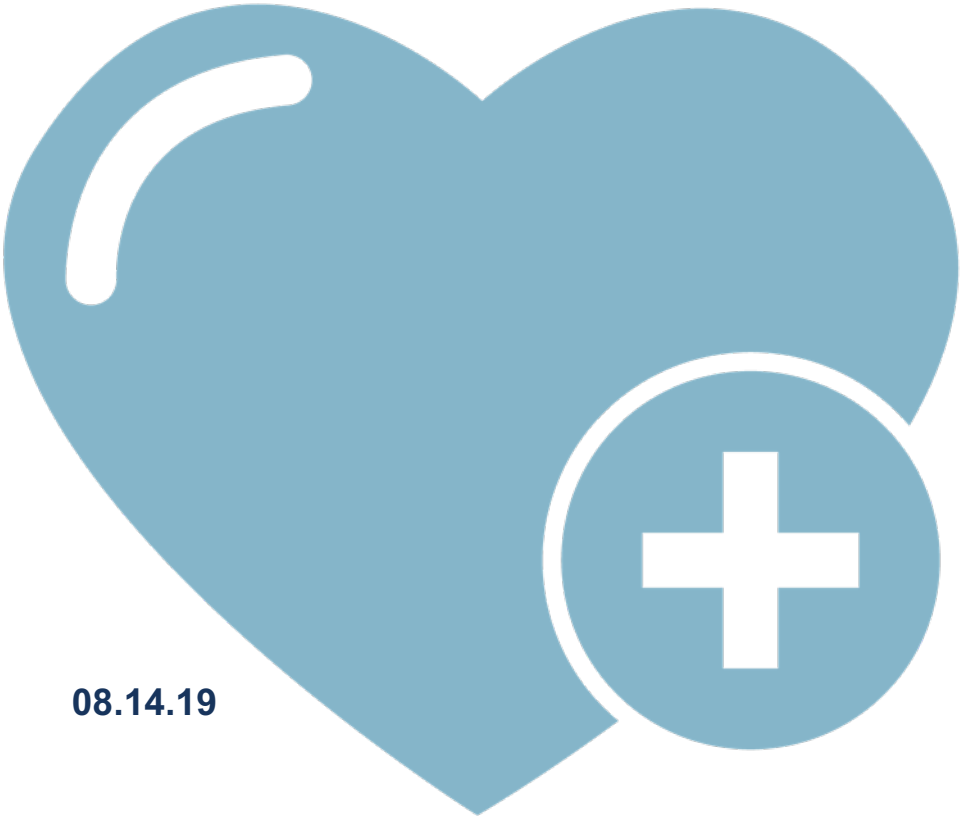
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

IND-enabling activities for a Phase 1 Study of Autologous CD4LVFOXP3 T Cells in Subjects with IPEX Syndrome

Application Number: CLIN1-11591	Review Date: 25 July 2019

Late Stage Preclinical Project Proposal (CLIN1)



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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

CD4+ T cells that have undergone lentiviral-mediated gene transfer of Forkhead Box P3 (FOXP3) and acquired regulatory T cell function.

Indication

Immune dysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) syndrome

Therapeutic Mechanism

Administration of autologous CD4LVFOXP3 that constitutively and stably express wild-type FOXP3 gene will replace the lack of functional regulatory T cells in patients with IPEX syndrome, a life-threatening pediatric disease due to FOXP3 gene mutation, and a prototype of genetic autoimmune disease.

Unmet Medical Need

IPEX has early severe onset and is a serious clinical challenge. Pharmacological immunosuppression can only partially control autoimmune manifestations and does not prevent organ damage. Allogeneic HSCT can cure, but lack of suitable donors and transplant complications lead to inferior outcomes.

Project Objective

Filing of IND application with the FDA

Major Proposed Activities

Complete nonclinical IND enabling safety and efficacy studies to meed the FDA requests.

GMP FOXP3 lentiviral vector production to generate CD4LVFOXP3 cell product for clinical use and establish its GMP manufacturing process and scale up.

File an Investigator New Drug (IND) application with the FDA to obtain approval to start the phase 1 clinical trial

Funds Requested

$5,527,984 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 13 GWG members

Votes for Score 2 = 2 GWG members

Votes for Score 3 = 0 GWG members

- A score of “1” means that the application has exceptional merit and warrants funding;
- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement;
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG’s recommendation.

Review Overview

Reviewers were supportive of this autologous gene therapy approach for a rare autoimmune disease termed IPEX. If effective, this therapy would offer a valuable alternative to the current standard of care options, which have significant toxic side effects. The applicants and reviewers agree that other future curative autologous gene-editing therapies are a longer-term goal, and the proposed therapy offers a bridging opportunity for treatment of IPEX. It could also impact other autoimmune diseases that do not have gene editing options. The program has some complex aspects that may present regulatory challenges, and there remain questions that will be challenging to answer before entering the clinic. However, reviewers thought this highly qualified team presented a reasonable and pragmatic path forward to an IND. The GWG unanimously voted this project as a vital research opportunity for CIRM; they then recommended that CIRM fund this project.

Assessment of Vital Research Opportunity

For projects that are not stem cell-based, the GWG must determine by a 2/3 majority vote whether they believe the project represents a vital research opportunity to permit funding. The vote tally is presented below.

GWG Vital Research Opportunity Vote

YES	**22**	**NO**	**0**

Review Summary

1. Does the project hold the necessary significance and potential for impact?

YES	**15**	**NO**	**0**

Reviewers considered the following:

a) Whether the proposed treatment fulfills an unmet medical need.

b) Whether the approach is likely to provide an improvement over the standard of care for the intended patient population.

c) Whether the proposed treatment offers a sufficient value proposition such that the value created by it supports its adoption by patients and/or health care providers.

d) If a Phase 3 Trial is proposed is the therapy for a pediatric or rare indication or, if not, is the project unlikely to receive funding from other sources?

Summary of Reviewers' Comments:

- IPEX is an autoimmune inflammatory disease caused by a FOXP3 gene mutation that leads to a

lack of regulatory T cells (Tregs) and is fatal if untreated. Although it is a rare disease, the development of new treatments or cures would be significant.

- Existing treatments are chronic immunosuppression or allogeneic hematopoietic stem cell transplantation (HSCT). Immunosuppression is not curative and there are insufficient HLA-matched donors for HSCT. Both options have problematic side effects.
- The proposed approach has important advantages over the currently available treatment choices. Most importantly, it is based on an autologous cell product that, in theory, should be available to all patients and will not cause graft versus host disease.
- If the proposed therapy is confirmed to be safe and its treatment effects prove reasonably long-lasting, it would likely represent a valuable alternative option to HSCT. While the latter offers the potential for a cure, the probability of GvHD and other HSCT risks could favor the choice of the less risky, even if not definitive, gene therapy approach.
- This treatment could be adapted for treatment of other autoimmune conditions where Treg cells are the underlying problem for which there are no CRISPR therapeutic approaches. If this approach shows these cells can persist and function, the possibility of reverse clinical development is interesting.

2. Is the rationale sound?

YES	15	NO	0

Reviewers considered the following:

a) Whether the proposed project is based on a sound scientific and/or clinical rationale, and whether the project plan is supported by the body of available data.

b) Whether the data supports the continued development of the treatment at this stage.

Summary of Reviewers' Comments:

- The hypothesis appears scientifically sound and is supported by good preliminary preclinical data from *in vitro* and *in vivo* models. The proposed therapy is worthy of continued development.
    - Preliminary preclinical data shows that genetic modification restores functional FOXP3, as well as Treg phenotype and function. The gene-modified cells persist for at least 14 days *in vivo*.
    - They have been able to produce the Tregs on a small scale and to demonstrate that they have the appropriate characteristics.
    - Some reviewers noted that the preclinical studies in humanized animal models were preventative in nature and raised questions about the stability and therapeutic effect of the Treg cells in the presence of inflammation.
- The applicant acknowledges the proposed product is not ideal and the team is developing gene-edited autologous HSCs in parallel but that approach will take longer to develop. This product could serve as a bridge therapy before autologous HSCT to improve the clinical status of the patient without the toxicity that is observed with the current immune suppression treatments.
- Questions remain as to whether these Treg cell products, especially after expansion, are phenotypically and functionally stable and how long will they survive *in vivo*.

3. Is the project well planned and designed?

YES	13	NO	2

Reviewers considered the following:

a) Whether the project is appropriately planned and designed to meet the objective of the program announcement and to achieve meaningful outcomes to support further development of the therapeutic candidate.

b) Whether the proposed experiments are essential and whether they create value that advances CIRM's mission.

c) Whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.

Summary of Reviewers' Comments:

- The proposed activities are appropriately designed and are necessary to answer safety questions posed by the FDA, operationalize manufacturing of therapeutic product, and obtain ethics and biosafety review which would enable filing of an IND application.
    - Conducting the proposed additional pre-clinical studies will add critical support to the proof of concept by assessing the effects of the gene-modified cells on the composition and function of the immune system in humanized IPEX mouse models.
    - Some reviewers were concerned that the proposed preclinical studies don't evaluate TReg stability and function in the presence of active inflammation. There was general agreement that the initial phase 1 clinical trial dose escalation design would minimize the risk and address these concerns.
- The applicants propose a time frame of 18 months to reach the IND submission, which seems reasonable given the complexity of the experimental plan required for Activity 1.

4. Is the project feasible?

YES	15	NO	0

Reviewers considered the following:

a) Whether the intended objectives are likely to be achieved within the proposed timeline.

b) Whether the proposed team is appropriately qualified and staffed and whether the team has access to all the necessary resources to conduct the proposed activities.

c) Whether the team has a viable contingency plan to manage risks and delays.

Summary of Reviewers' Comments:

- The described activities appear achievable within the proposed timeframes. In particular, the experiments of Activity 1 are based on established models that have yielded preliminary and interpretable data, which supports feasibility.
- This is a well-qualified team of investigators with the required expertise to perform the intended studies. The applicants have secured a list of experienced researchers, clinicians, and technology experts whose qualifications give the project excellent probabilities of success.
- The risks are not trivial but are acknowledged and mitigation plans appear reasonable. Five major risks are identified, predominantly related to potential manufacturing problems. In each case a mitigation strategy is proposed with identification of the source of additional funds that may be needed and the anticipated delay to the project.

CIRM Recommendation to Application Review Subcommittee

The CIRM recommendation to the Application Review Subcommittee is considered after the GWG review and did not affect the GWG outcome or summary. This section will be posted publicly.

RECOMMENDATION: Fund (CIRM concurs with the GWG recommendation).