November 16, 2021

Re: Application Review Subcommittee meeting for CIRM TRAN1-12895

Dear Independent Citizens Oversight Committee,

We thank CIRM and the Grants Working Group for their favorable reviews and recommendation for funding of our proposal, TRAN1-12895, Hematopoietic Stem Cell Gene Therapy for IPEX Syndrome. The reviewers were extremely positive noting:
“The applicants have provided strong supporting information for their approach”
“The data are compelling”
“The rationale is based on significant pre-clinical data in animal models”
“The assembled team is excellent”

The overall score of 86 from the Grants Working Group indicated the proposal shows “exceptional merit and warrants funding”.

The reviews contained essentially no criticisms of the existing data or proposed studies, however, some reviewers highlighted the fact the IPEX Syndrome is a rare disease and suggested that the impact of this proposal may be limited. We would like to address how this proposal has broader impacts beyond the target population and how this proposal meets the needs of underserved communities.

Broader impacts beyond IPEX Syndrome:

The study of IPEX Syndrome has been fundamental in our scientific understanding of autoimmunity. IPEX Syndrome results from a genetic defect in a cell type called a regulatory T cell (“Treg cells”). Treg cells act as a brake pedal of the immune system and prevent autoimmune attack on the body’s own tissues. Treg cells were first identified in 2001 by immunologists studying patients with IPEX Syndrome. IPEX is the most devastating and severe manifestation of autoimmunity; it is often fatal within the first 2 years of life due widespread immune attack on virtually every organ system. The severe autoimmunity seen in patients with IPEX Syndrome was eventually discovered to be caused by a profound dysfunction of Treg cells. Therefore, much of what we know about how Treg cells function within the immune system has been learned by patients with IPEX Syndrome and mouse models of the disease.

We now know that **defects in Treg cells underlie almost all most known autoimmune diseases such as type 1 diabetes, multiple sclerosis, lupus, myasthenia gravis, rheumatoid arthritis and others which affect millions of patients worldwide**. The clinical trial for IPEX Syndrome supported by this proposal will be the first in human demonstration of reprogramming stem cells of the immune system to prevent autoimmunity. **Therefore, the development of a new gene therapy to restore Treg cell function in IPEX Syndrome, proposed here, provides a proof of concept and roadmap for future therapeutics for common autoimmune diseases.**

This broader implication of this work was also recognized by the reviewers who noted that “The project meets an unmet need for a rare disorder plus the field could learn lessons for treating more common diseases” and “it may have impact in the wider T cell and regulatory T cell biology world.”

Meeting the needs of underserved communities:

While IPEX Syndrome is a rare disease with no currently published data on its demographic incidence, patients with autoimmune disease from underserved populations are disproportionately affected by inequities in diagnosis and care. The STRIDE (Study Targeting Recognition of Immune Deficiency and Evaluation) study from Mount Sinai examined the time to diagnosis of primary immune deficiencies (a broad disease category including IPEX Syndrome) and found that patients from underrepresented populations may receive delays or failure to the correct diagnosis either due to systemic healthcare bias or limited access to care.

As primary immune deficiencies are often challenging to diagnose due to a wide range of clinical symptoms, an effective tool to combat this discrepancy is the future development and implementation of widespread genetic newborn screening for IPEX Syndrome. This could provide an early, definitive diagnosis which is less susceptible to socioeconomic barriers to healthcare. Immunovec plans to build on existing relationships with the Immune Deficiency Foundation, Jeffrey Modell Foundation, and Clinical Immunology Society to **advocate for future newborn screening for IPEX**. This actionable item will **directly benefit patients traditionally underserved in healthcare to receive an early definitive diagnosis and promote better outcomes for these patients**.

Furthermore, while this proposal aims to study IPEX Syndrome, a rare disease without published demographic data, the broader impacts of ***this research will enhance our scientific understanding of autoimmunity and drive new treatments for autoimmune diseases beyond IPEX Syndrome***. The prevalence of autoimmune diseases is significantly higher in African American, Native American, and Latinx populations than in Caucasians. The problem is compounded by the fact that members of underrepresented populations are often disproportionately affected by all diseases and experience worse healthcare outcomes.

In conclusion, we sincerely appreciate the GWG’s positive feedback on our proposal. ImmunoVec is committed to developing life-changing gene therapies for fatal pediatric diseases and we hope the ICOC will support this project to directly addresses a clear unmet medical need.

Sincerely,

Katelyn Masiuk, MD PhD
Chief Scientific Officer
ImmunoVec