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Maria Bonneville
Vice President of Administration
Executive Director of the ICOC

DISC2 - Optimization of a human interneuron cell therapy for traumatic brain injury

Dear Members of the Board,

Thank you for your generous consideration of DISC2 applications this year and for the opportunity to address the meeting. Over the last 10 years, we have taken a step-wise strategy toward developing an interneuron cell therapy for TBI. We started by first demonstrating therapeutic efficacy using mouse progenitor cells in three different animal models of disease. This work has advanced to a stage where we are now manufacturing interneuron progenitors from human stem cells with high purity. We are thrilled to see that the CIRM Grants Working Group of scientific experts has **recommended our TBI program for funding with no concerns noted in the review**. Below, I briefly outline why we believe our project should be considered a high priority area for CIRM funding.

Unmet Need: Nearly 6 million Americans live with permanent physical or mental health problems resulting from TBI, and TBI is one of the most common causes of medically intractable epilepsy.

- 40% of patients discharged from the hospital after a TBI have long-term disabilities, at an estimated cost of $90 billion (~$10 billion to California) every year.
- There have been no significant clinical advances for restoring neurologic function after TBI.
- There are **no treatments** for post-traumatic epilepsy.

Our DISC2 Program: We propose studies to develop and optimize interneuron cell transplantation as a safe and effective therapy for TBI. This is a technology I pioneered, using fetal mouse MGE progenitors, for the treatment of epilepsy (Hunt, Nature Neuroscience, 2013). My laboratory at UC Irvine has extended this line of research by documenting the therapeutic efficacy of these cells in a genetic model of intellectual disability (*Chd2* haploinsufficiency; Kim, Neuron, 2018) and a contusion injury model of TBI (Zhu, Nature Communications, 2019). We now propose to test MGE-like progenitors, derived from human pluripotent stem cells, in a pre-clinical model of TBI.

- We have demonstrated therapeutic efficacy of fetal mouse MGE progenitors in **three different disease conditions**: epilepsy, intellectual disability and TBI.
- In all cases, MGE transplantation corrected severe impairments in **memory**, and in two different brain trauma models, this treatment also prevented **spontaneous electrographic seizures** for as long as we have monitored the animals (>5 months).
- All of our research in this area has been independently replicated by other laboratories within a few short years of publication.
- Our technology has **broad applicability** for a variety of brain disorders where loss of inhibition is a major contributor.
- Our program is now advancing novel protocols for manufacturing transplantable populations of MGE-like interneurons from human pluripotent stem cells. These cells have the expected cellular, molecular, **electrophysiological and synaptic signatures** of human MGE cells and reproduce all of the basic features of fetal rodent MGE that make these cells therapeutic.

Mechanism of action (MOA)

- Generation of a specific type of neuron that is lost after brain trauma, **MGE-like interneurons**.
- Enhancement of local **inhibition**.
- **Permanent electrophysiological incorporation** into brain circuitry.

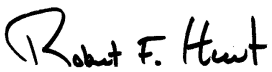
CIRM Portfolio: Our project will bring novelty to the CIRM portfolio.

- The current CIRM portfolio includes only two projects targeting either TBI or epilepsy; neither addresses post-traumatic epilepsy, which is among the most clinically-relevant epilepsies to target for cell therapy.
- We are **the only group in the world** to demonstrate a cell therapy of any kind can treat (or prevent) post-traumatic epilepsy. We are aiming for a near **complete reduction in seizures**, something we have already achieved using fetal mouse progenitors in two different animal models, and improvement in multiple forms of **memory**.
- This would be first analysis of human-derived GABA neurons in a pre-clinical model of TBI and the only CIRM proposal to **reconstruct neural circuitry** within damaged regions of the traumatically injured brain.
- Our project aligns well with CIRM interests in supporting research involving induced pluripotent stem cells and would broaden the scope of CIRM funding.

CIRM funding will allow us to move this exciting technology closer to the clinic by optimizing the human cell transplantation procedure, testing cell safety and efficacy in a pre-clinical model of TBI.

Thank you for considering our research program.

Sincerely,



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