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October 23rd 2019

Jonathan Thomas, Chairman
Independent Citizens Oversight Committee
California Institute for Regenerative Medicine
1999 Harrison Street, Suite 1650
Oakland, CA 94612

Re: CLIN2-11620, *"Clinical study to assess safety and efficacy of subretinal injection of human neural progenitor cells for the treatment of retinitis pigmentosa*"

Dear ICOC Committee members,

First, I would like to thank you all for the investment and partnership in our current regenerative medicine programs.

Overview: This new proposal continues our work of using stem cell treatments for incurable diseases and is based on over 10 years of cell and animal research including a CLIN1 grant from CIRM. This culminated in the FDA approving our IND in March of this year to perform a 16 patient clinical trial for retinitis pigmentosa and is the focus of the current proposal. ***Our application scored a perfect "1" with every one of the 15 reviewers finding exceptional merit and recommending funding.***

The disease: Retinitis pigmentosa (RP) is caused by various genetic mutations leading to the degeneration of light-sensing photoreceptor cells in the eye. These cells turn images of the world into electrical messages that travel down the optic nerve into the brain for visual perception. The loss of these light-sensing cells leads to permanent blindness.

While there are approaches using gene replacement therapy to treat recessive and single mutations, these approaches are not applicable to the majority of RP cases with autosomal dominant and multiple mutations. Thus, there is an urgent need to find a mutation-independent treatment for patients.

The new stem cell treatment: This clinical trial will test a novel stem cell treatment for RP that would be applicable to all patients regardless of their mutation. We have developed a human neural progenitor cell product (CNS10-NPC) that forms a protective layer adjacent to photoreceptor cells. Following a single subretinal injection into animal models of retinal degeneration, we have shown that the neural progenitors have long-term survival and result in preservation of both photoreceptors and vision through a number of mechanisms that include regulation of the immune system, release of pro-survival factors, upregulation of anti-apoptotic activity and Nrf2-mediated oxidative stress response, and an overall reduction in retinal inflammation. We want to emphasize that our single subretinal approach delivers cells directly to

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the anatomical location where they are needed and should have long-term impact. The primary outcome for this trial is safety but we will also be looking for changes in vision using a number of other secondary outcome measures.

How CIRM got us here: With previous CLIN1 funding from CIRM we successfully manufactured a cGMP clinical lot of CNS10-NPC and completed IND-enabling studies using this cell lot.
Our GLP study showed that these neural progenitor cells are safe and effective in a small animal model of retinal degeneration. The cells also survive and form a layer adjacent to photoreceptors following a single subretinal injection into a large animal model. All the nonclinical work led to the approval of an IND in March 2019 (currently active) allowing us to apply for the current CLIN2 award to perform the trial in humans with the goal of slowing down or stopping disease progression.

The team: We have assembled an outstanding local clinical team led by Dr. David Liao to perform this trial. This team has previously been involved with many similar clinical trials for RP (including some funded by CIRM) and has an outstanding track record.

Update on our current CIRM trial for ALS: The proposed trial complements our ongoing CLIN2 CIRM-funded clinical trial using a similar product, CNS10-NPC-GDNF. We have successfully enrolled and treated 18 ALS patients and all study visits have been completed. We have met every one of our CIRM milestones and have shown evidence of cell survival for up to 2 years in post-mortem tissues analyzed, proving further that this product can survive long-term following transplantation into humans. We are currently auditing all of the data for release within a few months. We will use the knowledge learned and infrastructure built during this study for the proposed trial. We are very confident we will be just as successful if the current CLIN2 for RP is awarded.

Closing statement: This team is extremely excited to have an active IND for this project thanks to the previous support from CIRM. We remain in close contact with the clinical site and our CRO to ensure that we are able to start the clinical trial as soon as possible. If CIRM awards this grant, we will have an opportunity to test this novel stem cell approach that could potentially have a direct impact on the life of patients with RP.

Yours sincerely,

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