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Re: CLIN2-17081

Dear ICOC Board,

I am writing to express my deep concern regarding the review of our CLIN2 grant application (CLIN2-17081) to advance an FDA authorized Phase 1b/2a trial (REGEN4HD) stem cell-based therapy for Huntington's disease (HD). HD is a devastating genetic neurodegenerative disease with no treatment that changes the course of the disease. CIRM has supported our program, approved its progress from DISC to TRAN to CLIN1, and worked with us on the path to IND, therefore we were shocked when we received a 3 based on failures of studies carried out well over a decade ago and a review that included factually incorrect comments.

This would be the first FDA authorized stem cell-based trial for HD. We received our IND for the trial in early February 2024, at which time we were ready to submit the CLIN2 application. The board paused all CLIN applications that month and we were not allowed to submit the application until July 2024. The discussion of the CLIN grant outcome was then also postponed until January 30, 2025. It will be a year since we received FDA authorization to proceed with the trial and we are now delayed even longer for a trial that falls exactly within the goal of CIRM for stem cells as regenerative therapy for rare diseases.

One of the comments in the review summary was that this protocol is high risk for potentially low benefit based on fetal transplants that did not show efficacy. However, the most recent fetal transplant trials commenced in 2001, were completed in 2013, nearly 12 years ago, and these studies were not powered for efficacy. Back then, they did not have the ability to control cell quality and characterization as we do now by utilizing a well characterized stem cell product, having access to advanced surgical methods with modern methods using MRI guidance, updated immune suppression protocols that are well tolerated, and patient staging. These were all issues with those early fetal transplant studies. Furthermore, recent trials for Parkinson's disease (Blue Rock) in which ESC-derived dopaminergic neurons are transplanted into the striatum, also show that cell-based therapies delivered to the brain are safe, that they are showing benefit.

We disagree about the conclusions regarding the results of our animal model preclinical work. There is no ideal animal model, but we used the three genetic mouse models that are most accepted in the field, each with different strengths and weaknesses in terms of what can be assessed. In a longer-lived HD mouse model, we were able to show complete prevention of a robust disease phenotype. Even in the more challenging R6/2 HD mouse model, which has severe HD phenotypes, we saw improvement in several behavioral assays. Importantly, we also showed improvements in multiple quantitative, molecular and neurocircuitry level disease outcomes. Notably, the HD field and neurodegenerative field in general has moved more in the direction of assessing efficacy using these types of molecular phenotype and not relying

on behavioral outcomes alone. The majority of this work has been published in journals with rigorous peer-review as well (e.g. Molecular Therapy).

Our clinical protocol was cleared by the FDA as a culmination of more than 12 years of continuous funding from CIRM through multiple grants. In addition to the preclinical work, we spent considerable time rigorously characterizing the cell product under the strictest criteria. We worked very closely with the FDA, other stem cell scientists working onstem cell-based therapies for HD and Parkinson's Disease (PD), and patient advocates to develop a clinical protocol that was cleared by the FDA. In fact, we held two CIRM-funded workshops on the trial design and outcome measures. The patient community is excited about and anticipating the start of this trial - I am contacted regularly by patients wanting to be part of the trial and asking for updates on the trial initiation.

I understand that we can re-apply when CIRM reopens the CLIN2 program and after at least a six-month delay, however we cannot sustain the program for another year without funding. I fear that our twelve years of extremely careful work in developing this program in close partnership with CIRM will come to an end because of reviewers placing too much emphasis on decade old studies and perhaps because we did not make it clear how much the technology has advanced in the field since that time. I would like to petition for an expedited re-review with new or additional reviewers to save the tremendous investment that has been made to get this potential therapy to the HD patient community.

Sincerely,

Leslie M. Thompson, Ph.D.