UNIVERSITY OF CALIFORNIA, IRVINE **UCI**

BERKELEY DAVIS IRVINE LOS ANGELES MERCED RIVERSIDE SAN DIEGO SAN FRANCISCO

SANTA BARBARA SANTA CRUZ

LESLIE M. THOMPSON, PH.D.
BREN PROFESSOR

Psychiatry and Human Behavior
Neurobiology and Behavior
4060 Gross Hall
845 Health Sciences Road
Irvine, CA 92697-1705
TELEPHONE: (949) 824-6756
lmthomps@uci.edu

February 19, 2024

Dear CIRM Governing Board,

I am writing this letter in response to the Memorandum from CIRM Leadership to the CIRM Governing Board recommending postponement of accepting new applications within the CLIN1 and CLIN2 programs starting immediately. Although new applications would not be accepted, the memorandum recommends that applications submitted by January 31, or resubmissions that are responding to a previous GWG review continue to be processed and reviewed. In addition, a new CLIN4 granting program for advanced pipeline projects to move to biologics license applications (BLA) will be opening up. This proposed action is to be reviewed at the February 22 meeting.

While I understand the reason for considering a pause, I would like to provide a strong alternative viewpoint on how the proposed action will impact CIRM researchers and describe how it would be devastating to our own work. Since 2011, I have received a series of CIRM awards to develop an embryonic stem cell-derived therapy for Huntington's disease, starting with candidate discovery, and culminating in IND acceptance by the FDA on February 7th, 2024. CIRM has been the sole supporter of all of this work and has seen us through many hurdles, including challenges caused by the pandemic. We have had three consecutive CIRM awards (TR2-01841, PC1-08117, CLIN1-10953) to carry out candidate identification, preclinical safety and efficacy studies, develop a manufacturing protocol, manufacture for the clinical trial and have an IND approved ready to launch a Phase 1/2b clinical trial for Huntington's disease. As one would expect, we have already invested months of effort on our CLIN2 application in anticipation of FDA clearance of our IND, with the intent to submit the application on February 29, 2024. We are currently in the process of readying all aspects required for a clinical trial, defined in our approved IND, to be carried out at UCI. The possibility that we may not be able to obtain CIRM funding soon for the clinical trial would deal a major blow to this program.

Below are some key points we would like the board to consider regarding our application and the need to keep the project moving forward.

1) The product is an embryonic stem cell derived neural stem cell (NSC) to be transplanted into the brain of Huntington's disease patients. This type of product would not receive funding from federal grants and in every sense has been enabled because of the existence of CIRM and the mission to deliver transformative regenerative medicine treatments.
2) HD is a severe, progressive neurodegenerative disorder that causes cognitive decline, psychiatric symptoms and uncontrolled movements that sufferers say is a combination of ALS, AD, and PD all at once. It is genetic with a 50% risk of children inheriting the mutant gene. It typically strikes in the prime of life and the disease devastates families both emotionally and financially. There are currently no

disease modifying treatments available. Recent clinical trials have failed. There is therefore a significant unmet need.

3) I am incredibly embedded in the global HD community, initially as part of the international consortium to identify the disease gene, and have been working my entire career to understand mechanisms underlying the disease and to find a treatment for HD. I also interact extensively with the California HD community and have been a strong proponent of the effort to garner support for Proposition 14, and to convey the potential impact of funding for cell and gene therapies to Californians at large. Indeed, we are having a CIRM-sponsored educational workshop on this very topic in the next few weeks that includes patient advocates. We are at the culmination of this goal, with patients, advocates, and other stem cell researchers in HD anticipating the start of this trial.
4) I appreciate that CIRM's mission has been to accelerate treatments to patients with unmet medical needs, and that under Prop14 there is a specific set-aside for programs working on neurological diseases. My understanding is that CIRM places a high priority in the advancement of its pipeline programs.
5) Our goal has always been to submit the CLIN2 application immediately after FDA IND clearance, and therefore, many individuals have invested significant time, energy, and resources on the proposal for months. To be told just two weeks before the application deadline that the program is closed for an indefinite period of time is devastating.
6) We do not have other resources to keep paying the very experienced team once the funds from the current CLIN1 award run out. That creates a potential gap of 5-6 months, at least, if the next application opportunity deadline is not until this summer and means we could lose critical team members.

In summary, CIRM has been fully responsible for enabling and funding this potential therapy for a devastating neurological disease for which we are eternally grateful. We therefore are writing to earnestly ask you to help accelerate this treatment into clinical trials in the first part of this year and allow us to apply without delay for a CLIN2 award.

Sincerely and with my utmost respect,

Leslie Thompson, Ph.D.