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To the Independent Citizen's Oversight Committee of CIRM:

I am writing to request that the CLIN2 application (CLIN2-15538) we are submitting this week be accepted by CIRM for review. This CLIN2 application represents the cumulative work from over the past decade to advance a hematopoietic stem cell gene therapy for adenosine deaminase severe combined immune deficiency (ADA SCID).

We have been funded, initially by a UO1 from NIAID in 2012, and then by CLIN2-09339 since 2016 for IND 15440. The results of our Phase I/II trials were so positive (100% overall survival, 96% event-free survival, n=50; Kohn, Booth et al *NEJM* 2021), that it was licensed from UCLA and University College London Orchard Therapeutics in 2017. This therapy has garnered FDA Designations for Orphan Drug, Breakthrough Therapy and Rare Pediatric Disease. The failure of Orchard to advance the program to BLA led to the return of the license to the Universities in January 2022. No patients received this treatment during this time and we accumulated a waiting list of 30 ADA SCID patients, receiving weekly ADA enzyme replacement therapy injections as a temporizing therapy.

We have worked intensively to advance this program, holding a Type B meeting with FDA in April 2022, and then opening a compassionate clinical trial in 2023. Four patients have now been treated to date and three more are being worked-up for treatment by the summer. In parallel, we have worked on all of the activities that would be needed to apply for a BLA for marketing authorization to make this therapy sustainably available to patients across California and the U.S. We engaged with National Resilience and together crafted a plan to perform the necessary CMC for the EFS ADA lentiviral vector Drug Substance and the Autologous CD34+ Hematopoietic Stem and Progenitor Cells Transduced with the EFS ADA Lentiviral Vector Drug Product. This plan was reviewed by FDA in a second Type B meeting held in January 2024, with some comments, but overall agreement with the plans. We have also established a Clinical Development Plan and a plan for a historical control group that FDA agreed with (the minutes are contained in our CLIN2 application package).

Resilience has agreed to partner with us on this project and have *pledged the 40% cost-share ($10 million) required for a CLIN2 application.*

The next step in the plan following the Type B meeting in December is to submit a CLIN2 application in February 2024 to support the initial components of the CMC manufacturing plans; if approved for funding, it will allow the CMC work to begin in June 2024. We have discussed this plan several times with CIRM staff, who were supportive of the plan. Thus, we were shocked when we learned that CIRM may call a pause on CLIN applications for at least 4 months. This will be yet another delay to making this therapy available to patients in need.

Our group has been a long-term partner with CIRM, starting with a training grant to CHLA that I led in 2005 and multiple successful clinical trials for ADA SCID, Sickle Cell Disease, X-linked Chronic Granulomatous Disease, Leukocyte Adhesion Deficiency I, and Cystinosis as well as several new disease-focused TRAN1 and DISC2-supported projects in the pipeline for future clinical trials. With our proven track record of accomplishing our goals, we have high confidence that we can successfully advance the ADA SCID HSC gene therapy to regulatory approval.

ADA-SCID has been one of CIRM's flagship programs; pictures of our healthy, cured children have showcased the importance of CIRM's mission to families, scientists, and the broader public. We are now in the final push to move this program to BLA submission and bring this cure to <u>all</u> patients in need, which will be a milestone achievement for CIRM. This program has high national prominence as an example of the challenges and hopes for developing treatments for rare diseases. We urge the ICOC to support the timely review of our CLIN2-15538 application and keep the momentum for this goal.

Thank you.

Sincerely,

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