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February 19, 2024

CIRM ICOC Board Members

Re: Pausing CIRM CLIN2 Funding

Speaking broadly for cell and gene therapy researchers, we are very grateful for the work that has gone into the CLIN programs, and appreciative of these efforts on all levels. The CLIN program has been incredibly important for accelerating the transition of cell and gene therapies from the research laboratory to patients, and is foundational to the Alpha Clinics (AC) and their mission to advance new therapies and cures.

Investigator-initiated trials are the culmination of CIRM's discovery and translational pipeline investments. The majority of the ACs have reserved funds for personnel and activities (such as the community engagement studios) to support CIRM-funded investigator-initiated trial developed by their faculty. Moreover, successful initiation of investigator-initiated trials is a critical read out for the ACs. Accordingly, pausing the CLIN program will negatively impact AC function, creating critical operational and sustainability issues for this capstone measure of CIRM's impact on regenerative medicine as a field.

In the specific case of the UCI AC, we have worked hard to build a pipeline for clinical translation. UCI started at a disadvantage, as the smallest of the CIRM-funded ACs, with a very small number of physician trialists able to conduct investigator-initiated clinical trials in cell and gene therapy arena. To date, we have only two funded clinical program stage grants (Dr. Leslie Thompson and Dr. Kyriacos Athanasiou under the CLIN1 RFA, as well as Dr. Henry Klassen under the original Disease Team RFA) and no CLIN2s – in contrast with other funded institutions. The most relevant public institution examples in southern California are UCLA, with which UCI shared a fractional proportion of original ASCC program funding, and UCSD. UCLA has had 13 investigator initiated CLIN level programs, UCSD has had 7. To address this disparity, UCI as an institution has heavily invested in hiring physicians with experience in conducting cell and gene therapy trials (such as Dr. Claire Henchcliffe, Chair of Neurology), completion of a GMP facility, co-funding the AC Clinical Trialist training program, and supporting additional positions in the newly created IND office in the UCI AC (which is also supported by CIRM through the UCI AC grant).

The results of these efforts are that UCI now has two applications that are now ready for CLIN2 submission with FDA authorized INDs: 1) "Phase 1B/2A study of the Safety and Tolerability of Human Neural Stem Cells for Huntington's Disease (PI Dr. Leslie Thompson; REGEN4HD, in pipeline with CIRM)"; and 2) "Phase IB trial of dual cytotoxic and immune-stimulatory gene therapy in combination with G-CSF for resectable, recurrent, IDH wildtype GBM patients (PI Dr. Daniela Bota, UCI AC Director; approved for submission after submitting the Eligibility Genetic Therapy form). Huntington's Disease and Glioblastoma are severe diseases with limited treatments and are ultimately fatal, and both of these applications fall within the crucial area of neurological disease, a critical target that has specific resource allocation identified under Proposition 14. Pausing CLIN2 funding will have significant implications for these two investigators and their research programs at this critical time. Furthermore, there will be an increased cumulative impact for academic

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investigator initiated translational pipelines - like UCI's - because a CLIN2 pause will also impact project eligibility for the proposed new CLIN4 program to support biologics license applications (BLA). A CLIN program pause will thus negatively impact the UCI AC and cell and gene therapy research at a time when significant human and financial resources have been invested over the last two years to support these grants.

For all of these reasons, the impact of this pause on the UCI AC clinical translation pipeline will be enormous. However, the impact of this pause on patients will be even greater. As you are well-aware, a critical mission of CIRM is to equitably serve all Californians, one that UCI has strongly embraced. Many UCI AC patients in the four counties that we serve (Orange, Riverside, Los Angeles and the Inland Empire) come from underrepresented and underserved backgrounds, and their ability to travel to remote institutions to receive experimental treatments for their disease is frankly lacking. Pausing the CLIN program will have a disproportionate and negating impact on academic institutions like UCI that cover large geographic areas, when they have finally been able to build the needed infrastructure to support the CIRM mission of advancing cell and gene therapies for all Californians. Worse, it will bring a negative cast to efforts by UCI and other academic institutions to educate the California public about the potential of cell and gene therapies to improve their lives.

In sum, pausing the CLIN program for academic investigator initiated clinical trials is a a critical issue that will affect the shape of what cell and gene therapy research will look like across the state going forward - in addition to the pace at which these advances are made. We urge you in the strongest possible terms to reconsider at least this category of funding within the CLIN2 program immediately.

Thank you for your consideration. Respectfully,

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