Children's Hospital LOS ANGELES
We Treat Kids Better

USC UNIVERSITY OF SOUTHERN CALIFORNIA

October 5, 2018

Re: Dr. Tracy Grikscheit's application DISC2-10979 "Universal Pluripotent Liver Failure Therapy (UPLiFT)"

Dear CIRM ICOC Board Members:

We are writing to express enthusiastic support of application DISC2-10979 "Universal Pluripotent Liver Failure Therapy (UPLiFT)", representing the clinical, scientific, and surgical interest at Children's Hospital Los Angeles (CHLA) in the rapid development of a novel therapy for pediatric liver-based metabolic disease. UPLiFT would treat an orphan indication, one of the foundational aspirations for CIRM. Pediatric liver-based metabolic diseases account for 30% of the 600+ children who require liver transplantation each year. Yet liver transplantation and the accompanying immunosuppression that it requires may not be necessary in order to treat some of these children. As of now the only treatment for these diseases is liver transplant, which carries high risks and is expensive and restricted. According to the Organ Procurement and Transplantation Network website, 709 pediatric liver transplants occurred in the United States in 2017, and 720 occurred in 2016. All of these were donations from deceased donors. There were still 599 children waiting for transplants in 2017, and 573 children still in need of a replacement liver in 2016.

Replacement of just 5-10% of liver mass can alleviate the need for transplants for some liver metabolic diseases. The project described in DISC2-10979, UPLiFT, proposed by Dr. Tracy C. Grikscheit is absolutely supported by CHLA. It is our mission to develop safe and lasting treatments for children who will either face liver transplant or death. UPLiFT would develop a cell therapy product for liver replacement with and without immune privilege that may be a first-in-baby therapy that would not require immunosuppression.

UPLiFT will be differentiated from an induced pluripotent stem cell that was made to fulfill national and international regulatory requirements for human transplantation. In work with David Russell, PhD, these donor cells have been genetically modified to evade the patient's immune cells, circumventing the need for immunosuppression and effectively becoming a universal product that could then be applied for the treatment of many other causes of liver disease.

- Of the 185 active project in the CIRM portfolio, only 9, or 4.8%, are directed toward pediatric targets, and of those nine grants, 2 are derived from pluripotent stem cells.
- CIRM currently funds 4 active liver grants, none of which are directed toward the pediatric population.
- This team and this investigator has had a record of success with translational objectives and a proven track record to accomplish previous milestones.

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We note that scientific review of this application resulted in the fourth highest ranked score generated by the grants working group, reflecting the proposal's excellence and the outstanding medical treatment and scientific rationale for support. Most important, the babies we treat with this orphan indication deserve progress in the therapies that are currently unavailable, thus representing a significant unmet medical need for the children of California and their families, and beyond.

This work has been enabled by significant financial and resource commitment from CHLA and builds on previous investments from CIRM. The institution and exceptional medical and science team are committed to seeing this work through translation to treat these highly vulnerable children.

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