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California Institute for Regenerative Medicine (CIRM)

Re: Support for Dr. Weissman's Appeal regarding CIRM application TRAN4-15225

To Whom It May Concern:

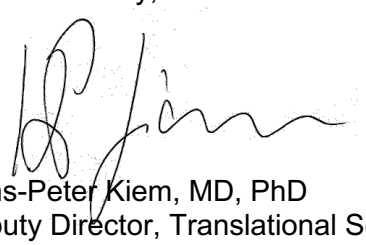
I strongly support Weissman's appeal for his recently reviewed and rejected CIRM application to purify CD34+CD90+ human hematopoietic stem cells (HSCs) for transplantation and treatment of malignant and other hematological disorders.

My lab also shares the vision to specifically purify and utilize the phenotypically defined and highly HSC-enriched $CD34^+CD90^+$ cell population for transplantation and treatment of various diseases. As documented in our publications, we utilized a similar strategy to enrich for HSCs in the nonhuman primate (NHP) large animal model in 2017 and demonstrated in multiple competitive transplantation experiments that this specific subset of cells is essential for the short- as well as long-term recovery of the hematopoietic system after myeloablation and autologous transplantation (Radtke et al. 2017, *Sci Transl Med*). Most importantly, we discovered that the recovery of animals after transplantation perfectly correlated with the administered dose of $CD34^+CD90^+$ cells, a level of predictability and precision that cannot be achieved with traditional transplantation of $CD34^+$ cells. Especially in the clinical setting, the ability to predict the onset of recovery in a patient is essential to provide the best care and guarantee the success of treatment.

With the goal to use this knowledge in a translational setting, we have further used the same purification strategy to genetically modify Rhesus macaque HSCs and reactive the expression of fetal hemoglobin for the treatment of sickle cell anemia (Humbert and Radtke et al. 2019, *Sci Transl Med*). The purification and direct modification of the HSC-enriched subset demonstrated a multitude of advantages including 1) the reduction of gene-modification materials needed to achieve high editing efficiency, 2) the minimization in risk for off-target editing in downstream progenitors, and 3) a decrease the overall price for HSC-mediated gene therapy approaches; all important aspects to make such approaches more broadly available, feasible, and efficient. Building upon these pre-clinical studies, we finally comprehensively compared different purification approaches of human HSCs for the translation of this highly promising approach into clinical applications (Radtke et al. 2021, *Mol Ther Methods Clin Dev*). As outlined by Irv in his application, we did compare the purification of human HSCs on various state-of the art cell sorting devices including machines from Sony, BD, and Miltenyi Biotech. Our in-depth evaluation showed that current developments in the field have significantly increased the feasibility and portability to perform the purification of human HSCs as a routine application even without the need of complex, rare, and expensive cell processing facilities.

As a result of our own research and the tremendous improvement we have seen in the outcome of our NHP studies, our lab is entirely focusing on the use of $CD34^+CD90^+$ cells for autologous as well as allogeneic transplantation for various indications and treatment modalities. The ability to have a highly HSC-enriched cell population with predictive engraftment potential is highly advantageous for any related studies in the pre-clinical as well as clinical setting, and I am therefore highly enthusiastic and supportive of Dr. Weissman's application to bring this highly promising approach to patients.

Yours sincerely,



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