Stanford University
Department of Medicine
Division of BMT Faculty

Stanford HEALTH CARE
STANFORD MEDICINE



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Ms. Maria Bonneville
Vice President of Administration
Executive Director of the ICOC
California Institute for Regenerative Medicine
mbonneville@cirm.ca.gov

Re: CLIN2-11431: A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants

Dear Members of the Independent Citizen's Oversight Committee:

Replacement of blood forming stem cells by transplantation of allogeneic donor or autologous gene-corrected cells is a curative therapy for a vast number of inherited and acquired disorders. The disease classes successfully treated by this process of hematopoietic cell transplantation (HCT) include immune deficiency syndromes, hemoglobinopathies, cancers of the blood, and autoimmune diseases. Although HCTs have high curative potential, the risks of the procedure are substantial. One major risk is "conditioning" of recipients to accept donor blood stem cells because current conditioning treatments use DNA-damaging modalities of radiation and/or chemotherapy to ablate recipient stem and progenitor cells in order to make space for donor cells to engraft. In addition, donor grafts themselves contain passenger T cells that can cause potentially morbid and lethal complications.

Children with severe combined immune deficiency (SCID) are particularly vulnerable to the toxicities of DNA-damaging treatments and are highly sensitive to the dose of T cells contained in donor grafts. Hence, safer and better treatments for these children have been on the leading edge of innovation for the HCT field.

Our ongoing clinical study aims to eliminate the use chemo/radiation in HCT with a first-of-its-kind monoclonal antibody directed against the molecule CD117, also known as c-Kit. CD117 is present on the surface of blood stem cells. We are testing in SCID patients if this antibody can target and safely deplete recipient blood stem cells and permit engraftment of purified donor blood stem cells.

We are very happy to report that in all patients treated to date, this anti-CD117 antibody has been safe and well tolerated. Patients have shown no evidence of significant changes in blood counts or clinical status. In fact, the patients have done so well, the treating clinicians are inquiring about making the procedure for some of these patients an outpatient one. **Importantly, even in the early stages of our trial we see evidence of successful long-term donor blood stem cell engraftment.** This evidence includes the presence and persistence of donor granulocytes which prior to our transplant procedure

were completely absent; development of donor B cells, which prior to this transplant were negligible to very low; and increasing levels of donor T cells. We can confidently say that patients treated on the study to date have gained clinical benefit. Our study has attracted the attention of the international community of pediatric transplant clinicians, and our positive data has resulted in accelerated enrollment of patients onto our trial.

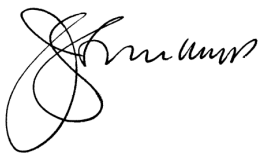
We have sufficient clinical grade anti-CD117 antibody to complete the current trial as well as other planned follow-on trials. This material is on an active stability program and the data support several years of additional stability. We have plans to manufacture additional GMP grade material as part of our overall drug development plan, but that additional material is not required to complete the current trial under consideration for CIRM funding.

We wish to express our deep appreciation for the support CIRM has given our team in translating this approach from the bench to the bedside. We are also grateful for the Tier 1 score our proposal received from the GWG and to CIRM for their recommendation to continue funding of this study.

We believe, based on the trajectory of our early safety and efficacy data from our ongoing study that this conditioning antibody will transform the way HCTs will be performed in the future. The potential impact of this approach is broad, ranging from the near term application of addressing a critical unmet need for SCID patients to reducing the toxicity and improving the engraftment of gene-modified autologous stem cells for blood disorders including life-threatening anemias such as sickle cell disease. In the longer term we envision that targeting stem cells with antibodies will replace and/or augment conditioning therapies for all indications for which HCT can be curative including autoimmune disorders and cancer.

We are eager to continue the development of this novel approach to transplant conditioning and thank you for considering funding of our ongoing clinical study.

Respectfully submitted,



Judith Anne Shizuru, M.D., Ph.D.
Professor of Medicine
Division of Blood and Marrow Transplantation
Stanford University Medical Center
Stanford, CA 94305