MEMORANDUM

Date: July 18, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR2-05365

Enclosed is a petition letter from Dr. Judith Shizuru of Stanford University, an applicant for funding under RFA 10-05, CIRM Disease Team Therapy Development Research Awards. This letter was received at CIRM on July 18, 2012 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

We respectfully submit this extraordinary petition to the ICOC for DR2-05365 because we find that all points of concern raised by the Grants Working Group are in fact manageable and relatively minor, and wish to explain why.

We proposed to target blood forming stem cells in patients with a biologic agent, a monoclonal antibody (mAb), that binds the stem cell receptor, c-kit (CD117), to selectively deplete stem cells and create 'space' to permit engraftment of healthy purified donor blood stem cells. We aim to cure young patients with a rare genetic disorder called severe combined immune deficiency (SCID) by allowing the safe replacement of diseased stem cells with those from the healthy donor. Currently, toxic radiation and/or chemotherapy are the only ways to remove dysfunctional stem cells. This reagent is the first of its kind that will be used to test the idea that biologic therapy can replace toxic methods. Enthusiasm for using this approach in children with SCID is evidenced by the many letters of support submitted on our behalf from leaders in the field of pediatric transplantation. The implications of our studies extend beyond the treatment of SCID to all aspects of stem cell therapy, including but not limited to, transplants of gene-modified stem cells, the treatment of autoimmune disorders (i.e., multiple sclerosis, childhood diabetes) and the induction of immune tolerance to organ grafts. This broad range of applications derives from the importance of the blood system in controlling which cells and molecules the body sees as foreign. Transplants of blood stem cells derived from adult or embryonic sources in conjunction with other cell or tissue grafts from the same donor source can result in permanent graft acceptance without the need for immune suppressive drugs. Thus, the safe and successful depletion of blood stem cells that allows donor stem cells to replace them would be a major advance for the stem cell field.

The discovery that an anti-CD117 mAb can deplete blood stem cells emerged from a search for molecules expressed on these cells. In 2007, we showed in mice with a genetic defect analogous to SCID, that a mAb against CD117 permitted robust engraftment of purified blood stem cells and cured the mice. We planned to generate a homologous mAb for humans, but fortuitously determined that a large, multi-national biotechnology company headquartered in California, hereafter referred to as "the Company" had already produced an anti-human CD117 (hCD117) mAb safe for human use. In 2010 we began collaborating with the Company and determined that their anti-hCD117 mAb might be ideal for targeting human blood stem cells. In 2011, the Company revealed that they would no longer pursue the use of the reagent for their indication and would cease its production. However, the Company generously agreed to provide us with anti-hCD117 mAb, which was produced under GMP-compliant conditions. The Company provided for our CIRM application manufacturing information, and results from non-human primate and first-in-human studies.

RESPONSE TO REVIEW: No concerns were expressed with regards to the Significance and Impact, Rationale, or Therapeutic Readiness**.** Rather concerns centered on Feasibility of the Project Plan, with 8 concerns listed overall, but there were two major concerns (#1 and #2):

#1: Major concerns were raised about the overall feasibility of this project. Existing supplies of the candidate mAb are set to expire prior to completion of the proposed clinical trial and no clear path has been secured to ensure the applicant has continued and necessary access to this resource, especially in the long term. Reviewers considered these issues to be show-stoppers.

A similar question was posed to us by reviewers in April 2012, at which time we outlined our plan to address this issue by three potential solutions: (1) extension of the anti-hCD117 mAb clinical lot expiration date; (2) obtain the nucleotide sequence from the Company and clone the sequence to generate a new line and master cell bank (MCB) to enable further manufacturing of the product; and (3) work with the Company to manufacture more batches of the mAb via their existing CHO-MCB, the details which have yet to be worked out between the Company and Stanford.

Our path to guarantee access to an anti-hCD117 mAb for the completion of the proposed studies is as follows: Within the first months of funding obtain the anti-hCD117 mAb nucleotide sequences from the Company, and secure an agreement with a CMO who will transfect the cDNA sequences of the H and L chains into a stable host cell line for manufacturing capable of high production titers. Early activities will include selection of a high producing line, development of process manufacture (GMP), selection, characterization of an MCB, and evaluation of the comparability between the two manufactured antibodies. Hence, within a year, a new antibody producing cell line will be generated by us capable of producing anti-hCD117 mAb, which can be banked, stored and used for production of additional mAb if needed. In parallel, we will initiate a (GMP) stability program to extend the expirations date for the existing hCD117 mAb drug product. We will also continue to work with the Company to determine terms to allow their mAb to be produced via their existing CHO-cell line at a CMO of their choice. The Company has confirmed their

support and willingness to work with us on ensuring our access to anti-hCD117 mAb by these approaches in a letter dated July 16, 2012. This letter contains proprietary information and thus it can only be provided confidentially to the scientific staff and to the Board in executive session as confidential proprietary information.

#2: The supporting antibodies and methodology for selecting and sorting donor HSC are in a preliminary state of development. Manufacturing of these reagents to cGMP grade for the clinical trials will require substantial effort, time, costs, and potentially separate regulatory approval, none of which has been adequately addressed in the proposal.
The supporting mAbs and methods for selecting and sorting donor hematopoietic stem cells (HSC) by CD34 and CD90 selection are in an advanced, not preliminary state. This method was established ~20 years ago by a group led by I. Weissman (consultant). From 1996-98 the Stanford transplant group conducted a clinical trial using this approach to rescue blood formation in patients with metastatic breast cancer. These patients received marrow ablative chemotherapy and blood production rescued by infusion of $CD34^+CD90^+$ sorted HSC. Blood formation was prompt and sustained. In 2011 J. Shizuru (PI) and colleagues published the long-term follow-up of these patients (13 yrs after study close) demonstrating normal blood formation and better than expected survival of these women from breast cancer. Two other trials showed similar safety and feasibility for this method of rescuing blood formation. In total >60 patients were transplanted with $CD34^+CD90^+$ HSC using the same CD34 and CD90 mAbs we plan to use.

Re: Manufacturing, time, costs: As noted in our grant, we executed an MTA from a different California-based biotech company for the anti-CD34 and anti-CD90 producing hybridomas which originated in the 1990s. In February 2012 these hybridomas were transferred to a California-based contract research organization, Pacific GMP, as specified in our grant. The estimated time to complete serum-free adaptation and generation of the GMP MCBs is August 2012. Preliminary ELISA data show the cells are producing >100 mg/L antibody. If funded, the qualification, viral clearance, and cGMP runs plus fluorochrome conjugation can be completed by March 2013. Validation of the cell sorting of HSC will occur in April 2013. These downstream activities were budgeted for and delineated as milestones in our grant. Our current trajectory suggests we will meet or beat our projected timeline and stay in budget. Thus, based on the factors above, we do not find this second major concern to be valid. (Re: Regulatory approval: see next section)

#3: To improve the product development strategy, reviewers recommended an earlier pre-IND discussion with the Food and Drug Administration (FDA) to obtain feedback on the proposed toxicology studies prior to their initiation.
In November 2011 our Disease Team held a pre-pre-IND phone meeting with the FDA to discuss the intended $CD34^+CD90^+$ purified HSC product. We specifically discussed regulatory guidelines for the generation of anti-CD34 and anti-CD90 mAbs from an MCB created prior to 1997. The FDA representative noted that if a new batch of mAbs were manufactured under GMP conditions in accordance with the current FDA guidelines (PTC 1997), including full validation of viral clearance steps, then the mAbs could be used as indicated. New MCBs are being generated and characterized in a manner that meets FDA guidelines as set out in the ICH Harmonized Tripartite Guideline Q5D, dated July 16. 1997. Thus, we are proceeding with the production of the CD34 and CD90 mAbs MCBs and toxicology testing as recommended by the FDA. As noted, we are on track regarding timeline and budget.

#4: The project design lacks alternate plans should the investigational mAb fail to support engraftment in the patients and also interfere with, or multiply the risks of proceeding with standard of care.
Our protocol was carefully designed and reflects one developed by experts from 13 major centers in N. America that constitute the Primary Immune Deficiency Consortium (PIDTC) (see support letters from PIDTC leaders) for SCID patients diagnosed at birth. Patients eligible for our study are 1) older patients who have engrafted and have T but no B cell immunity; and 2) newly diagnosed SCID infants of defined subtype. Patients >18 yrs will be evaluated first to determine safety and pharmacokinetics that will guide us in mAb dosing. If an unlikely effect occurred with mAb treatment, i.e., decrease in T cell immunity, a boost infusion using the same donor without mAb will be done. We have >30 years experience performing such cell boosts in SCID patients, and they are effective for enhancing T cell immunity. For the cohort of newly diagnosed SCID patients, our center's standard treatment is transplantation without conditioning. Thus, as we state in our grant, we will cryopreserve standard $CD34^+$ cells as back up grafts. It should be noted that no preclinical or human data exists to suggest the mAb would either interfere with engraftment or increase the risk of the measures outlined above. However, in the event of such a circumstance, we will employ standard chemotherapy to achieve engraftment. If the mAb alone does not show efficacy we will evaluate the mAb plus low dose busulfan, comparable to studies by M. Dinauer (see support letter) who achieved engraftment of gene-transduced HSC using anti-CD117 mAb plus low dose radiation in mice with chronic granulomatous disease.

#5: The half-life of the investigational mAb needs to be sufficiently short so as not to interfere with bone marrow engraftment, an issue that has not been well-addressed in the proposal

Our proposal discussed the half-life (T½) of anti-hCD117 mAb, and referred to existing data generated by the Company in humans supporting the idea that the T½ of this mAb will not interfere with its use for HSC engraftment. We are happy to provide the raw data to the ICOC. A single i.v. dose of 5 mg/subject (~0.1 mg/kg) showed a T½ of ~2 days with minimal residual drug remaining by 10 days. In mice given 25 mg/kg, the homologous mAb, takes ~9 days to be undetectable in the serum. Of note, in mice infusion of HSC before 9 days (5-6 days) still resulted in improved engraftment, suggesting that complete mAb clearance may not be needed for efficacy. A time frame of anti-hCD117 mAb delivery with HSC infusion 7-14 days later is acceptable for a clinical transplant regimen. That said, we recognized that the clearance of anti-hCD117 mAb is of central importance to its clinical utility. Hence, we purposefully designed our trial so that the first cohort, who is at relatively low risk from this therapy, will provide important information regarding the kinetics (linear vs non-linear) and HSC depletive capability. Further, as discussed in our grant, we have tested the concomitant infusion of high dose i.v. immunoglobulin to accelerate catabolism of the anti-hCD117 mAb by inhibiting the FcRn pathway, which traffics antibodies away from the lysosomal degradation pathways. This approach dramatically accelerated anti-CD117 mAb clearance in immune deficient mice.

#6: The proposal lacks adequate description of the manufacturing process and analytical methods to test, characterize, release and demonstrate the stability of the investigational mAb.

As described in the July 16, 2012 above referenced letter, the Company, a highly qualified manufacturing firm with a substantial drug development experience notes it will provide the requisite chemistry manufacturing and controls (CMC) documentation associated with the current clinical lot to support a US IND filing by the Stanford Disease Team. In addition, the Company is willing to provide information and analytical advice in support of this Disease Team's manufacturing needs if additional mAb production is required as discussed above.

#7: While the PI and Co-PI have commendable track records in hematopoiesis and bone marrow transplantation, reviewers were concerned by their lack of suitable experience with biologics product development.

In the review of our Disease Team's Planning award, it was noted that our team is led by investigators with "expertise in relevant animal models, the influence of the niche on engraftment and experience in performing pediatric transplants, [and that we] assembled a strong team including consultants with relevant regulatory and technical expertise to develop the proposed program." This positive evaluation directly contradicts the above stated criticism of our grant. In fact, we are certain we have assembled and/or have access to the necessary expertise to provide the biological reagents we require for our clinical study, and to test these reagents in a safe and effective manner.

#8: License and access agreements for the investigational therapeutic candidate have not been finalized and remain to be negotiated.

As demonstrated in their letters, the Company has expressed its commitment to good faith negotiations with Stanford to work out the specific terms for the continued use of its mAb. In their July 16, 2012 letter of support, the Company restated their good faith intentions to achieve a licensing agreement with Stanford, and in doing so emphasized that it is in their best interest to facilitate ongoing investment and advancement of the utility of anti-CD117 mAb.

In closing, research, development and translation, the mission of CIRM, is not without risk. Thus, the questions facing the CIRM ICOC is, in our case, is there reasonable risk and does the potential of the project justify the level of risk? If successful our research will create a break-through for translational medicine with immediate clinical applications and in doing so will open up new areas of stem cell therapy. Hence, the potential of this research is undisputed. Secondly let us speak specifically to the risk of the #1 "show-stopper" concern. We have been incredibly fortunate to be in the position to utilize an existing reagent developed by the Company, a premier California firm, and to have them wholeheartedly collaborate with us. This collaboration rather than creating risks, has in fact presented an enormous attenuation of the R&D risks because: a) the Company has already shouldered the vast majority of R&D risk by successfully producing a humanized anti-CD117 mAb; b) the antibody has been proven to be safe in human subjects; and c) has already been proven to be effective in animal models. The only risk around this matter is therefore, a commercial one. In response to this concern, we have listed three reasonable contingency plans. The Company supports these plans. These commercial risks, in light of the history of the relationship with the Company, and the potential to them, clearly should seem manageable and relatively minor to fundamental R&D risks which CIRM was created to challenge. We hope that the ICOC will consider our petition and decide positively in our favor.