MEMORANDUM

Date: June 18, 2010

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application RM1-01710 (**LATE**)

Enclosed is a petition letter from Dr. Hadeiba of the Palo Alto Institute for Research and Education, an applicant for funding under RFA 09-03, CIRM Stem Cell Transplantation Immunology Awards. This letter was received at CIRM on June 18, 2010 after the requested deadline of 5 business days prior to the ICOC meeting, but we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

Extraordinary Petition

RM1-01710: Application of Tolerogenic Dendritic Cells for Hematopoietic Stem Cell Transplantation.
Primary Investigator: Dr. Husein Hadeiba
Institution: Palo Alto Institute for Research and Education, Inc.

To the Chairman of the Independent Citizens Oversight Committee (ICOC) and the Chief Scientific Officer of CIRM.

We would like to thank the reviewers for their kind feedback and helpful comments. We feel the review was appropriate, but due to limited space in the grant application we were not able to address the pressing issues of some reviewers who did not feel confident about our approach. The reviewers felt that the "*success of our approach is highly dependent on the presumed inactivity of the trafficking receptors and tolerance potential of fixed cells; reviewers were doubtful that this would be the case and, therefore, were not convinced that our new markers offered any advantage over past efforts to exploit dendritic cells*". We would like to assure the reviewers that the use of antibodies targeted to trafficking receptors on dendritic cells (DCs) did not affect (i) their tolerogenic capabilities *in vitro* and *in vivo* and (ii) their homing capacity to different tissue sites: this was tested many times to ensure that approaches for their isolation do not impact their efficacy. This is really important for us to stress to all the reviewers and to the ICOC as it seemed such a central concern in the review process. The mouse experiments were done using therapeutic DCs sorted with antibodies and their immunosuppressive effects were demonstrable *in vivo*. Further, after the submission of the grant we obtained more supportive data in the human that tolerogenic DC populations from blood products selected using antibodies to trafficking receptors, did not impact their immunosuppressive properties.

We also feel the need to emphasize why we strongly advocate our approach for using trafficking receptor expression on DCs for the isolation of tolerogenic DC populations and fixation for the preparation of immunosuppressive DCs:

(i) There are currently no approaches developed to specifically isolate immunosuppressive DCs out of populations generated primarily *in vitro* in many studies. The use of antibodies to costimulatory ligands on DCs (a potential candidate), have failed to maintain their immunosuppressive state in some of our initial studies since the submission of the grant. We would therefore like to share the importance of trafficking receptors in the definition, isolation and targeting of tolerogenic DCs: our recent studies (manuscript in preparation) demonstrate that the expression of unique trafficking receptors such as CCR9, targets immunosuppressive DCs to sites of immune tolerance such as the thymus (where they are able to induce central tolerance to tissue antigens) or the intraepithelial environment of the gut. The expression of such receptors therefore defines potent tolerogenic DCs as they endow them with the capacity to home to important sites of immune tolerance. Since antibodies to these trafficking receptors did not affect their homing capacity and function, we feel this approach will be key for their identification, isolation and targeting.

(ii) This approach does not require additional immunosuppressive or pharmacologic agents that are very non-specific: Using carefully sorted DCs (with antibodies to CCR9, CD103 or potentially other trafficking receptors that define tolerogenic DCs) we were able to observe 100% survival and perfect health in animals that would have otherwise succumbed to graft-versus-host-disease (GVHD) after allogeneic bone marrow transplantation. In this context, cell therapy using DCs can be aimed at specifically suppressing allogeneic responses to the stem cell graft in the absence of additional immunosuppression that has plagued many patients with painful side-effects.

(iii) Fixation of DCs provides an attractive approach for the use of non-live cells for specific immunotherapy. The use of live cells in immunotherapy has generated many concerns about good manufacturing procedures (GMP) and the fear of potential microbial agents present in live cell products. We strongly advocate further research into developing specific immunotherapies that are more safe and have the potential to elicit specific immunologic effects. Further, the stability of the tolerogenic DC phenotype after fixation will probably not require the use of additional (and undesirable) immunosuppressive agents that, for example, prevent DC activation during the immune response. In preliminary GVHD animal studies, we found co-localization of allogeneic T cells and fixed DCs in the spleens of irradiated recipients suggesting that potential hematopoietic sites after irradiation, such as the spleen, are capable of trapping fixed DCs where they can interact with live T cells and facilitate immunosuppression. We are convinced in our mouse studies that a similar approach can work in humans too and will be very effective using matched and potentially fixed immunosuppressive DCs (matched both for major and minor histocompatibility antigens).

As a concluding remark, it is precisely the fact that there are very few clinical approaches using immunosuppressive DCs to tolerize to allogeneic stem cell grafts that we strongly feel they should be encouraged. The work we are proposing here has the support of an excellent educational facility with outstanding mentors in the field of bone marrow and HSC transplantation. We hope that the ICOC will consider the need for this research in improving tolerance outcomes to allogeneic stem cell transplants. Thank you for your support.

Sincerely,
Husein Hadeiba, Ph.D.
Research Scientist.
Laboratory of Eugene C. Butcher, MD.
Palo Alto Institute for Research & Education.