MEMORANDUM

Date: June 15, 2010

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application RM1-01705

Enclosed is a petition letter from Dr. Cheng of the University of California Los Angeles, an applicant for funding under RFA 09-03, CIRM Stem Cell Transplantation Immunology Awards. This letter was received at CIRM on June 15, 2010 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

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June 15, 2010

Re: extraordinary petition

RM1-01705: IMMUNE TOLERANCE BY ES-CELL DERIVED DENDRITIC CELLS

Dear Mr. Klein and Dr. Trounson,

Thank you and reviewers for considering our application entitled “IMMUNE TOLERANCE BY ES-CELL DERIVED DENDRITIC CELLS”. We are submitting this petition to bring your attention several key points of our proposal that may not have been fully appreciated by the review panel. We would also like to point out that, while the review panel appreciated the impact of tolerigenic dendritic cells to facilitate acceptance of a range of tissue grafts, no single dendritic cell therapy application was recommended for funding.

I would greatly appreciate it if the CIRM Independent Citizen's Oversight Committee (ICOC) and the CIRM board can reconsider our application, which we believe will make strong impact in the field of Stem Cell Transplantation Immunology.

Sincerely yours,

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Extraordinary Petition RM1-01705:

IMMUNE TOLERANCE BY ES-CELL DERIVED DENDRITIC CELLS

Application Summary

The overall goal of this proposal is the development of tolerance-inducing transplant protocols utilizing dendritic cells (DCs) derived from human embryonic stem cells (hESCs). DCs function mainly as antigen-presenting cells, activating T cells, and so, with appropriate manipulation, these cells could be harnessed to promote tolerance to subsequent tissue grafts. The applicant proposes three Specific Aims: (1) to determine the best approach to deriving tolerigenic DCs from mouse ESCs (mESCs); (2) to assess the tolerigenic properties of these mESC-derived DCs in a mouse model; and (3) to adapt the DC derivation protocol to hESCs.

Critiques from the Reviewers

Reviewers did not find this proposal to be particularly innovative. They noted that the hypothesis that DCs can be used to induce tolerance is not novel, nor are the specific approaches proposed to generate tolerigenic DCs. Reviewers agreed that this project could have an impact if successful as the approach could be used to facilitate acceptance of a range of tissue grafts.

Comments from investigators:

Although the general idea that DCs can be used to induce tolerance is not novel, our proposal is focused on how to derive tolerigenic DCs from embryonic stem cells, which is not only novel but also offers tramendous advantages over the regular myeloid dendritic cells (mDC). Currently, only very few laboratories are able to effectively differentiate DCs from human embryonic stem cells. Our group was among the first to define the directed differentiation of human T cells and macrophages from human ES cells. We have recently defined a feeder cell free differentiation protocol to produce up to 80% ES-DC that can be repeatedly frozen and recovered. The major challenge in the field of Transplantation Immunology is how to develop an effective, stable and large scale protocol to facilitate acceptance of a range of tissue grafts. We believe our approach of manipulating ES-DC instead of mDC will achieve this goal.

Critiques from the Reviewers

Reviewers cited a number of weaknesses in the research plan. They noted that while the scientific rationale for pursuing tolerigenic DCs is appropriate, the research plan is lacking key elements. For example, the applicant does not propose to test DC response to inflammatory signals, their phenotypic stability in vivo, or expression of chemokine

and homing receptors necessary for migration to the appropriate locations to induce tolerance. Reviewers noted that the experimental design also lacks critical details, including host preparation prior to DC immunization and conditioning regimens for subsequent transplants. A major reviewer concern was that the applicant does not thoroughly address the specificity of tolerigenic DCs. These DCs may be generally immunosuppressive rather than allospecific and nonspecific tolerizing effects may not be beneficial.

Comments from investigators:

We have proposed several key criteria of measuring our experimental approaches, which include those to: 1) determine the properties of the tolerigenic ES-DCs and their target effective cells such as regulatory T-cells using numerous cell surface markers and cytokine expressions; 2) Assess tolerization potential using activation of primary transgenic T cells and mixed lymphocyte reactions; 3) measure in vivo tolerization potential using allogenic bone marrow and skin transplant models. Due to the space limitation, we did not include experiments addressing the fate of ES-DCs in vivo. However, we have already generated GFP expressing DC derived from mouse and human ES cells, which can be used to track the stability and homing of these cells.

Our current proposal is aimed to use ES-DCs to facilitate transplantation of tissue derived from the same ES cells onto organisms with different genetic backgrounds, which does not require us to create tolerigenic DCs for any specific antigens. As an example from the Aim 2 of our proposal, we will use tolerigenic ES-DC from 129 mice to educate BALB/c mice and let BALB/c mice to accept skin from 129 mice. In addition to the proposed research, we have also developed antigen specific tolerigenic ES-DC llines in hope to treat patients with antigen specific autoimmune diseases in the future.

Critiques from the Reviewers

Reviewers praised the Principal Investigator (PI) and assembled research team. They described the PI as an experienced investigator with an outstanding record of publication and many high-profile publications. They also appreciated the contributions of the highly qualified Co-Investigator in the fields of hESC biology and DC differentiation. Reviewers noted that the proposal brings together three excellent research groups at the applicant institution, creating a team well-qualified to carry out the proposed research.

Comments from investigators:

We appreciate the positive comments from the review panel about the outstanding team we brought together with this proposal. Indeed, we have both experienced and junior investigators with an outstanding record of publication and many high-profile publications. Most imporantly we have productive collaborations in the past several years to generate robust ES-DC differentiation and manipulation protocols. We also have extensive experience in both innate and adaptive immune responses.

Critiques from the Reviewers

Overall, while reviewers agreed that this proposal has a sound scientific rationale and is supported by an excellent research team, the proposal was not novel and flaws in the research plan led reviewers to conclude that the proposal was unlikely to succeed.

Comments from investigators:

Dendritic cells are not only the most effecitve and physiological relavent professional antigen presentation cells but are also critical imunune modulatory cells to determine the antigenic or tolerogenic immune responses. Current work relies on DCs derived bone barrow cells or blood cells, which are small scaled and hard to manipulate. We have recently developed a robust approach that allow us to stablly express tolerogenic molecules in mouse and human ES cells and effectly differentiate them into large numbers of tolerogenic DCs. We propose to compare several different tolerogenic molecules and determine their abilities to induce immune tolerancce and protect tissue transplantation rejections. We believe our approaches are novel and feasible and have tramendous advantages over traditional DC therapy.

We also noticed that the 15 applications recommended for funding by this CIRM RFA 09-03 include 3 regulatory T-cells, 3 thymic cells, 2 NK cells and 2 neural cells. While the review panel appreciated the impact of tolerigenic dendritic cells to facilitate acceptance of a range of tissue grafts, no single dendritic cell therapy application was recommended for funding. Although UCLA is recognized as one of the best tissue transplantation institutes, no application from UCLA was recommended for funding by this Stem Cell Transplantation Immunology Awards.