MEMORANDUM

Date: June 17, 2010

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application RM1-01716 (**LATE**)

Enclosed is a petition letter from Dr. Liu of the City of Hope Medical Center, an applicant for funding under RFA 09-03, CIRM Stem Cell Transplantation Immunology Awards. This letter was received at CIRM on June 16, 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.

City of Hope™

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June 15, 2010

Robert Klein, J.D., Chair
Independent Citizens' Oversight Committee
Alan Trounson, Ph.D.
President and Chief Scientific Officer
California Institute for Regenerative Medicine

Re: Extraordinary Petition for the proposal
RM1-01716 "Immune modulation to improve stem cell engraftment"

Dear Mr. Klein, Dr. Trounson, and Distinguished Members of the ICOC,

Thank you for the opportunity to submit a CIRM Stem Cell Transplantation Immunology Awards Research Proposal for funding consideration. With due respect for the peer review process of the Grants Working Group, I would like to bring to your attention the certain key points of our proposal that may not have been fully appreciated by the review panel, perhaps due to lack of clarity on our part.

I appreciate the very helpful discussions with CIRM scientific staff and your attention in providing me the opportunity to submit an Extraordinary Petition in support of our proposal. Attached is a 3-page petition highlighting key points and critical considerations for your review for funding.

The potential impact of our proposal for the treatment of cancer and autoimmune diseases such as type 1 diabetes, that more than a million of Californians face today, is substantial. While the heavy emotional, physical and financial impacts of these diseases are felt by patients and their families, a significant economic burden is also felt by the State, costing California billions of dollars every year. Current surgical, chemo, and radio- therapies have not been optimal in treating these patients. Our pioneering work with antigen-specific regulatory T cells, known to be at least 100-fold more effective than other regulatory T cells with diverse antigen specificities in inducing immune tolerance, offers tremendous promise for treating these diseases. Our approach has the unique ability to selectively target antigen-specific therapy in individuals transplanted with adult or embryonic stem cells. Therefore, our proposed approach has the significant potential to greatly advance stem cell-based therapy by overcoming the obstacles causing conventional treatment failures, and leading to improved clinical outcomes for the patients.

We very sincerely appreciate the commitment of CIRM and its governing board in supporting and accelerating the best and most advanced science for the likely hood of translating the findings to clinical applications. We truly appreciate your consideration of our petition for funding.

Respectfully,

Chih-Pin Liu, Ph.D.

Extraordinary Petition RM1-01716: "Immune modulation to improve stem cell engraftment"

I. Background: More than 1 million Californians have a history of cancer, and an estimated nearly 150,000 new cases will be diagnosed in 2010. In addition, autoimmune diseases such as type 1 diabetes and multiple sclerosis, also affect hundreds of thousands of Californians every year. The potential impact of our proposed research for the treatment of cancer as well as autoimmune diseases such as type 1 diabetes is substantial because these patients ultimately fail available surgical, chemo-, radio-, and chemical therapies. Similarly, stem cell graft transplantation often leads to immune rejection. Treatment failure results in significant health and quality-of-life impacts on patients as well as a marked burden on the economy and health care system of California.

Our novel approach will reprogram the host immune system, using unique antigen-specific regulatory T cells (Treg), to reduce rejection of transplanted stem cells thus improving therapy outcomes without the need for the use of harmful immunosuppressive drugs. Successful outcome of this proposed therapy will improve patient health and quality-of-life given that the life-long use of available immunosuppressive drugs is associated with significant health and costs concerns.

II. The research team and leadership: The objective of this grant application is to determine whether reprograming the host's immune system to control auto- and allo-immunity can promote stem cell-based therapy by improving acceptance of stem cells and their derivatives. Specifically, we will test the novel hypothesis that using Treg to (re)establish immune tolerance in recipients can prevent stem cell graft rejection, thus improve stem cell engraftment and therapy. I have assembled an excellent multidisciplinary team of investigators, consisting of highly qualified experts with complementary skill sets. My extensive background in immunology and diabetes, with specific training and expertise in key research areas (immune regulation, auto/allo-immunity and inflammation), will permit me to successfully carry out this innovative translational research project. As the Principal Investigator (PI) or co-investigator, I effectively administered and/or served as a contributor to several peer reviewed and funded grants, resulting in the production of numerous peer-reviewed publications. I have the expertise, leadership and motivation necessary to successfully carry out the proposed work.

The co-PI Dr. Stephen Forman, a world-renowned clinician specializing in human hematopoietic stem cell transplantation and control of graft-versus-host disease, will provide his invaluable expertise in the proposed studies involving HSCs. In addition, Dr. Teresa Ku, a successful stem cell researcher in diabetes, will provide her documented expertise in studies involving mouse and human ESCs to derive insulin-producing cells. In summary, we have a demonstrated record of successful and productive research projects and feel that our expertise and experience as a team have prepared us well to lead the proposed innovative project.

III. Our novel approaches to improve stem cell-based therapy to treat cancers and type 1 diabetes:

I would like to summarize the following key points of our proposal:

1. The RFA states that "The purpose of the CIRM Stem Cell Transplantation Immunology initiative is to support transformative research leading to the development of immune tolerance of pluripotent stem cell derivative and the potential correction of autoimmunity."

Our novel approach is designed to precisely address the need identified by the RFA. We will use the unique populations of antigen-specific Tregs, which are known to be at least 100-fold more effective than other regulatory T cells with diverse antigen specificities in inducing immune tolerance. As stated in the proposal, our research team has already successfully demonstrated the following:

(a) We have successfully generated Tregs specific for self-antigens that can inhibit type 1 diabetes.

(b) These very potent antigen-specific Tregs can effectively inhibit not only the autoimmunity causing type 1 diabetes, but also the alloimmunity responsible for rejection of stem cell grafts in the hosts.

(c) Due to their higher potency in tolerance induction, it is expected that fewer antigen-specific Tregs will be required to achieve successful therapeutic outcomes. As a result, the use of antigen-specific Tregs is expected to significantly reduce the risk of toxicity and potential induction of systemic immune suppression associated with other approaches.

(d) We will use a novel translational humanized animal model to examine the effect of human Treg in controlling rejection of human adult and embryonic stem cells.

(e) We have derived insulin-producing cells from human embryonic stem cells (hESC). The ability to examine the effect of human Treg on preventing hESC rejection in the novel humanized model will help facilitate the translation of our studies to the clinic.

(f) We have obtained institutional approval (Institutional Review Board (IRB), Institutional Animal Care and Use Committee (IACUC), and Institutional Biosafety Committee) for the proposed studies.

In summary, we have a research team with extensive and complementary expertise, as well as the environment, infrastructure, technology, and track record to carry out the proposed studies. We are poised to take on the challenge of testing a potentially revolutionary immune tolerance induction approach, using antigen-specific Tregs to improve stem cell-based therapy to potentially treat cancer and type 1 diabetes.

2. Criticism of our review focused on select aspects of the rationale and lack of clarity in some of our experimental plans including questions on the roles of Tregs specific for a self-antigen, and whether our novel approach would be a better one than the use of immunosuppressive drugs causing systemic immune suppression.

(a) We certainly share the reviewer's concern. Therefore, we have included in our proposal the results from previous studies that our self-antigen-specific Tregs were able to effectively inhibit not only autoimmunity causing type 1 diabetes, but also alloimmunity that may cause tissue graft rejection.

(b) Other than the use of Tregs specific for self-antigens, we also will include Tregs specific for alloantigens. We will examine whether a combination of these Tregs would lead to a more profound protective effective in improving stem cells engraftment, thus reducing their rejection from the host. The proposed research also has the exciting potential that the use of Tregs may be able to prevent graft-versus-host disease.

(c) We are pleased that the reviewers noted that combining the use of human Tregs with humanized animal models would certainly help us better understand their roles in protecting human stem cells, a critical step to moving our research findings toward clinical studies.

(d) By potentially eliminating the need for continued patient use of immunosuppressive drugs, our novel use of antigen-specific Tregs addresses the concern of the RFA regarding the severe and adverse side effects associated with the use of these drugs.

(e) The proposed approach, if successful, will revolutionize treatment of hematological and autoimmune diseases. The next exciting step will be to compare in pre-clinical and clinical studies the immunomodulatory effects of Tregs with those of currently available immunosuppressive drugs.

Taken together, we hope that we have clarified all the confusions and concerns raised by the reviewers. We truly believe that our approaches, supported by our very promising preliminary studies, will not only lead to important novel findings but also facilitate near future translation of our findings from the bench to the bedside.

3. We thank the reviewers for recognizing the potential significant impact of our approach. The reviewers also stated that the proposal contained elements of innovation and creativity. In particular, if human Tregs prove to facilitate engraftment and enable the survival of human stem cells and hESC -derived insulin-producing cells in the humanized mouse model, our work would represent a significant finding and advance the clinical applicability of stem cells.

4. Potential future impact of our proposed studies in treating cancer and type 1 diabetes patients.

The proposed studies capitalize on the novel use of Treg with unique humanized animal models to induce immune tolerance that improves human stem cell engraftment and their therapeutic potential in cancer and type 1 diabetes. Results obtained from these pre-clinical translational humanized animal models will pave the way for future translation of stem cell-based therapy for not only various types of cancer but also autoimmune diseases from bench to clinical trials.

In summary, we are well prepared to undertake the proposed research as our research team has the scope and breadth of expertise in (1) generation of antigen-specific Treg and associated immunology studies, (2) translational and clinical studies for hematological and autoimmune diseases, and (3) mouse and human stem cell culture and differentiation. Our team is poised to achieve definitive outcomes in the proposed studies.

We sincerely appreciate the commitment of CIRM and the Members of the ICOC to support the best, most advanced science, providing critical research opportunities to expedite the translation of novel therapies from the bench to the bedside. We thank you and appreciate your consideration of our petition for funding of our innovative and high impact studies.