MEMORANDUM

Date: June 15, 2010

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application RM1-01721

Enclosed is a petition letter from Dr. Martinez of Stanford University, an applicant for funding under RFA 09-03, CIRM Stem Cell Transplantation Immunology Awards. This letter was received at CIRM on June 14, 2010 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

STANFORD
SCHOOL OF MEDICINE
Stanford University Medical Center

OLIVIA M. MARTINEZ, Ph.D.
Professor

June 10, 2010

To the Chairman of the ICOC and President and Chief Scientific Officer of the CIRM,

I am submitting this extraordinary petition regarding my proposal for the CIRM Stem Cell Transplantation Immunology Awards, RFA 09-03 to reiterate my standing as a transplant immunologist, to respond to the critique of my research plan, and to present my argument for why funding this project is critical for stem cell research in California.

I was born and raised in East Los Angeles, have been educated in California (was the first Latina in my field to receive a Ph.D. from UC Berkeley), and have spent my entire scientific career in California. I have been a productive investigator, with research interest focused largely on liver transplantation, and a leader in the area of transplantation immunology for over 20 years. As such I have served on several editorial boards of leading journals, chaired and served on numerous NIH study sections in transplantation, held leadership positions in the American Society of Transplantation and American Association of Immunologists, and was the recipient of the Basic Science Award from the American Society of Transplantation in 2004. Three years ago I established a collaboration with Dr. Theo Palmer, my colleague at Stanford University, to bring stem cell biology to my laboratory. Dr. Palmer is a CIRM grant recipient and I am a collaborator on his CIRM award. Our collaboration also formed the basis for a "Branch Out" grant I received from the American Society of Transplantation to study the immune response to neural/progenitor stem cell allografts. Thus, my CIRM proposal on the transplant immunology of ESC-derived hepatocyte-like cell (ESC-HC) allografts builds from over 20 years of work in the field and is a natural extension of my research program.

Over the course of my scientific career I have been strongly committed to increasing diversity in science and making science accessible to young, talented students in California communities like the one I grew up in. Many under-represented minorities specifically seek out my laboratory for training. In addition to the state of the art research experience, they receive mentorship and guidance from someone who has first-hand knowledge of the challenges they face. In the past two years three under-represented minority students from California have trained in my laboratory. One of these individuals graduated from Stanford and is currently at Harvard enrolled in a joint Medical and MBA degree program. A second student is graduating from Stanford Medical School this month and will begin his residency at UC San Diego. The third is an Immunology graduate student in my laboratory. Each of these outstanding students plans to pursue their career in California and I expect that each will become a leader in their field and in their community. I am firmly committed to training the future generation of scientists and physicians and exposing them to stem cell research in my laboratory, clearly in line with the specific goals of the recent CIRM Diversity Workshop "(1) to gain a greater understanding of how population diversity affects, benefits and advances CIRM's mission and (2) to use the knowledge to ensure that CIRM's funding initiatives support diversity in regenerative medicine."

In response the Reviewers Critiques:

1. The work in Aim 1 has already been completed.

We respectfully disagree with the Reviewer that much of the work in Aim 1 has been done. Comprehensive studies that include carefully done, integrated analyses of innate and adaptive

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immune responses to ESC-HC and the impact of local environment have not been reported. One of the lessons of my 20+ years in transplant immunology is that the immune response and graft outcome vary considerably depending on the type of allograft, the variable expression of MHC, innate, and co-stimulatory molecules, the location of the graft, and the immune status of the recipient. It would be a mistake to assume that responses observed in one type of stem cell transplant will be identical in others. For this reason it is incumbent to apply our extensive expertise in analyzing cellular and molecular pathways of alloreactivity to the ESC-HC system.

2. Tolerance to ESC-derived specialized allogeneic cells should be the focus of the proposal.
We agree with the Reviewer that the greatest impact lies with ESC-HC and would certainly focus the proposal on these cells. This would also address the criticism that the work cannot be completed in three years as the proposal would be sharply focused on ESC-HC.

3. Should have used real time PCR based analysis from livers or kidneys.
Our laboratory was one of two labs to simultaneously publish the first intragraft PCR analyses in 1992 (Krams et al. *Transplantation* 53: 151,1992 and Martinez et al. *Transplantation* 53:449, 1992). We perform real-time PCR analyses in all our transplant models and planned to include it in these studies but didn't expand upon it due to space constraints.

4. Stem cell tracking would be better accomplished using genetic markers or congenic markers.
This is a good suggestion by the Reviewer and represents a "tried and true" approach in transplant immunology. We would modify our donor-recipient combination to include genetic or congenic markers for this purpose. This would also obviate the concern with the immune response to GFP that could complicate interpretations.

5. The PI proposes to use BALB/c mice as recipients and C57Bl/6 as donors.
The Reviewer is incorrect in this statement. In fact, I indicate on page 5 of the application that C57Bl/6 mice are the allogeneic recipients. I also state on page 5 that stem cell grafts are derived from BALB/c mice. Having worked in the field of transplant immunology for over 20 years I am well aware that the appropriate, and more stringent, combination is BALB/c-> C57Bl/6. Indeed many of the knockout mice we utilize as recipients are on the C57Bl/6 background so that BALB/c->C57Bl/6 is the combination we routinely use.

6. Perform flow cytometry on leukocytes isolated from liver tissue as regularly done by others.
Isolation of infiltrating cells and flow cytometry is useful in phenotypic and functional analyses and, indeed, we have extensive experience in isolating infiltrating cells from the liver going back to 1995 (Egawa et al. *Transplantation* 59:97-102, 1995; Ogura et al. *Transplantation* 71:1827, 2001; Hsieh et al. *Transplantation* 77:121, 2004; Obara et al. *Am J Transplant* 5:2094, 2005; Hsieh et al. *Eur J Immunol* 36: 2170, 2006; Fujiki et al. *Liver Transplant* 16: 147, 2010) and most certainly would utilize this approach. We included the immunohistochemical analysis because that can provide additional information on localization of infiltrating cells relative to the graft. Because of space limitations we didn't include a description of possible flow-based analyses of graft cells but would certainly include that in our study. Indeed, our laboratory owns a flow cytometer (operated as a service center to the rest of the campus) and routinely perform this type of analysis in our transplant models.

I want to reassure the ICOC that the research would be successful and would result in important findings that would directly benefit California citizens.

As I am sure you are aware, data from the US Census bureau indicates that over 36% of Californians are of Hispanic origin. Hispanic men and women have a rate of chronic liver

disease that is twice that of the white population and are twice as likely to die of chronic liver disease according to the Office of Minority Health, US Department of Health and Human Services. According to a study by the American Medical Association 1 in 50 Hispanics is infected with Hepatitis C virus (HCV) and Hispanics have a 40% greater chance of being infected by HCV than the general population (*JAMA* 264:223, 1990). Thus, my CIRM proposal focusing on transplantation of stem cells to treat liver disease is directly relevant to the health concerns of a substantial proportion of Californians.

A key theme of the recent CIRM Diversity Workshop, as noted in the report of April 27, 2010, is the challenge in recruiting underrepresented populations for participation in research studies. An obvious strategy to overcome this obstacle is to support and engage scientists from underrepresented populations who themselves are established investigators working in the stem cell field. Indeed it is specifically mentioned in the report that "researchers should be able to relate the goals of basic research to community health needs". My work in stem cell transplantation for liver disease is clearly targeted to this goal. I am well aware that there are a very small cadre of scientists like myself in California, but I contend that I represent a "familiar face" to my community in East Los Angeles, the Central Valley, the Mission district and numerous other regions of California that are highly populated with Latinos. I would gladly participate in outreach to establish partnerships and educate Latinos about stem cell research. Surely the combination of expertise in transplant immunology, the fact that the proposal addresses important issues related to adaptive and innate immunity as noted by the reviewers, the focus on the area of liver disease, and our link to underrepresented populations together make a compelling case to support this proposal. I hope you will reconsider and award funding for our proposal.

Sincerely,

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