MEMORANDUM

Date: October 15, 2010

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application TR2-01797 **(LATE SUBMISSION)**

Enclosed is a petition letter from Dr. Meyers and Dr. Lam of the University of California Davis, an applicant for funding under RFA 10-01, CIRM Early Translational II Awards. This letter was received at CIRM on October 14, 2010 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

UNIVERSITY OF CALIFORNIA, DAVIS

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October 14, 2010

Independent Citizens Oversight Committee
California Institute for Regenerative Medicine

RE: **TR2-01797, UC Davis, Principal Investigator: Kit Lam, MD, PhD**

Dear Members of the ICOC,

We sincerely appreciate the insightful and constructive comments provided to us by the reviewers. In this letter we would like to take the opportunity to provide further information regarding our application. We hope to reassure the reviewers that we can isolate acute myeloid leukemia (AML) cells with a ratio of AML vs. non-leukemic hematopoietic stem cell populations sufficient enough to be therapeutically effective. We believe our model has the real potential for eventual translation into human studies, and respectfully ask the ICOC to please consider moving this otherwise well-scored proposal up into the funding range.

Our nanotherapeutic platform is unique and comprised of oligocholic acid based micelles with drugs loaded inside and cancer targeting ligands decorating the micelle surface. We have already demonstrated that such paclitaxel-loaded nanoparticles, even without cancer targeting ligands, exhibit superior toxicity and efficacy profile in xenograft models when compared to the FDA approved free drug (Taxol®) or nanoparticle drug Abraxane®). Furthermore, we have just completed a Phase I trial of this paclitaxel-nanoformulation in companion dogs with spontaneous lymphomas, and found the drug can be given safely to a large animal. A phase II trial in companion dog with solid tumor has just been initiated with promising preliminary results. Based on these studies, we have already initiated the filing of an IND with FDA on the clinical development of the basic nano-taxane discussed above, but without targeting ligands. A Phase I study will be carried out at UC Davis Cancer Center next year under the direction of Dr. Lara, Associate Director of Translational Science.

We have already demonstrated that the targeted nanoparticles can deliver high dose daunorubicin and fluorescent payload to the target leukemia stem cells. We therefore expect that this proposed nanotherapeutic to be successful and that significant improvement in survival of the leukemic mice (implanted with human AML cells) will be seen. By year three of this proposed CIRM project, we shall follow the same track of IND filing and clinical development at UC Davis Cancer Center as outlined above for this novel AML nanotherapeutic

The following new information is intended to attenuate reviewer concerns (highlighted in bold).

1. **Concerns on difficulties in the assessment of efficacy.**

The best way to assess the efficacy of a novel anti-leukemia therapy in a murine model (similar to human patients) is to compare the survival of and toxic side effects on the leukemic mice treated with standard therapy and the novel nanotherapeutic. Maximum tolerated dose (MTD) of the drugs will be determined and compared. Toxicities will be evaluated by blood counts, liver function tests, renal panel, histology, daily weight, and general appearance and activities of the mice. While it may be difficult to definitively conclude that the longer survival is due to the therapeutic effects on leukemia stem cells, we could still obtain supportive evidence to indicate that may be the case (see below). Regardless of the mechanisms, if the nanoformulation with targeting ligand can

greatly improve the therapeutic index of daunorubicin, it will be a triumph for us and for many AML patients, particularly the elderly patients who many of them cannot tolerate even standard induction chemotherapy.

"Aim II of this project is to compare the *in vivo* drug delivery and therapeutic efficacy of LSC-targeting nanotherapeutics (LTN). NSG mice with human AML xenografts are a model that is the most physiologically close to human patients with AML. We have already established the model as shown in the preliminary data. After we optimize the development of LTN *in vitro* as specified in Aim I, we will inject LTN into immune deficient NSG mice through the tail vein just as intravenous chemotherapy is given to clinical patients. We will then assess the efficacy with two approaches: drug delivery and therapeutic efficacy. Our system forms an excellent humanized model of drug treatment in a platform that can be accepted by the FDA in the future.

To assess drug delivery, we will euthanize the mice at different time points after drug administration, isolate LSC based on the surface markers CD34+ CD38- and CD123+. The isolation of LSC using these three markers has been well established and published in the literature. We have successfully performed the isolation using these three markers with a ratio sufficient enough to be therapeutic. To determine the efficacy of LTN, we will isolate different cell populations to evaluate the efficiency of the drug delivery. Once determined we will compare the efficacious dose of LTN and other therapeutic agents by looking at the drug concentration of cells isolated from different mice treated with different therapeutic agents: LTN, free daunorubicin and liposomal daunorubicin.

To assess the therapeutic efficacy, we will also use NSG mice with human AML xenografts. Daunorubicin in LTN or other formulations will be administered through tail vein injection. We will check blood counts, bone marrow biopsy and smear, overall survival and toxicity in the same approach as the clinical assessment of treatment for AML patients."

2. Concerns about the specificity of targeting

Although absolute binding specificity of our targeting ligands to LSC is ideal, it is not necessary as long as the targeting ligands do not preferentially deliver the toxic drug to vital organs such as liver, kidney, lung, and normal hematopoietic stem cells. Rituxan, the anti-CD20 antibody, that has revolutionized the treatment of B-cell lymphoma in this past decade, is far from specific. In fact the antibody will eliminate all the normal B-cells during treatment. However, the patient's B-cells will recover after the antibodies are eliminated from the body. The patients usually do not experience any significant side effects from Rituxan treatment. Herceptin is another example of cell surface targeting agent that is not highly specific and yet can exhibit significant benefit to cancer patients (breast cancer). Our proposed *in vivo* toxicity studies will allow us to evaluate if packaging daunorubicin into LSC-targeting nanocarriers will greatly improve the therapeutic index of daunorubicin.

We will target three cell surface molecules that are expressed on LSC. Two of the molecules, CD123 and CLL1, have been characterized and published. Besides the data shown in the proposal, we also have new data showing that the ligands targeting these molecules bound to CD34+ CD38- cells isolated from leukemia specimens, but did not bind to normal hematopoietic stem cells collected from healthy donors. PLZ6 is a novel ligand that we developed in our lab. As shown in the proposal, it binds to LSC, but not to normal hematopoietic stem cells from healthy donor and 19 other cell lines. We realize that CD123 is also expressed in peripheral blood dendritic cells, monocytes, eosinophils, and basophils. However, in patients with AML, the normal hematopoiesis is greatly suppressed by leukemia and these normal cells will be greatly diminished already in numbers. A more specific LSC therapy will avoid killing the normal hematopoietic stem cells in the marrow microenvironment, so that all hematopoietic components can be replenished. This will overcome a problem with the standard leukemia drugs that kill both normal and leukemic stem cells, as well as many cells in non-hematopoietic tissues.

3. Concerns on the lack of evidence that higher dose of the chemotherapeutic agent will kill LSC

Only the outcome of the proposed *in vivo* therapeutic studies in mice will definitively answer this question. Significant improvement in long term survival of the mice will prove that the LTN is effective in killing the LSCs. In addition to the evidence outlined below (from the orginal grant proposal), it is important to note that

there is good evidence that nanoparticle drugs, delivered into the target cells, via the endocytic pathway, can overcome the multi-drug resistant mechanism of cancer cells. (Dong and Mumper, Nanomedicine, 2010, 4:597-615; Liang et al Methods Mol Biol, 2010, 596:467-88; Liu et al, Mol Pharm, 2010, 7:863-869).

"As cited in our proposal, two articles published in New England Journal of Medicine in 2009 by two independent groups showed that higher dose of daunorubicin (135 mg/m^2 versus the conventional 45 mg/m^2) could improve overall survival in AML patients with long-term disease-free survival (Fernandez et al. NEJM. 2009; 361:1249. Lowenberg et al. NEJM. 2009; 361:1235). Also cited in our proposal, high-dose daunorubicin could induce complete remission in refractory or resistant AML, and improve overall survival (Cortes et al. Cancer. 2001; 92:7). Low toxicity of daunorubicin in our LTN formulation allows administration of high-dose daunorubicin that itself can kill LSC and leukemia cells. If LSC cannot be killed by chemotherapy, all AML patients will have recurrent AML. Treatment of lymphoma and testicular cancer with high-dose chemotherapy and autologous stem cell rescue (therefore, non immune-mediated killing of cancer/leukemia cells) can cure some patients with refractory or resistant diseases. All of this evidence suggests that a higher dose of chemotherapeutic agents can kill cancer including leukemia stem cells. Our LTN can deliver high-dose daunorubicin to LSC through two approaches: (i) formulation of daunorubicin in nanoparticles allow administration of daunorubicin at higher dose without increasing the toxicity; (ii) targeted delivery of LTN to the interior of LSC via targeting ligands, allowing specific killing of LSC."

The proposed targeting nanoplatform can be readily applied to other cancer stem cells and leukemic stem cells, with modification of the targeting ligands. The impact of the research can be far reaching beyond the treatment of AML. Thank you for taking the time to reconsider funding for this important project, which was initially funded by CIRM as a junior investigator grant to the Co-PI physician-scientist Dr. Pan.

Sincerely,

Fred Meyers MD

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