MEMORANDUM

Date: April 28th, 2009

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application TR1-01232

Enclosed is a letter from Dr. Leon Hall of the Jackson Laboratory, West, an applicant for funding under RFA 08-05, CIRM Early Translational Research Awards. Although this letter was not received at CIRM at least five working days prior to the April ICOC meeting, we were able to review the extraordinary petition. We are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

I have reviewed the petition (referencing reviewer comments and the submitted application as necessary) in consultation with Dr. Csete and the scientific staff, and concluded that the petition does not present compelling evidence that should alter the recommendation or score of the Grants Working Group (GWG).

This proposal "addresses a bottleneck in stem cell research: access to models of human disease optimized for preclinical testing of human stem cell (HuSC)-based therapies". We believe that the GWG members' concerns "about the potential impact and feasibility" are appropriate and are appropriately reflected in the score and rank of this proposal. We note, however, that the reviewers' opinions on this proposal were widely varied. Some reviewers gave this proposal very high scores, recognizing the need for complex animal models of disease (for stem cell testing) that are the same from lab to lab. Reviewers who gave the lower scores did so in large part because they felt there was not a sufficient 'market' for these animals. Although no GWG member chose to author a minority opinion, the overall score and rank of this application reflect the split among the reviewers. After reviewing the submitted application and the reviewers' critiques, Marie Csete, CIRM staff and I feel that the animal models are a critical resource for our grantees, and this proposal has the potential to have high impact.

The reviewers' opinions regarding the feasibility of this proposal were also varied. Specific biosketch information on the named investigators was not included in the proposal. Some reviewers felt that the track record of the institution was sufficient to determine that "the necessary expertise was present among the named investigators", while other reviewers felt that additional information, such as biosketches, was needed to make that determination. Although the applicant provides some new information in the extraordinary petition, CIRM staff recommends that the ICOC not consider data or information that was not made available in the application to the GWG. Under our system of expert scientific review, it is essential that the ICOC have the opportunity to hear the GWG's assessment of scientific propositions asserted by applicants. CIRM agrees with the GWG's conclusion that the applicant did not sufficiently indicate in the application the individual expertise of the named investigators, but that the institution has an excellent track record within this field.

CIRM staff will be prepared to provide further analysis should that be requested by any member of the committee.

Redactions, if any, have been made pursuant to the policy in consultation with the author(s) of the letter. An unredacted version will be available for review in closed session.

The enclosed letter represents the views of its author(s). CIRM assumes no responsibility for its accuracy.

In addition, a copy of the CIRM Review Summary for this application is provided for reference.

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April 23, 2009

Robert Klein, J.D.
Chairman, ICOC
Alan Trounson, Ph.D
President and Chief Scientific Officer, CIRM

Extraordinary Petition: Clarification of Reviewer Comments on TR1-01232: Mouse Models for Stem Cell Therapeutic Development

I would like to thank the members of CIRM's Scientific and Medical Research Funding working Group for considering our application TR1-01232: Mouse Models for Stem Cell Therapeutic Development and to take this opportunity to clarify points raised by the reviewers.

Before moving to the details, we want to reinforce the overarching benefit of this proposal to CIRM:

> Advancement of novel, effective human stem cell (HuSC) therapies into the clinic requires that they undergo pre-clinical testing, using validated animal models, in order to assess their safety and efficacy prior to clinical application. Development of HuSC therapies will slow, if not halt, without the appropriate models.
>
> The laboratory mouse is the most widely used animal model in preclinical research, but current models have not been optimized for HuSC engraftment. All of the methodology required to optimize mouse models for this purpose is available today. However, the current approach to mouse model development and transfer, which relies on individual investigators to share models developed for their own purposes, is slow and inefficient. Furthermore, models are not bred under health conditions suitable for widespread distribution, and are not necessarily robust or reproducible.
>
> CIRM has a limited timeline in which to achieve its objectives, and requires validated, effective models. This proposal will allow CIRM to provide the California stem cell research community with access to well documented, reproducible and reliable models for preclinical testing in the shortest timeframe possible. Further, CIRM's funding will leverage JAX West's newly expanded infrastructure for mouse model development and distribution in Sacramento, ensuring long-term, local access to these models at no additional cost to CIRM.

Clarification of Reviewers Concerns

1. Is there a critical mass of investigators w/facilities and expertise to monitor models, but not produce them? We read this question to mean: if an investigator has the capability do experiments with the model to begin with why they can't just produce them themselves and second, is there a critical mass in demand for preclinical models.

There is typically a difference in scale between basic/early discovery research and preclinical efficacy studies. Even in when a lab has all the resources to perform the early smaller scale studies they often don't have the space to produce enough animals at one time for larger scale studies.

As to the question of critical mass: we expect a tidal wave of demand for preclinical-scales studies in the coming months/years as the research investments in stem cell therapeutic discovery begin to pay off.

Support for this proposal will position CIRM investigators to rapidly make the transition from early discovery to preclinical testing.

2. Do immunodeficient animal models have predictive value given that many of the disease models require the presence of inflammatory cells or would immunospression be a better approach?

This issue figured extensively in our deliberations on model selection. We believe that this first set of models, except as noted in the application, should be developed on an immunodeficient background. It is important to keep in mind that no single animal model is a perfect surrogate for the human disease and must be chosen carefully based on the question at hand. As an example, the MPTP induced model of Parkinson, which is well characterized and commonly used for traditional drug discovery, is ideally suited for evaluating stem cell replacement therapy since the cause of the loss of dopaminergic cells is irrelevant to the therapeutic approach and, at least initial engraftment and function does not involve the immune system or inflammatory cells.

By no means do we wish to understate the potential for the continued process of disease to lead to the loss of the engrafted and differentiated cells but it does allow you to answer the first, critical question – if the neurons engraft do they ameliorate the symptoms of the disease.

Another important note - immunosuppression does not fully alleviate impact of the immune system on future cell loss/function and it adds an additional concern related to the side effects of these drugs that may interfere with any long-term evaluation of experimental success as noted in the International Society for Stem Cell Research (ISSCR): Guidelines for Clinical Translation of Stem Cells.

3. Justify your model selection

The models were chosen based on three key criteria: 1) scientific relevance to the applications of stem cell therapies; 2) well-characterized in small molecule drug development and as a result are well known to agencies that will be responsible for reviewing preclinical research before approval of clinical trials; 3) they can be reliably and cost effectively produced and distributed. All of the models we've selected meet these criteria.

4. Feasibility of the research plan

As the reviewer noted, these models are quite sophisticated and require a great deal of knowledge and technical expertise. This in part is why it is so important that the community have access to reliable source of the models. The PI, Senior Scientist, and technicians at

Jackson-West – all highly skilled in the techniques required to produce these models - are responsible for the day to day development activities. But, they are supported by the research Professors and laboratory staff located at our Bar Harbor campus who have already developed and optimized a number of the proposed models on various genetic backgrounds. Their protocols and expertise will be critical to successful development of these models and they are committed to providing the required collaborative support.

In addition, our board-certified veterinary histopathologists, Dr.'s Oded Foreman (Sacramento facility) and Anoop Kavirayani (Bar Harbor facility) have expertise in the models proposed in the application.

Further, as a complement to these induced disease models we are proposing, we anticipate offering a variety of genetic models for Type 1 Diabetes, ALS, and DMD on immunodeficient backgrounds in the future. These models are under development in Dr. Lenny Schultz's lab at Jackson-East and will be transferred to Jackson-West for scale up and distribution to the stem cell community as they become available.

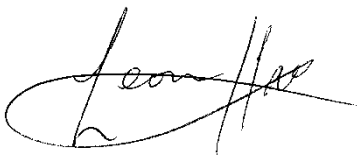
As noted by one reviewer The Jackson Laboratory and in particular the Sacramento based in vivo service laboratory have a "major track record in producing animal models". We are wholly confident in our ability to successfully execute the proposed work and develop the stated models in the timeline indicated within the application.

5. Transportability of the STZ model of diabetes

Addressing the concerns of the reviewer regarding the short time window during which animals made diabetic by STZ can be maintained hyperglycemic and suitable for transport to investigators: we are confident our development plan that takes this issue into account. We anticipate, based on preliminary studies looking at islet transplantation, that 75% of the mice that undergo acute STZ induced hyperglycemia induction will be viable 8 days post-STZ treatment and will be responsive to islet engraftment. This makes transfer of mice within California feasible and also permits transfer of this model outside of the state. In addition, recognizing that mice do not respond to all insulin products we have identified a swine insulin to which mice do respond and we are confident that under aim 3 we will be able to establish the conditions required to ensure adequate viability of mice following shipment to make this a practical model for distribution.

Thank you for this opportunity to address the concerns of the committee. If any further documentation, such as biosketches from collaborating colleagues, is required we would be happy to provide this.

Regards,



Dr. Leon L Hall, Ph.D.

Program Director, The Jackson Laboratory In Vivo Core Service

TR1 - 1232: Recommended if funds available (66)

EXECUTIVE SUMMARY

This proposal addresses a bottleneck in stem cell research: access to models of human disease optimized for preclinical testing of human stem cell (HuSC)-based therapies. While there are well-characterized models available for some of the diseases of interest to CIRM grantees, many of these models do not support sustained HuSC engraftment because they have normal immune systems. In Aim 1 the applicant proposes to develop immunodeficient mouse models of type 1 diabetes, Parkinson's disease (PD), spinal cord injury (SCI), stroke, traumatic brain injury and myocardial infarction (MI), to expand the models that can be used for testing cell therapies. Experimental autoimmune encephalomyelitis (EAE), the most commonly used model of multiple sclerosis (MS), will also be developed in an immune competent background. In Aim 2 the applicant will comprehensively characterize each of the new models, using large-scale studies to optimize protocols, establish therapeutic windows for treatment and validate each model's utility for disease research. In Aim 3 the applicant proposes to develop scaled-up production and distribution processes for these models.

Reviewers' opinions about the potential impact of this proposal varied widely. One reviewer felt strongly that the applicant's approach should be supported; noting that widespread availability of immunodeficient models of disease to investigators would accelerate development of stem cell therapies. However, this reviewer was uncertain whether there is a critical mass of investigators with the facilities and expertise to monitor and study these models but not to produce the models themselves (a market concern). Other reviewers questioned the predictive value of immunodeficient models for some of the proposed diseases. They noted that the natural pathology of many diseases depends on immune function. For example, the development of the desired phenotypes in the models of PD, stroke, MI and SCI may require the presence of inflammatory cells. In these cases, the phenotypes may be more easily achieved by immunosuppression following the induction of disease. Reviewers also questioned the desirability of standardized models for certain diseases. For example, some labs have years of experience generating the EAE model using different protocols than the one proposed by the applicant, and may not want to switch models. One reviewer also noted that a standardized model of MI is currently available for purchase but rarely used. For these reasons, reviewers thought it would have been helpful for the applicant to justify the choice of model of diseases for which multiple models exist.

Reviewers also expressed varied opinions about the feasibility of the research plan. One reviewer cautioned that the proposed models are very sophisticated and it would be a formidable challenge to develop and characterize models for multiple diseases. It was unclear to this reviewer that the necessary expertise was present among the named investigators. In the section of the proposal describing resources, two PhD-level program directors and four PhD-level study directors with expertise in a wide range of diseases are mentioned, but no further detail is provided. The reviewer would have appreciated more information about these collaborators, including biosketches if possible. Without this information, the reviewer was not confident there would be an optimal assessment of pathology in the model systems. However, other reviewers found the research plan both feasible and likely to succeed, and pointed out that the applicant institution has a major track record in producing animal models. They specifically cited the strong preliminary data describing the development of models of stroke, MS, PD and diabetes. One of these reviewers did raise concern about the induction of diabetes using streptozotocin, which provides only a short time window during which animals can be maintained hyperglycemic and suitable for transport to investigators and treatment with cell-based therapies. This timing issue could complicate distribution of the model, but investigators may be able to use insulin therapy prior to treatment with cells.

The reviewers generally found the applicant and research team to be well-qualified to carry out the proposed studies. One reviewer felt the applicant clearly has the experience required to lead the research effort and praised the senior scientist's strong research track record. However, another reviewer raised

concerns about expertise in specific disease models and would have been reassured if collaborations had been established with investigators with specific experience developing and analyzing the various disease models. Reviewers agreed that the applicant's resources and research environment are outstanding and appreciated the proximity of production facilities to California's academic and biopharmaceutical research centers, allowing for rapid distribution of the disease models.

Overall, while reviewers appreciated the goal of increasing access to immunodeficient models of disease, they raised significant concerns about the potential impact and feasibility of this proposal.