CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

MEMORANDUM

Date: April 28th, 2009

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application TR1-01266

Enclosed is a letter from Dr. Philip H. Schwartz of the Children's Hospital of Orange County, 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 fully review the his extraordinary petition. We are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

As required by that policy, 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).

Briefly, reviewers considered this proposal to address "two bottlenecks in the stem cell-based treatment of lysosomal storage diseases (LSDs)" and to have the potential for "high impact". However, the GWG expressed several concerns with the research plan and feasibility of the project, and CIRM staff believes those concerns are justified. The petition presents several point-by-point comments that largely represent a difference of expert scientific opinion or point to information that was not adequately or clearly discussed in the application. CIRM staff believes that the score, and recommendation to fund if funds are available, appropriately reflects the GWG's estimation of the merit of this proposal relative to all applications in this competition.

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.

CHOC Children's

Tuesday, April 21, 2009

TO: Robert Klein, JD, Chairman of the ICOC
Alan Trounson, PhD, President of CIRM
Marie Csete, MD, PhD, Chief Scientific Officer of CIRM

RE: Extraordinary Petition for TR1-01266 - Stem Cell Transplantation for Pediatric Neurodegenerative Disease, Philip H. Schwartz, PhD, PI

The lysosomal storage diseases (LSDs) present a unique and very promising opportunity to successfully move a novel stem cell therapy (SCT) into the clinic. The reviewers apparently agree as they said "that this proposal has the potential for high impact." The reviewers also noted I have "considerable experience in NSC [neural stem cell] research and transplantation into animal models and that [my] assembled research team contributes expertise in iPSC [induced pluripotent stem cell] line derivation and neurodegenerative disease as well as clinical experience with HSCT [hematopoietic stem cell transplantation]."

The proof-of-principle for SCT in the LSDs has already been demonstrated and is in clinical practice. Thus, we and others have shown that bone marrow transplantation (BMT) is clinically effective in some LSD patients. BMT, however, although effective for the peripheral manifestations of LSDs, has little effect on central nervous system (CNS) manifestations. Stem Cells, Inc., has recently sponsored a clinical trial to address the efficacy of SCT in the CNS of a select group of LSD patients. These trials have been allowed by the FDA based, in large part, on preclinical data derived from mouse models. Unfortunately, the two LSDs chosen for the trial also have peripheral manifestations, as almost all LSDs do; thus, even this novel SCT is unlikely to stand alone as a therapy for these LSD patients. Our proposal addresses this major bottleneck and clear and unequivocal need in LSD patients – how do we treat a whole body disease with SCT?

The second major bottleneck that our proposal addresses is that of potential immune rejection. While data exist that show that 1) the CNS possesses a degree of immune privilege, 2) stem cells themselves possess a degree of immune invisibility, and 3) some patients transplanted with fetal-derived tissue do not appear to need immunosuppression, it is still clear that immune-matching of transplanted cells to the recipient is of utmost importance. This is particularly germane as we consider subjecting very young children to a lifetime of immunosuppression. As we have already shown in animal models that neural stem cells (NSCs) transplanted directly into the brain have significant ameliorative effects and that the source and engraftment characteristics of these NSCs was irrelevant, two extremely important conclusions can be drawn: 1) engraftment as it relates to differentiation of specific cells types or integration into the nervous system is not as important as engraftment as it relates to migratory ability of the cells and their ability to take up long term residence in the nervous system and 2) given that iPSCs can be derived from a particular donor and that NSCs can be derived from these iPSCs, just as we have derived them from ESCs, then that same donor can be the source of stem cells for SCT of the periphery (via BMT) and the CNS (via NSCs differentiated from the iPSCs). Thus, immune rejection and long-term immunosuppression become irrelevant. The reviewers agreed … "that the strategy of using immune-matched (to the donor marrow used in BMT), iPS-derived

cells for CNS transplantation could have widespread applicability for tissue-specific transplantation."

While I fully appreciate that CIRM and the ICOC are faced with daunting challenges when it comes to deciding what and whom to fund, given the extraordinarily high level of stem cell research in this State and the limited funds available, I nevertheless feel compelled to make a case for the project described in our proposal, especially as there may be no other chance to do so. In addition to the scientific aspects of the proposal I address below, I want to make it clear that my laboratory and CHOC Children's are dedicated to the pediatric population we serve and we have focused all of our translational research efforts on the particular patient population described in the proposal. This means 1) that the laboratory has only one translational research focus and we have derived a novel mouse model specific to this focus, 2) that we have been and will continue to host an annual symposium of translational researchers focused on this patient population, 3) that we are fast becoming the institution of choice for treatment of this patient population, 4) that we have expanded our clinical approach to these patients to include a multidisciplinary clinic designed to serve the various needs that these patients present, and 5) that we have already begun cutting edge multimodal treatment strategies with these patients, including becoming an infusion center and combining enzyme replacement therapy with BMT.

One reviewer felt that the "justification for using stem cell[s] to address this bottleneck is debatable, noting that microglia could provide an effective vehicle for enzyme replacement in the CNS and these cells enter and migrate freely within it". It has, indeed, been shown that the CNS of certain LSD patients, such as Hurler's, do benefit from a BMT, if done at a very early age. This is thought to be due to infiltrating microglia, yet other patients such as Hunter's and Sanfilippo's show no such benefit raising a doubt as to the supposed mechanism. Further, if BMT is done at a later age, no beneficial effect on the CNS is seen suggesting that a certain "leakiness" of the blood-brain barrier must be present for microglia to enter the CNS in sufficient numbers to provide clinical benefit. A more robust treatment strategy that is effective over a larger age range and in more LSDs is needed and that is what we have proposed.

The reviewers also questioned whether "the creation of iPSCs from stromal cells and their differentiation into a pure NSC population with the capacity to migrate widely and engraft" was feasible. It is difficult to reconcile this concern with the available data, given that iPSCs have been derived from just about every cell population that has been examined, that neural differentiation is among the easiest things to do with PSCs, and that, as mentioned above, cells exactly like this have been produced from ESCs and successfully used, by us, in a similar animal model as described in our proposal.

One reviewer felt that ... "monitoring the persistence and integration of neurons and glia derived from the transplant might provide a better readout, and should be done with animal studies." This is, indeed, why we devised our long-lived immune deficient mouse model. Mouse models based on the SCID background alone are too short-lived to answer this exact question. The planned detailed immunohistochemical examination of the brains of these long-lived transplanted animals, as described in our proposal, will indeed provide the needed data.

A reviewer also noted that "while the derivation of a mouse model for Hurler's disease bred into an immunodeficient background should aid NSC engraftment it may not be a suitable test bed for evaluating potential benefits of immune-matching transplanted HSCs and NSCs." The reviewer suggested "parallel experiments with mismatched transplanted populations to demonstrate the effectiveness of the tolerogenic strategy." The mouse model we propose provides the platform to ask and answer the primary question in a system without immune

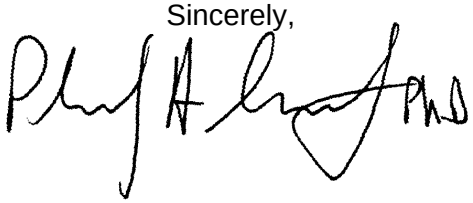
system confounds: Does the combination of peripheral and CNS SCT provide an adequate and effective therapy for a disease that affects the whole body? If one is basing a therapeutic strategy on a current clinical approach, BMT, as the first step, then mismatching of subsequent NSCs would only occur if the iPSC strategy fails. The strategy is not a tolerogenic one, per se, it is one aimed at treating two different body compartments while at the same time obviating immune rejection of the cells in the CNS compartment.

Another reviewer said, “The applicant proposes to use a nonmyeloablative conditioning regimen prior to HSCT but provides no specifics. The applicant is concerned about engraftment of human stem cells in the mouse model and mentions the possibility of supplementing conditioning with cyclophosphamide and fludarabine, but presents no data that fludarabine will work in this model.” These data are presented in the references cited. Further, the collaboration of[REDACTED] , the scientist who originally devised the immunodeficient model and whose laboratory supplies the model world-wide, assures that appropriate considerations for HSCT engraftment have been taken.

Finally, a reviewer noted that “human T cells will follow successful HSCT and have the potential for causing graft-versus-host disease, a possibility that isn't discussed in the proposal.” The probability of T-cell-induced GvHD is significantly reduced in this model by using the highly purified population of CD34+ cells we describe. Moreover, the literature cited shows that, in this model, there is little to no GvHD noted after CD34+ cell transplantation. Nevertheless, the extensive histologic analyses described in the proposal will, indeed, show if GvHD is present.

It is my sincere hope that CIRM and the ICOC will appreciate the strong scientific basis of this proposal and its focus on a patient population and disease worthy of CIRM support.

Sincerely,



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TR1 - 1266: Recommended if funds available (66)

EXECUTIVE SUMMARY

This proposal addresses two bottlenecks in the stem cell-based treatment of lysosomal storage diseases (LSDs), a group of inherited metabolic disorders that result in the accumulation of unprocessed macromolecules in lysosomes, causing cellular dysfunction and severe clinical complications. The applicant proposes that the major bottlenecks in the development of effective therapies for LSDs are: 1) the ineffectiveness of hematopoietic stem cell transplant (HSCT) for disease manifestations in the central nervous system (CNS); and 2) the need for life-long immunosuppression in patients receiving neural stem cell (NSC) transplants to treat CNS manifestations. To address these issues the applicant proposes to treat both peripheral and CNS pathologies in a mouse model of a LSD (Hurler's disease) by using HSCT, supplemented by NSC transplants into the brain. The NSCs will be derived from induced pluripotent stem cells (iPSCs) derived from mesenchymal stromal cells (MSCs) cultured from the same bone marrow donor used for HSCT. This strategy guarantees immune-matching and could eliminate the need for immunosuppression. These experiments will be carried out in a novel, long-lived, immune-deficient mouse model of Hurler's disease generated by the applicant.

The reviewers agreed that this proposal has the potential for high impact. Allogeneic HSCT from healthy donors is currently used to treat patients with LSDs such as Hurler's disease. But a major problem with this approach is that correction of the enzyme deficiency mainly improves peripheral manifestations of these diseases without affecting CNS manifestations, presumably in part because of limitations of HSC trafficking across the blood/brain barrier. For this reason patients generally also receive enzyme replacement therapy, also with limited effectiveness. This proposal intends to address this bottleneck by supplementing HSCT with injection of NSCs into the CNS. However, one reviewer felt that the justification for using stem cell to address this bottleneck is debatable, noting that microglia could provide an effective vehicle for enzyme replacement in the CNS and these cells enter and migrate freely within it. Therefore the need for neural stem cells, whose capacity for functional integration has not been fully characterized, is unclear. Reviewers agreed that the second bottleneck is potentially important and that the strategy of using immune-matched (to the donor marrow used in BMT), iPS-derived cells for CNS transplantation could have widespread applicability for tissue-specific transplantation.

The reviewers raised a number of questions about the research plan and its feasibility. They described the plan as complex and cited a number of significant challenges, including the creation of iPSCs from stromal cells and their differentiation into a pure NSC population with the capacity to migrate widely and engraft. One reviewer felt that, given the goal of prolonging survival of transplanted NSCs, the proposed examination of the CNS is inadequate. The emphasis is on behavioral and biochemical analyses but monitoring the persistence and integration of neurons and glia derived from the transplant might provide a better readout, and should be done with animal studies. This reviewer also noted that while the derivation of a mouse model for Hurler's disease bred into an immunodeficient background should aid NSC engraftment it may not be a suitable test bed for evaluating potential benefits of immune-matching transplanted HSCs and NSCs. The reviewer suggested parallel experiments with mismatched transplanted populations to demonstrate the effectiveness of the tolerogenic strategy. Another reviewer raised a number of concerns about the experimental design. The applicant proposes to use a nonmyeloablative conditioning regimen prior to HSCT but provides no specifics. The applicant is concerned about engraftment of human stem cells in the mouse model and mentions the possibility of supplementing conditioning with cyclophosphamide and fludarabine, but presents no data that fludarabine will work in this model. Finally, this reviewer noted that human T cells will follow successful HSCT and have the potential for causing graft-versus-host disease, a possibility that isn't discussed in the proposal.

The reviewers noted that the applicant has considerable experience in NSC research and transplantation into animal models. The assembled research team contributes expertise in iPSC line derivation and neurodegenerative disease as well as clinical experience with HSCT. One reviewer noted that the choice of an international collaborator for immunology was not fully justified, and that the lack of a specialist neuroscientist for the analysis of data arising from NSC transplantation was a weakness. Another reviewer remarked that the budget seems very large and lacked adequate justification.

Overall, while the reviewers appreciated the novel approach and potential impact of this proposal, they raised a number of concerns about the research plan and its feasibility.