MEMORANDUM

Date: May 17, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application TR3-05660

Enclosed is a petition letter from Dr. Stuart Lipton of the Sanford Burnham Medical Research Institute, an applicant for funding under RFA 11-02, CIRM Early Translational III Awards. This letter was received at CIRM on May 16, 2012 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

CIRM staff will be prepared to address any questions or concerns regarding the points raised in this petition, but overall conclude that this petition is without merit.

Sanford|Burnham
Medical Research Institute

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Extraordinary Petition for RFA 11-02: CIRM Early Translational III Research Award Application TR3-05660

We wish to file an extraordinary petition for application **TR3-05660:** Programming Human ESC-derived Neural Stem Cells with MEF2C for Transplantation in Stroke, PI Stuart A. Lipton. The basis of this petition is two-fold. First is the importance of producing a stem cell-based transplantation approach for the treatment of stroke (cerebral ischemia), currently the third major cause of death of adults in California. Currently, there is one disease team funded by CIRM for stroke, but the approach is to use neural stem cells (NSCs or NPCs) that may be capable of hyperproliferation and hence tumor formation. The current application solves this potential safety problem by transiently programming human ESC-derived NPCs with a transcription factor, MEF2C, which our group originally discovered and showed can drive terminal differentiation of virtually 100% of NPCs to neurons, thus eliminating the potential for hyperproliferation or tumor formation (Li et al., J. Neurosci., 2008). This advance will provide safer regenerative therapy to patients with stroke than any currently=funded CIRM approach.

Second, there were misinterpretations of our application by the Study Section, which we elaborate below, that ended up giving us a borderline score. Given the extraordinary conditions of needing to develop a regenerative therapy for stroke that lacks any potential to form tumors in the recipient, we ask the ICOC to consider the statements outlined below (*Reviewers' comments are in italics*, **followed by our responses in bold**).

Objective and Milestones
It is not clear that this project will be ready to advance into IND-enabling studies in three years. The proposal is premature for a Development Candidate Award and would be better suited for a Development Candidate Feasibility Award.
In reply, we have already published the use of a form of the Development Candidate in Li et al., J. Neurosci, 2008:28:6557-6568. We propose here to perfect the candidate by detailed dose-response studies, as required for preIND work by the FDA. As detailed preliminary data with the Development Candidate in the appropriate animal model are already demonstrated in the application and in the prior publication in J. Neurosci., as required of a Development Candidate Award, this criticism is not correct.

The Target Product Profile (TPP) mixes clinical information with preclinical animal studies. The TPP should describe desired clinical attributes of the proposed therapeutic. In addition, the desired safety profile should be specific to the proposed product without referencing other products.
In response, the issue of mentioning the desired clinical attributes in human along with prior animal studies, or in contrast with other products, is an issue of grantsmanship and not really a criticism of the proposal as a whole. In point of fact, the TPP is viewed as a document in transition that is continually updated and used to detail the clinical attributes of the desired therapeutic. The submitted TPP achieved that goal and was not

criticized on that basis but rather on an issue of grantsmanship or presentation.

Rationale and Significance
The choice of patient population is not well justified. Reviewers noted that the proposed treatment window post-stroke is too early to assess the patient's likelihood of improvement. They suggested a later time point that would allow for patient stabilization and stratification.
In reply, with the advice of our Neurology Stroke Specialists (of which the PI, Dr. Lipton, a board certified neurologist, is one at UC San Diego), we proposed to treat human patients at least one week after a massive stroke. Other experts might wish to wait one to three months post stroke. We are certainly willing to wait a 1 to 3 months after the stroke if the FDA feels that this is necessary, but note that clinically, most strokes are completed by the end of one week, so this time point was not necessarily incorrect by current clinical standards. Moreover, this criticism does not affect the current application at all, which proposes preIND work for the Development Candidate, and hence should not be used against the proposal.

Research Project Feasibility and Design
Very large numbers of animals are proposed in the budget section, which are not feasible over the course of a three year award. That these very large numbers are required to achieve statistical significance suggests that the biological effect of NPC transplant in animal models of stroke is very small.
In response, the numbers of animals proposed were based on current use, so in point of fact we are performing that number of strokes now in our laboratory and it is therefore achievable. We explicitly state that numbers of animals used are to perform a detailed dose-response curve with the Development Candidate, but the Referee later complained that we did not propose a dose-response with the number of animals used (see exact quotation from our proposal, below). Moreover, in our publication with the Development Candidate, (Li et al., J. Neurosci., 2008), we show a robust improvement in the animals receiving transplants after stroke, as reproduced in the Preliminary data section shown in the original grant application. Hence, the effect is NOT very small, as the Reviewer stated, but in fact quite robust, demonstrating improvement in the animals treated with this cell therapy after a stroke. Therefore, based on the facts presented in the original application, this criticism is completely unfounded.

The applicant proposes that the viral vector will result in transient gene expression but does not propose experiments to confirm this hypothesis. Vector expression may be diluted in dividing NPCs or may persist in postmitotic neurons. In addition, no data are provided regarding the efficiency of gene expression using this vector in NPCs.
In reply, the AAV2 vector discussed in the proposal has already been demonstrated to induce robust but transient expression (Fig. 5 of the preliminary data). Experiments have already shown that the expression is not persistent, as previously published and cited in the application. We plan to continue to monitor efficacy of gene expression and its transient nature in each batch of vector produced, as stated in the application.

The preliminary data demonstrating NPC differentiation and integration following transplant is encouraging. The functional improvement in an animal model of stroke is modest but statistically significant.
In reply, the improvement in the rats treated with the Development Candidate was much greater than "modest," and in fact the animals showed a robust improvement, as demonstrated not only in the Preliminary data but also in the publication showing these data (Li et al., J. Neurosci., 2008). Not only were the animals improved histologically but

also in functional neurobehavioral testing on multiple tests (Figs. 3 and 4 of the preliminary data).

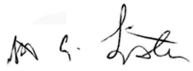
The research plan does not include a thorough investigation of safety endpoints. In particular, the potential for newly transplanted neurons to cause abnormal activity and seizures should be examined.
In response, there is an entire section in the grant about monitoring electrical activity in these cells using the latest optogenetic/electrophysiological techniques (Milestone 3). There is even a whole section in the preliminary data showing these electrophysiological experiments, which would detect both normal electrical behavioral and seizures (Figures 6 and 7 of the preliminary data). This criticism is therefore totally incorrect and, with due respect, demonstrates a poor reading of the original application by this Reviewer. Additionally, as alluded to above, a very important safety endpoint followed here is the lack of hyperproliferation or tumor formation in animals followed for over two years using stem cells programmed to differentiate into neurons with the transcription factor MEF2C.

The robust animal studies do not include a significant effort to optimize the cell transplantation and dosing regimens.
In reply, this criticism is not factually correct. In the application, we propose a detailed dose-response curve. On page 2 of part B of the application, we explicitly state "We initially transplant 5x10^5 cells into the rat after stroke. In this study we will perform a dose-response varying the number of transplanted cells, which will inform our decision on the proper dose for the human subjects."

Qualification of the PI (Co-PI and Partner PI, if applicable) and Research Team
The PI has a strong track record in neuroscience research. However, the team does not appear to have much experience in product development.
In response, as stated in the application, the PI has extensive experience in product development and meetings with the FDA, being the inventor on patents, the company founder, and the developer of the latest FDA-approved drug for Alzheimer's disease (memantine/Namenda®). Moreover, the PI has retained as a part of the development team an FDA regulatory expert, Dr. Alice Varga, Senior Consultant of the Biologics Consulting Group, Inc., as stated in the application. Hence, this point raised in the review is not correct.

The proposed budget is considerable and the very large number of animals is not justified.
In reply, the budget justification for the number of animals to be used is very carefully laid out in the grant and in justification section, e.g., stating that approximately 10 animals are needed for each data point in the detailed dose-response curves to be generated for the Development Candidate, as determined by our Statistician's Power Analysis (last paragraph, page 10 of Part B of the Application). In fact, the Reviewer requested such a dose-response curve in another section of the critique (see above), making it apparent that this statement in the review was made in error.

Sincerely,



Stuart A. Lipton, M.D., Ph.D.