MEMORANDUM

Date: July 17, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR2-05272

Enclosed is a petition letter from Dr. Stuart Lipton of The Sanford Burnham Medical research Institute, an applicant for funding under RFA 10-05, CIRM Disease Team Therapy Development Research Awards. This letter was received at CIRM on July 13, 2012 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

Sanford|Burnham
Medical Research Institute

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Dear Dr. Jonathan Thomas and ICOC Members: 12 July 2012

We wish to file an **Extraordinary Petition** for application **DR2A-05272,** entitled "hESC-derived NPCs Programmed with MEF2C for Cell Transplantation in Parkinson's Disease" under RFA 10-05 Disease Team Therapy Development Awards Program, PI Stuart A. Lipton, which received a score of 59. The basis of this petition is three-fold. ***First*** is the importance of producing a stem cell-based transplantation approach for the **treatment of Parkinson's disease (PD)**, currently the major cause of motor disability in adults in California. Currently, there is no disease team funded by CIRM for PD, only earlier stage experiments. ***Second***, in contradiction to the CIRM Review Report, the approach used here is the only one using neural stem/progenitor cells (NPCs) that produces nearly pure dopaminergic neurons to combat PD while preventing hyperproliferation and hence tumor formation. The current application solves the problem of tumor formation while promoting dopaminergic differentiation by pre-programming human ESC-derived NPCs with a transcription factor, MEF2C, which our group originally discovered. This drives terminal differentiation of virtually 100% of NPCs into neurons, and thus **eliminates the potential for tumor formation** (Li et al., J. Neurosci., 2008; Cho et al., 2011). Additionally, because we made a Stable Stem Cell Line with MEF2C, the **100% purity of our stem cell line** is a great advantage over existing techniques. Our cells also manifest increased dopaminergic neuron production over all published methods with >85% of the cells becoming dopaminergic. Moreover, the **anti-apoptotic effect of MEF2C** promotes long-term stability of the transplant. ***Third***, there are misstatements in the Review leading to misinterpretation of our application, as elaborated below. Given the extraordinary and acute need for a regenerative cell therapy for PD, we ask the ICOC to consider the statements described below (*Reviewers' comments are in italics*, **followed by our responses in bold**).

- Some reviewers saw this approach as not significantly novel and therefore of limited potential impact over other therapeutic approaches under development.
Reply: This is the first approach avoiding tumor formation while producing >85% dopaminergic neurons from stem cells. To achieve this, we use a novel transcription factor originally discovered, cloned, and characterized by the PI.

- The potential impact of this approach is unclear, as reviewers were not able to discern whether the proposed therapy would avoid the adverse side effects that have been observed in other cell transplantation studies for PD.
Reply: This approach, unlike previous, shows significant and robust improvement in PD motor signs (Fig. 4B,C) while avoiding motor dyskinesias and tumor formation (as shown in our publications, Li et al., 2008 and Cho et al., 2011, which are cited in the application).

- Important details regarding the implementation and duration of the immune suppression strategy are not elaborated in the Target Product Profile.
Reply: In fact, very Detailed information on our immunosuppression strategy with Cyclosporine A was provided under the Project Plan in Part B, page 17, paragraph 2 entitled, "Site, Mode and Method of Delivery of Transplanted Cells," lines 14-19.

- Rationale -- No convincing data are provided to demonstrate why MEF2C expression is a better approach than the best available method for deriving dopamine-producing cells.
Reply: Using MEF2C combined with the Studer floorplate differentiation protocol, our approach achieves a purity of >85% dopaminergic neurons, greater than any other known method, including the Studer protocol alone (Kirks et al. Nature, 2011). Moreover, as we show in the application, in addition to providing new dopaminergic neurons, our method, unlike previous, protects the transplanted cells via the antiapoptotic effect of MEF2C, increases endogenous dopamine fibers in the host brain, and avoids tumor formation. We have published these results in top peer-reviewed journals (Li et al., 2008; Cho et al., 2011, cited in the application), and provide key figures in the application.

- The preliminary data provided for efficacy were not convincing. Data were shown for only one of the two behavioral study models. Only modest improvements were seen in vivo which barely reached a statistically significant difference from the control.

Reply: This statement is not correct. Two behavioral models are shown (Fig. 4B,C) on (1) rodent turning and (2) paw preference, with robust significant improvement ($P < 0.03$).

- A reviewer noted that the behavioral experimental data provided were difficult to interpret, as it was unclear whether the described improvements were due to the effects of transplanted cells or from sprouting of residual fibers that may not have been completely lesioned.
Reply: The controls did NOT show behavioral improvement, so incomplete lesioning (performed in the same fashion in the controls) cannot account for the results. Whether the transplanted stem cells also manifest a trophic effect on endogenous cells is not important here, as clinical improvement is the important finding for our PD patients and for approval as a cell-based therapy by the FDA, not the mechanism.

-Reviewers noted that data from several recent publications raise the possibility that serotonin modulation could be contributing to some of the observed effects, which was not discussed.
Reply: The mechanism for improvement is not critical to the FDA or to our human PD patients, only the fact that our data show that the cell therapy improves PD.

- Therapeutic Development Readiness -- The applicant has not shown definitive proof of concept linking dopamine production by transplanted cells with an improved outcome in vivo.
Reply: In fact, we do demonstrate significantly more dopamine-producing cells in vivo in the transplants (Figs. 4G,H, $P < 0.0001$ compared to control). Moreover, the mechanism for improvement is not critical to the FDA or to our human PD patients. What is important is the fact that our data show that this cell therapy improves PD signs and symptoms.

- Reviewers were concerned about the purity of the proposed development candidate and the poor characterization of other cell types in the population. The application lacked detailed cell characterization.
Reply: The proposed developmental candidate is a PURE CLONAL CELL LINE, 100% pure, as we explicitly state in the application. Indeed, the prior CIRM Review of our Disease Team Planning Grant commented that the strength of our approach was the Stable [pure] Cell line that we had developed. Details of cell characterization were also provided in the current application (histological markers in Fig. 4G-I, and detailed electrophysiological characterization in Figs. 5-7). In our recent experiments using the Studer differentiation protocol, as detailed in the original application) >85% of the stem cells become dopaminergic neurons, as needed to treat Parkinson's diseases (PD). The remaining cells all become terminally differentiated neurons, as we also show.

- Reviewers felt the project is at an early stage of therapeutic development readiness.
Reply: The Developmental Candidate has already been used to treat both rodents and non-human primates (monkeys) with successful results, proving therapeutic readiness.

- Research scale feasibility data is shown but the master cell bank has not yet been developed which must then be qualified and tested.
Reply: This grant application proposes to develop the Master Cell Bank, which is allowed under the RFA instructions. Hence, this is not a legitimate criticism of this grant application.

- One lot of cells appears to be sufficient to treat only a single patient. Production methods may be adequate to get to an IND filing and conduct safety studies but the ability to scale up to conduct later phase clinical trials is unclear.
Reply: This is a misinterpretation. As we state, the Stable Stem Cell Line representing the Developmental Candidate is capable of treating many thousands of patients because it can proliferate, and a Master Cell Bank is being developed under GLP conditions.

- Reviewers felt it was premature to conduct studies using a clinically relevant animal model. Furthermore, the panel disagreed with the applicant statement that two preclinical models would necessarily be required by the FDA.
Reply: This statement is not correct. In a recent preIND meeting with FDA, the PI was told that two-animal tox studies were required (rodent and non-rodent), and experiments in a clinically relevant animal model were now required, as stated in our original application.

- Feasibility of the Project Plan -- Feasibility of the project plan was questioned in light of the limited characterization of the product. There was no discussion of product heterogeneity,

transgene copy number, and other important aspects of the cell population.
Reply: A PURE Stem Cell Conal Line is used here with two copies of the transgene (verified by sequencing). As published, there is no heterogeneity of the product during the passage numbers to be used, and this will be monitored with each passage, as we stated in the application.

-The application lacked data demonstrating duration of MEF2C transgene expression in vivo. Furthermore, the proposal did not address the possibility of gene silencing in vivo and resulting loss of efficacy.
Reply: We mention that we monitor each batch of the cell line for MEF2 activity. Additionally, we have monitored MEF2-activated gene expression in vivo in mice for up to 1-year post-transplantation and found evidence of continuous activity (Figs. 4H,I).

- One reviewer disagreed with the method proposed to determine the dose for the clinically relevant animal model. It was suggested to perform the lesion and then dose to see an effect rather than extrapolating the dose from other preclinical models.
Reply: A wide range of dosing was suggested for testing until an effect was seen, not dissimilar from the suggestion of this referee. In fact, preliminary experiments have already demonstrated effects after transplantation in the relevant animal (monkey) model, alleviating this concern.

-If the transplanted cells exert their effect through a neurotrophic mechanism, then it would be important to consider this in the clinical trial design.
Reply: We agree with the Referees, and in fact the clinical trial design outlined took into account both direct stem cell effects and neurotrophic effects, as described in the original application.

- Principal Investigator (PI) and Development Team -- some reviewers were concerned about the PI's lack of experience in developing a cell therapy product for clinical transplantation.
Reply: Since there is currently no FDA-approved stem cell product for transplantation therapy for brain, no PI could possibly have the experience requested here. In fact, the PI is unique among academicians in that he has developed an FDA-approved product (the drug memantine/Namenda), giving him considerable regulatory expertise. Additionally, the Disease Team has a stem cell-based FDA regulatory expert (Dr. Alice Varga), who has also worked with other CIRM Disease Teams.

- Although reviewers were impressed by the quality of consultants engaged, it was unclear what role some of those identified would play in the project.
Reply: The role of each Consultant is given in great detail in Part A, pages 7-12 under "Role Description," where the role is described for every Consultant. In brief, clinical consultants advise on the clinical trial design and inform us about other concurrent stem cell trials for PD worldwide; hence, our Disease Team will be up-to-date on trial design.

- The intellectual property status and whether the applicant would have freedom to operate with the proposed cell line and/or the viral vector used was not fully addressed. . . this was not judged to be a barrier to the ability to conduct the proposed studies,
Reply: As we stated in the IP section, we already have issued patents for each step of our process, including for MEF2C, which will fully support product development.

- Reviewers did not find the histological data provided in response to the conditions of the Planning Award to be convincing ["showing robust neurite outgrowth (3-5 mm from graft, volumetric evaluation)"]. However, the GWG felt that condition had been addressed sufficiently to permit eligibility and scoring of the application.
Reply: In fact, Figs. 4D,G show the requested neurite outgrowth with actual measurements shown on panel D (representing ~3 mm of neurite outgrowth).

In summary, we have replied to each of the concerns of the reviewers, and ask the ICOC to fund the Team given the importance and timeliness of treating PD with a stem cell treatment.

Sincerely yours,

Amy M Peake

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

Amy Peake, Senior Director, Sponsored Research