MEMORANDUM

Date: October 14, 2010

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application TR2-01785

Enclosed is a petition letter from Dr. Havton of the University of California Los Angeles, an applicant for funding under RFA 10-01, CIRM Early Translational II Awards. This letter was received at CIRM on October 13, 2010 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

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October 13, 2010

Extraordinary Petition

TR2-01785 Repair of Conus Medullaris/Cauda Equina Injury using Human ES Cell-Derived Motor Neurons

Principal Investigator: Leif A. Havton, M.D., Ph.D.
Institution: University of California, Los Angeles

To the Chairman of the Independent Citizens Oversight Committee (ICOC) and the Chief Scientific Officer of CIRM

We wish to thank the reviewers for their kind and helpful comments on our project, which involves Leif A. Havton, M.D., Ph.D. (UCLA) (Principal investigator), and co-investigators Harley I. Kornblum, M.D., Ph.D. (UCLA) and Bennett Novitch, PhD (UCLA). The reviewers were very supportive of our disease target, experimental design, team of investigators, and outcome measures. However, the reviewers also expressed some concern about certain aspects of our proposal. Based on their feed-back, we would like to make some clarifications and provide an itemized response to the reviewers' comments. Please see below our response.

Comment #1 from Reviewers: "Reviewers agreed that this proposal addresses an important unmet medical need and could have significant impact on the patient population if successful. Further, the rationale for this approach was viewed as sound, since traumatic CM/CE injuries result in degeneration and death of both motor and autonomic neurons, making this condition a suitable target for stem cell replacement therapy".

Response #1 from Investigators: We thank the reviewers for recognizing that conus medullaris/cauda equina (CM/CE) forms of spinal cord injury represent an unmet need and that the rationale for our approach was sound. We agree that our proposal could have a significant impact for this underserved population of patients, if successful. Historically, very few investigations have aimed at developing new treatments for bladder dysfunction after spinal cord injury.

Comment #2 from Reviewers: "Reviewers found the experimental plan to be generally well designed, and they appreciated the solid electrophysiological outcome measurements for bladder function".

Response #2 from Investigators: We thank the reviewers for recognizing the design of our experimental plan and the value that our urodynamic studies provide for the proposed studies.

Comment #3 from Reviewers: "However, reviewers did not think the proposed experimental goals were achievable. In particular, reviewers were not convinced by the preliminary data that effective, anatomically accurate and topographically precise reinnervation could be achieved with the transplanted cells".

Response #3 from Investigators: For functional reinnervation of the lower urinary tract, we do not believe that a particularly high degree of topographically precise reinnervation will be required. Specifically, a functional bladder is in only one of two states at any one time, i.e. storage phase or elimination phase. Efferent motor and autonomic neurons innervating the lower urinary tract should either be active or not. It is an “on” or “off” function. The precise graded activation of, for instance, muscles controlling the hand for fine-tuned dexterity tasks would not likely be required for a functional micturition reflex to be restored after a CM/CE injury. We believe that our chosen model and experimental design is appropriate for early attempts of achieving functional peripheral target reinnervation using a stem cell therapy approach. In addition, the proximal location of the bladder and therefore relatively modest peripheral distances required for peripheral reinnervation also increase the likelihood for success.

Comment #4 from Reviewers: “The preliminary data suggested that the transplanted cells exerted a trophic effect rather than participating in direct reinnervation. Additionally, the data supporting survival and migration of neural precursor cells were not compelling, and reviewers felt that both activities would be necessary for reinnervation to be possible”.

Response #4 from Investigators: Our preliminary data did not demonstrate or claim a neuroprotective effect being provided by the transplanted stem cells. Instead, our submitted preliminary data showed that the reimplanted avulsed ventral roots had a neuroprotective effect, which doubled the survival of the transplanted stem cells/progenitors. As a cell therapy approach would need to be combined with also this surgical ventral root repair procedure, our preliminary data show an added advantageous feature provided by our treatment strategy.

Comment #5 from Reviewers: “Furthermore, the applicant did not address potential inhibitory effects of myelin on reinnervation, and alternate plans were not discussed in the event that the proposed immunosuppression regimen proved ineffective”.

Response #5 from Investigators: We are aware of the inhibitory effect of myelin after injury to the central nervous system. However, motor neurons are able to regenerate axons towards and into spinal cord scar tissue (Cullheim et al., Neuroscience, 1989; Lindå et al., J Comp Neurol, 1992). Furthermore, the avulsed ventral roots provide a growth promoting effect to regenerating spinal cord axons, presumably an effect from Schwann cells, and provide a local environment that is able to promote and support regeneration by motor axons (Hoang et al., Neuroscience, 2006, Hoang et al., J Neurosci, 2006). We are also aware of alternative protocols for immunosuppression. However, our current pharmacological approach to immunosuppression after cell transplantation has so far demonstrated to be successful. If our degree of immunosuppression in the future were to become less efficient, more aggressive dosing or switch to other agents are certainly feasible therapeutic options for our studies. In the original application, this was not discussed as an alternative plan, as we had not had problems to date with immunosuppression, and space limitation was a factor when preparing the application.

Comment #6 from Reviewers: “In addition to these critical concerns regarding the ability of the team to achieve the stated goals, reviewers expressed strong reservations about other aspects of the project's feasibility. Limited preliminary data demonstrating the ability of the research team to produce the therapeutic cell populations were included in the proposal. This deficiency raised serious doubts about production and purity of motor neurons. Additionally, data demonstrating the production of autonomic neurons were completely lacking”.

Response #6 from Investigators: We have published on the derivation of motor neurons from ES cells (Karumbayaram et al., Disease Models and Mechanisms, 2009, 2:189-95), using the HB9 reporter to identify the cells. In our studies of iPSC-derived motor neurons, we have shown that the cells are functionally active, and we have found that virtually all HB9 cells bear the characteristics of motor neurons after differentiation. Therefore, we feel that we have the technical expertise to scale up the procedure sufficiently. With respect to purity, we do not feel that 100% purity is an absolute requirement for the proposed initial feasibility studies. If

our early feasibility studies are successful, a high purity approach for motoneuron production will be applied.

With regards to the autonomic subtypes of motor neurons, there is certainly a great need in this research field to explore the conditions that may influence differentiation of embryonic stem cell-derived motor neurons to motoneuron and autonomic neuron subtypes. Recently, the Wichterle laboratory reported important progress in this direction (Peljto et al., Cell Stem Cell, 2010, 7: 355-366) with the description of conditions that resulted in a sympathetic motor neuron subtype. We may be able to capitalize on their recent advances and experience. We believe that our proposal in this regard is timely to address these understudied areas, in part because we have the tools to determine whether functional autonomic neurons may be differentiating in our CM/CE injury and repair model after cell transplantation. Specifically, urodynamic studies will be able to tell the difference between peripheral target reinnervation from autonomic (parasympathetic) connections using cystometry and from motoneuron innervation of skeletal muscle using external urethral sphincter muscle electromyography (EMG).

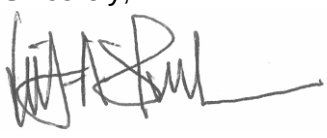
Comment #7 from Reviewers: "The reviewers praised the principal investigator (PI) and research team, calling them well suited to carry out the proposed research. The PI has extensive experience in SCI and is an expert in the motor and autonomic pathways associated with the CM/CE. The collaborators provided first-rate expertise in motor neuron and stem cell biology. There was some concern as to whether the team possessed adequate expertise in the field of cell therapy for the damaged spinal cord".

Response #7 from Investigators: We disagree with this latter assessment. While we have not yet published manuscripts as a team to document therapeutic efficacy of stem cells in spinal cord, our preliminary data demonstrate our ability to prepare and transplant both human and rodent derived stem cells/progenitors into the rat spinal cord Dr. Havton's laboratory has an extensive publication record from publishing studies on spinal cord repair using e.g. nerve root reimplantations, a procedure that was developed in Dr. Havton's lab for repair of lower urinary tract function after CM/CE injuries (Hoang et al., J Neuroscience, 2006; Hoang et al., Neuroscience 2006; Chang and Havton, Experimental Neurology, 2008). Dr. Havton also has over 5 years of experience from implanting cells into the spinal cord. Dr. Kornblum has published experience in neural stem cell grafting in the brain, in identifying and characterizing spinal cord stem cells (Kelly et al., PLoSONE, 2009), generating motor neurons in vitro (Karumbayaram et al., Stem Cells and Disease Models and Mechanisms, 2009) and Dr. Novitch is a recognized authority on spinal cord and motor neuron development (see e.g. Novitch et al., Neuron, 2001, Novitch et al., Neuron, 2003, Rousso et al. Neuron, 2008; Karumbayaram et al. Stem Cells, 2009). We feel that this team is, in fact, uniquely poised to succeed in these experiments. It is true that they may fail, but we feel that this will not be due to a technical inability to perform them.

We thank you for considering our comments. We hope that our responses are helpful in your review of this application, which addresses the needs of a truly underserved patient population.

Please do not hesitate to contact me if I may be of any additional assistance.

Sincerely,



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