



**MEMORANDUM**

**Date:** October 22, 2009

**From:** Alan Trounson, PhD  
CIRM President

**To:** Independent Citizen's Oversight Committee

**Subject:** Extraordinary Petition for Application DR1-01422

Enclosed is a letter from Dr. Aileen Anderson of the University of California Irvine, an applicant for funding under RFA 09-01, CIRM Disease Team Research Awards. This letter was received at CIRM at least five working days prior to the October ICOC meeting, and 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 the CIRM scientific staff.

The applicant highlights instances of possible factual inaccuracies regarding the proposed studies and also criticisms that are not directly relevant to filing an IND. Upon careful review, we find that many of the issues raised can be attributed to differences in scientific opinion where the reviewers found parts of the preliminary data inadequate, inconsistent or not compelling. For example, the applicant suggests that reviewers did not understand that only volumetric mock injections are proposed in the studies. In fact, reviewers understood that, but viewed it as a deficiency because the proposal did not include the development of the full delivery technique (cells plus immunosuppressant and the specific injection technique to be used in man). This point may have not been clearly made in the review summary, but reviewers felt this is critical for clinical translation.

The applicant also notes that the focus of the Disease Team RFA is simply to provide a clear mechanism for filing an IND. This is not entirely accurate as the RFA requested proposals that can not only achieve an IND filing in four years but also that provide a therapeutic strategy based on strong scientific rationale that will have a significant impact on disease and will offer an advantage over other therapies in practice or in the development pipeline. Thus, reviewer criticisms regarding the specific rationale of the approach and its expected outcome to patients are appropriate and justified. Ultimately, the panel was not convinced, despite noted merits of the proposal, that the applicant demonstrated a significant superiority of neural stem cells over fibroblast controls or vehicle controls in the preliminary data or that delivery of cells to the injury site would result in a significant benefit.



This response provides an overall assessment by CIRM staff, based on our careful review of each of the factual errors asserted by the applicant. A point-by-point response would require reference to confidential or proprietary information. CIRM staff is prepared to provide that at the ICOC meeting, should a member so request.

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

A copy of the CIRM Review Summary for this application is provided for reference.

# UNIVERSITY OF CALIFORNIA, IRVINE

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October 20, 2009

Re: Request for ICOC Extraordinary Petition  
DR1-01422  
CNS Derived Stem Cells for the Treatment of Thoracic and Cervical Spinal Cord Injury

Attention: Alan Trounson, Ph.D., President of the California Institute for Regenerative Medicine  
Robert Klein, Chair of the Governing Board of the California Institute for Regenerative Medicine  
California Institute for Regenerative Medicine  
210 King Street  
San Francisco, CA 94107

Cc: Dr. Gil Sambrano, California Institute for Regenerative Medicine

Dear Sirs,

Thank you very much for the review summaries for our submitted Disease Team application. We greatly appreciate the critical importance of the review process, and the value of the reviewers in maintaining scientific integrity and a high quality of funded work. Despite the best efforts of the review process it is of course the case that there can be differences of scientific opinion that influence the overall scores, however, in the case of the review of this particular proposal, the majority of the comments cited do not pertain to issues regarding possible differences in opinion, but rather significant factual inaccuracies or deviations from the RFA that are of fundamental concern.

Accordingly, I would like to respectfully request a formal review by the ICOC on the basis of an extraordinary petition to clarify the public record.

To set the record straight, I have identified those comments from the review that reflect factual inaccuracies. Moreover, I have also addressed several comments that may have been driven by deviations from the published RFA, as indicated in my responses. These are addressed in the order they are made in the critique summary to permit ease of review of the overall documents. Whether these points would have altered the final placement of this proposal relative to the others evaluated is of course difficult to determine, but the errors are numerous and substantial.

Thank you for your consideration of this request.

Sincerely,

A handwritten signature in cursive script that reads "Aileen J. Anderson".

Aileen Anderson, Ph.D.

## **Response to Review Points in Order of the Review Summary**

*Response in indented italics*

### **.....To prepare for entry into the clinic, the team will also develop cell delivery techniques in a relevant, immunocompetent spinal cord injury animal model.**

*This statement is derived from the reviewer's summary of the proposal. While not directly a part of the critique it reveals a serious inaccuracy in the reviewer(s) concept of the grant that again arises repeatedly in later critiques. Specifically, there is no proposal to develop a cell delivery method in injured immunocompetent non-human primates (the animal model referred to in this case). Mock injection volume studies were proposed for safety only, in accordance with previous experience with clinical neurotransplantation of these cells for two trials, one completed, and one ongoing, for other disease indications, as discussed in the text. It is clearly stated that the proposed model is for volumetric testing only – i.e., a mock surgery protocol - no cell transplantation is proposed and no injuries are proposed (p8, p17, Project 8). This is critical, because as noted below, the critique comments return to this issue several times. Specifically, the reviews later comment that “plans to extrapolate from immunodeficient models were insufficiently described”, and that “the PIs apparent lack of experience with the immunocompetent SCI model left reviewers uncertain”, but these issues are irrelevant given that immunocompetent SCI models were not proposed. Additionally, if efficacy in immunosuppressed or other models were an issue, this data is readily available to the reviewer in Table 1, which summarizes the efficacy data in four animal species/strains, including immunosuppressed immunocompetent C57BL/6 mice (this data is also described in p6 text under Efficacy).*

### **.....they questioned the underlying rationale that reversing demyelination will be sufficient to improve function in humans. Additionally, they felt that the applicant had not adequately considered the impact of other factors that inhibit SCI recovery such as glial scarring and soluble inhibitory factors.**

*This comment is not consistent with the goal of an IND filing which is the stated central purpose of the RFA. According to the RFA “The mission of these teams will be to conduct the necessary research and regulatory activities to prepare and file a complete, well supported IND with the FDA, to enable Phase I clinical testing.” As stated in the application on page 11, under Pre-Clinical Plan and Project Activities for Thoracic IND, the FDA has provided critical opinions regarding the steps necessary to enter clinical testing of the donor cell for spinal cord injury. Based on these interactions with the FDA, the pathway towards a successful IND filing is very well understood, particularly with regard to the animal platform for establishing preliminary efficacy. The data set preliminarily reviewed by ethics and regulatory bodies is described in detail in Table 1 Page 7 of the grant application. Locomotor efficacy, donor cell engraftment and predominant donor-cell differentiation to myelinating oligodendrocytes were sufficient endpoints for both the regulatory and ethical reviews, and the proposed efficacy and safety studies described in the grant application have incorporated specific recommendations based on these reviews.*

*While we agree that there may be multiple possible contributions of cell transplantation to recovery and alternative approaches for SCI, for this RFA, the goal was to focus on a clear mechanism for IND filing. The proposal and exploration of multiple mechanisms of action is not required for initial IND authorization and Phase I testing. Accordingly, given the interactions described above, remyelination was selected as one proposed mechanism to highlight for the IND application.*

### **.....In particular, the preliminary data do not demonstrate a correlation between engraftment and efficacy.**

*The statement that no correlation is demonstrated is factually incorrect. A linear correlation based on stereological determination of engraftment is explicitly described in*

the text of the proposal (p6) and referenced in our PLoS One paper (<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0005871>; Fig 11A).

**.....Furthermore, preliminary results revealed no statistically significant difference in the benefits derived from hCNS-SC as compared to fibroblasts in the in vivo SCI model. Reviewers suggested that a head to head comparison of autologous fibroblasts and hCNS-SC...**

*Not one but two head to head comparisons have been published (referenced in Table 1), and data from one of these studies is included in the ladder beam results shown on p6 of the application. A simple review of this figure shows that fibroblasts are not improved over controls, which is the salient question - only hCNS-SCs exhibit improvement. Fibroblasts simply don't show enough engraftment in the hostile environment of the cord - while the fibroblast engraftment is not discussed in depth due to lack of space (only hCNS-SC engraftment is), the reviewer(s) interpretation of this data is fundamentally inapplicable. Further, as noted above, efficacy for this cell population has been accepted (described in the application on p11). Given the scope of this particular RFA in focusing on IND submission, it is not for the reviewer(s) to select other possible cell populations that could be pursued in additional basic science research, but to focus on thoroughly reviewing the data presented regarding the clinical pursuit of the cell population in question.*

**.....confirmation that hCNS-SC would, indeed, myelinate demyelinated axons and more convincing efficacy data would strengthen the proposal.**

*This statement by the reviewer(s) is factually incorrect. Axonal myelination by hCNS-SCs is both explicitly described and shown on p7, and demonstrated in multiple models in Table 1. Moreover, as noted above, efficacy for this cell population has been accepted as described in the application on p11.*

**Reviewers also expressed concerns about the selected outcome measurements and a number of additional aspects of the project's feasibility. In particular, they considered the open field locomotor test to be insufficient as a functional measure and suggested that the applicant require efficacy in more demanding, species-appropriate, volition based functional tests.**

*This comment is factually incorrect. Open-field testing is only one of several tasks shown and proposed in the application. For thoracic, we show preliminary data in horizontal ladder beam (p6), discuss CatWalk data in the text, and reference all open-field and supplemental measurements in the Table 1 (p7). For thoracic, we expressly propose open-field, horizontal ladder beam, and CatWalk in the experimental design section, including power analyses (p13). For cervical, we show horizontal ladder beam model data and reference the cylinder model data (p9), and expressly propose cylinder, horizontal ladder beam, autonomic dysreflexia, and cortical imaging (p17).*

**.....From a safety perspective, concern was expressed that re-myelinated neurons could produce aberrant transmission and result in development of serious pain syndromes.**

*This comment ignores the existing extensive allodynia data summarized in Table 1, discussed on p8 (under the heading Allodynia), and the graphs of quantification of CGRP (pain fiber) connections shown on p8. In addition, and despite the lack of allodynia detected in any of the data shown, allodynia assessments were proposed in all studies in accordance with the safety testing anticipated for IND filing and the concerns noted. Hence, this comment is irrelevant to a salient review of the application.*

**.....Reviewers felt that the immunocompetent preclinical model studies were inadequately addressed, and plans to extrapolate from immunodeficient models were insufficiently described.**

*As noted above, it is clearly stated that the proposed ‘immunocompetent model’, as the reviewer(s) term it, is for volumetric testing only - specifically a mock surgery - no cell transplantation is proposed (p8, p17, Project 8), Accordingly, plans to extrapolate from immunodeficient models are irrelevant as no such studies involving injection of cells were included.*

**.....Description of the surgical cell delivery technique, a critical component for translating the program to the clinic, was lacking. Reviewers also found that contingency plans for problems that may arise were lacking, and this and other omissions led reviewers to question whether the applicant had sufficient experience to lead the translational effort.**

*Cell delivery technique is clearly addressed under Route (p3), specifically referencing one of the foremost clinical neurosurgeons in North America as a central facet of this program.*

*Further, the Disease Team RFA stated the following: “This program will support multidisciplinary teams staffed by professionals with diverse expertise. ....The team leader (Principal Investigator, PI) provides vision, strategy, and overall project direction, has scientific and financial accountability, and should be a practicing professional with a record of effective scientific leadership. In addition to these two key individuals, Disease Teams might include members with the following expertise, either as full time or advisory members: basic science, stem cell biology, .... the design and conduct of clinical trials. Team composition is likely to be dynamic, and staffing needs will evolve as projects progress toward the clinic. As projects move through development, basic researchers might decrease their involvement and translational experts or advisors (e.g. process development, regulatory and clinical trial design) would become more actively engaged.”*

*Accordingly, as clearly stated in the proposal, during year 2-4, co-PI ship transferred from a stem cell expert as Co-PI collaborator to a clinical neurosurgeon as Co-PI/collaborator, for the express purpose of providing a strong clinical translation link as a part of the Disease Team effort. Moreover, as stated, this clinical neurosurgeon Co-PI has led two previous FDA approved neurotransplantation INDs using this stem cell population. An appropriate review would follow the stated guidelines of the RFA in this context.*

**.....the PIs apparent lack of experience with the immunocompetent SCI model left reviewers uncertain...**

*Again, as noted for the summary statement, a lack of experience with non-human primate spinal cord injury models is irrelevant. An immunocompetent large animal model was proposed only for the purpose of mock surgical safety testing (n=4 non-human primates under the guidance of the three clinical neurosurgeons involved in the project), which is clearly stated in the proposal text as summarized above.*

**The team would benefit from the inclusion of a clinical neurosurgeon with neurotrauma and clinical trial expertise, a transplant surgeon familiar with immunosuppression and a clinical neurologist. The available resources and environment are excellent, as is the external advisory board.**

*Again, as noted above and as clearly stated in the proposal, during year 2-4, co-PI ship transfers from a stem cell expert as Co-PI collaborator to a clinical neurosurgeon as Co-PI/collaborator, for this express purpose. Moreover, the advisory board includes two of the most renowned neurosurgeons in North America as clinical consultants. An appropriate review would follow the stated guidelines of the RFA for inclusion of Co-PIs and advisory members in the Disease Team application for these roles.*

## REVIEW REPORT FOR CIRM RFA 09-01: DISEASE TEAM AWARDS I

**DR1-01422:** CNS Derived Stem Cells for the Treatment of Thoracic and Cervical Spinal Cord Injury

**Recommendation:** Not recommended for funding  
**First Year Funds Requested:** \$4,920,490

**Final Score:**  
**Total CIRM Funds Requested:** \$11,719,774

### **Public Abstract (provided by applicant)**

Spinal cord injury is a particularly debilitating form of trauma, in part because there is no current curative treatment. The unmet medical need in patients who have suffered paraplegia or quadriplegia has long been recognized as one that is in need of novel therapeutic approaches. Stem cell-based strategies may offer a broad regenerative platform that may address many aspects of the injury to the spinal cord and create opportunities to intervene long after the initial trauma. Spinal cord injury (SCI) affects a variety of neural cells, such as neurons and oligodendrocytes. The latter produce myelin, an insulating sheath that ensures normal conductivity. Therefore, an approach that offers the replacement and/or restoration of function to damaged cells holds much promise. Research has now shown that cell therapy may be capable of producing more than one effect in the injured spinal cord. The spectrum of benefits derived from this approach explains why this area is now a major research focus not only for SCI, but other neurological diseases as well.

Research with central nervous system stem cells derived from the human brain have demonstrated that these cells survive after transplantation, differentiate into neurons and oligodendrocytes, and most importantly improve neurological function in animal models of SCI. One of the first steps prior to testing a potential therapy in humans is to conduct animal experiments in models that reflect the human trauma as closely as possible. Therefore the primary goal of this research is to establish further evidence that the human central nervous system stem cell (HuCNS-SC) is safe when transplanted into the spinal cord, and that it also leads to a better recovery when compared to animals that did not receive transplantation. The research proposed will study the effects of HuCNS-SC cells in the setting of lower SCI (thoracic cord trauma that results in paraplegia) and upper SCI (cervical cord trauma that leads to quadriplegia) in animal models that will allow survival of the human cells. Effectiveness will be tested by measuring neurological function and determining the degree of improvement after transplantation of the human cells. Safety will be tested by closely examining the animals to show that there are no adverse reactions to the transplanted cells.

Investigating the effects of human central nervous system stem cells in these animal experiments will enable collection of data necessary to begin human clinical trials. The regenerative therapy potential represented by stem cells for patients with spinal cord injury has captured the imagination of scientists and patients alike. The opportunity to embark on this exciting field of research shows that new approaches are on the horizon and the field of cell therapy for spinal cord injury will be significantly advanced by the results obtained in this research program.

### **Statement of Benefit to California (provided by applicant)**

Spinal cord injury (SCI) causes a devastating condition; its effects vary depending on the level and degree of damage to the spinal cord. The trauma usually occurs at younger ages and results in a lifetime of paralysis which becomes associated with other medical complications and creates significant demands on the health care system. SCI is the second leading cause of paralysis in the US and it is currently estimated that there are approximately 1.3 million affected individuals. Although there are no official estimates, it is projected that there are more than 140,000 Californians living with SCI. In addition to the considerable personal burden placed on the individual and family, the economic impact of SCI is highly significant. The estimated costs related to loss of wages and health care for affected patients may be higher than 1.5 billion dollars annually for patients living in California. A therapy that can restore at least some spinal cord function has the potential for a significant improvement not only in the patient's quality-of-life, but also the shared costs of health care and loss of productive employment.

The use of stem cells, and in particular human central nervous system stem cells (hCNS-SC) , as therapeutics for SCI holds much promise for ailing patients. Most clinical investigations for SCI have focused on developing treatments that are aimed at very early time points after injury and have not been associated with major changes in outcome. This research will focus on developing an approach that will have broader applicability in terms of larger window of treatment after injury and include both upper and lower levels of spinal cord trauma. The development of a novel treatment that can address time points beyond the acute phase of trauma, and include thoracic as well as cervical levels, will more fully address the unmet medical need of the entire spectrum of patients with SCI. The range of potential benefit to patients includes improved sensory, motor, bowel/bladder, and even important reflex, or autonomic, function. A change in any one or combination of these deficits, if only for one or two spinal cord functional levels, could translate into improved quality-of-life for a patient.

The results of the research proposed will enable the regulatory approval and execution of clinical trials using hCNS-SCs to treat spinal cord injured patients. This research program will capitalize on the combination of a team of world-class scientists and clinicians in California that together can advance this field of endeavor. The outcome of the proposed studies will help not only those Californians with SCI, but will more globally pave the way for the use of stem cells in a variety of diseases. Additionally, our California-based effort will not only help individuals ailed by this state, but will also ensure that California ranks very highly in terms of SCI therapeutic advances and benefits from jobs created and retained.

### **Review Summary**

This proposal plans to develop human central nervous system stem cells (hCNS-SCs) to treat sub-acute to chronic spinal cord injury (SCI). hCNS-SC can differentiate into oligodendrocytes, astrocytes and neurons. The applicant proposes to transplant hCNS-SCs to injured spinal cords where they will differentiate into oligodendrocytes and re-myelinate axons spared by the spinal cord injury, promote their survival, and thereby restore neurological function. The team plans to perform preclinical studies to permit the filling of INDs for the treatment of both thoracic and cervical SCI within four years.

The applicant has established methods for the generation of clinical grade hCNS-SC; therefore, the preclinical development plan will focus on IND enabling safety and efficacy studies following hCNS-SC transplantation. The bulk of these studies will use immunologically-compromised rodent spinal cord injury models. The first series of experiments will address thoracic injuries. Long-term safety studies will evaluate histopathology in CNS and peripheral organs including tumor or cyst formation, tissue disruption and grafted cell fate up to nine months. Pharmacology/toxicology studies seek to determine behavioral improvements from the therapy at various times post injury and will also check for allodynia, an abnormal pain response to a non-painful stimulus. Following the refinement of the cervical injury model and development of outcome measures, a similar series of pharmacology and toxicology studies will be performed in a cervical injury model. To prepare for entry into the clinic, the team will also develop cell delivery techniques in a relevant, immunocompetent spinal cord injury animal model.

Spinal cord injuries result in devastating loss of function and quality of life. For acute injuries, early interventions have only limited success, while for chronic injuries; there are no effective treatments. If successful, the proposed treatment could have great impact and fill an unmet medical need. Reviewers also felt hCNS-SC to be an appropriate therapeutic cell type for SCI. However, they questioned the underlying rationale that reversing demyelination will be sufficient to improve function in humans. Additionally, they felt that the applicant had not adequately considered the impact of other factors that inhibit SCI recovery such as glial scarring and soluble inhibitory factors.

Reviewers appreciated the well-written proposal, its logical plan and the detailed description of most experiments. The ability to make clinical grade hCNS-SC and the teams' successful IND experience with these cells enhance feasibility of the proposed program. However, reviewers noted significant weaknesses in the feasibility based on both insufficient preliminary data and deficiencies of the selected in vivo models. In particular, the preliminary data do not demonstrate a correlation between engraftment and efficacy. Furthermore, preliminary results revealed no statistically significant difference in the benefits derived from hCNS-SC as compared to fibroblasts in the in vivo SCI model. Reviewers suggested that a head to head comparison of autologous fibroblasts and hCNS-SC, confirmation that

hCNS-SC would, indeed, myelinate demyelinated axons and more convincing efficacy data would strengthen the proposal.

Reviewers also expressed concerns about the selected outcome measurements and a number of additional aspects of the project's feasibility. In particular, they considered the open field locomotor test to be insufficient as a functional measure and suggested that the applicant require efficacy in more demanding, species-appropriate, volition based functional tests. From a safety perspective, concern was expressed that re-myelinated neurons could produce aberrant transmission and result in development of serious pain syndromes. Reviewers felt that the immunocompetent preclinical model studies were inadequately addressed, and plans to extrapolate from immunodeficient models were insufficiently described. Description of the surgical cell delivery technique, a critical component for translating the program to the clinic, was lacking. Reviewers also found that contingency plans for problems that may arise were lacking, and this and other omissions led reviewers to question whether the applicant had sufficient experience to lead the translational effort. Lastly, milestones and go/no-go decision points did not provide adequate quantitative success measurements.

Reviewers praised the PI's extensive publication record in the SCI field and expertise in SCI models and cell therapy. The team provided further SCI and stem cell therapy expertise. However, the PIs apparent lack of experience with the immunocompetent SCI model left reviewers uncertain whether the PI could supervise the entire program. The team would benefit from the inclusion of a clinical neurosurgeon with neurotrauma and clinical trial expertise, a transplant surgeon familiar with immunosuppression and a clinical neurologist. The available resources and environment are excellent, as is the external advisory board.

In summary, this is a proposal to use neural stem cells to treat spinal cord injuries. Strengths of the proposal include its focus on a significant medical need, the ability to produce clinical grade hCNS-SC, and an experienced research team. Major weaknesses include serious concerns about the project's feasibility and overall maturity. These factors led reviewers not to recommend this program for funding.

**The following scientific Grants Working Group members had a conflict of interest with this application:**

None.