MEMORANDUM

Date: July 20, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR2-05320

Enclosed is a petition letter from Dr. Clive Svendsen of Cedars Sinai Medical Center, an applicant for funding under RFA 10-05, CIRM Disease Team Therapy Development Research Awards. This letter was received at CIRM on July 18, 2012 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

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Jonathan Thomas, Ph.D., J.D. Chair Independent Citizens' Oversight Committee

Alan Trounson, Ph.D. President and Chief Scientific Officer, California Institute for Regenerative Medicine

July 19, 2012

Dear Dr. Thomas and Dr. Trounson,

We would like to submit an Extraordinary Petition to the Governing Board for our grant application DR2A-05320 "Human neural progenitors releasing GDNF for the treatment of ALS".

We appreciate the work of the reviewers and CIRM with regard to our Disease Team II application and were very encouraged to see that with our score of 64 we were right on the border for funding. Our goal is to deliver human neural progenitor cells (hNPC) that have been engineered to produce a powerful growth factor (GDNF) to a selected area of the lumbar spinal cord. We predict that the maturation of the cells into astrocytes will detoxify the area of the transplant, and the release of GDNF will further slow motor neuron degeneration. This is a very powerful rationale based on many published reports from groups around the world. It would be the first combined growth factor stem cell therapy for a neurological disease. We have responded to the reviewers concerns below.

Significance and Impact: The reviewers noted that the only therapy for ALS has limited efficacy and they agreed that this is a highly significant project that could have a "*ground-breaking impact on the treatment of ALS*".

Project Rationale: There was reviewer concern regarding the *therapeutic efficacy of GDNF, especially at late stages of disease.* We have previously shown significant effects of GDNF released from hNPC on neuronal survival even at end stage in models of Parkinson's disease, Huntington's disease and ALS (Ebert et al, Exp. Neurol, 2008; Ebert et al, Exp. Neurol 2010; Suzuki et al, Plos One, 2007). An additional concern was that this was *a focal therapy for a diffuse disease.* We agree, and have stressed that this is a targeted cell therapy for lower limbs to **gather direct evidence that progenitor cells releasing GDNF can slow degeneration and protect motor neurons in a single region of the spinal cord, perhaps including functional effects on leg strength**. If successful we would clearly be able to move to other crucial segments of the spinal cord that control other limbs and breathing. Indeed, the company Neuralstem has just received FDA approval to do a second stem cell transplant on an ALS patient who had previously received a similar transplant.

Therapeutic Development Readiness: The reviewers and program correctly point out that although the stem cells releasing growth factor have a powerful, reproducible effect with regard to protection of motor neurons both in vitro and in vivo (our main efficacy outcome), *this does not result in improved limb function (behavior).* This appears to be the major reason for our slightly lower score that moved us out of the approved funding zone. **We feel very strongly that this is a lack of understanding of the principles upon which our pre clinical data is based and provides the "extraordinary circumstance" that forms the foundation for this letter.** We stress in the grant that our pre clinical animal studies have a number of practical limitations

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common to many stem cell studies. In fact, I was recently invited to discuss these challenges at an FDA/NIH sponsored meeting in Washington.

Comment 1. No behavioral recovery. The first major challenge is the animal model itself that we used in our pre clinical studies. **Unfortunately, there is no animal model of sporadic ALS (the target patient group for this grant). The only rat model available represents a rare form of familial ALS and expresses massive amounts of mutant SOD1 protein in order to cause motor neuron loss.** While this model provides an environment where motor neurons degenerate and pull back from the muscle and may predict to some degree how the cells would behave in the human disease, it may have no relation to the sporadic disease. Remarkably, even in the face of massive SOD1 accumulation, we reliably saw over 90% protection of motor neurons just in the region of the transplant at mid stages of disease progression, and significant protection even at end stages of the disease. While these motor neurons disconnected from the muscle and lost function as the mutant SOD1 accumulated - they still survived. The stem cells also survived, migrated into this damaged area, intertwined with the dying motor neurons and were capable of surviving even at the very end stages of the disease and continued to deliver the therapeutic product GDNF (see Figure 1, right). This, to us, is the most important outcome of these pre clinical studies and provides the strong rationale for moving to sporadic patients.

The second major challenge is the limitation of using xenografts (human cells into animals) to predict clinical outcomes. We are using human neural progenitor cells that migrate well after transplantation but take up to 4 months to mature into the astrocytes that could further protect motor neurons (in addition to GDNF effects) and their projection to muscle. **Unfortunately the ALS rats die within 3 months of transplantation before the astrocytes have time to fully mature.** We predict that in patients the cells will have more time to mature into functional astrocytes before motor neuron death and hence have more powerful effects on motor neuron health and their connections to the muscle.

Comment 2. No comparison of immune suppression regime in animals and patients. Reviewer concern over our lack of immune suppression comparisons in our animal and human studies is confounded by the fact that the animal pre clinical studies are xenografts and the human studies are allografts. The FDA suggests that we do all animal pre clinical studies using our final product. But unfortunately there is no good way to predict immunological outcomes in humans with regard to rejection in a xenograft animal model. For this reason we suggested a standard immune suppression regime in patients similar to what is currently used for organ transplants. Using a rat to rat allogenic approach is one option, but rat and human neural progenitor cells behave so differently that the relevance to human studies is questionable. Newer humanized mouse models are also being developed. However, the size of the mouse spinal cord makes targeted injections of stem cells very challenging.

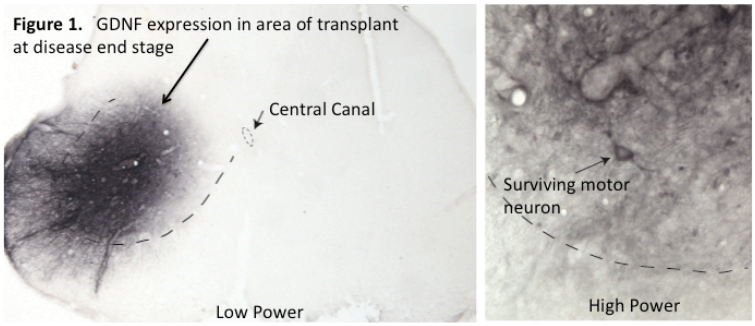

Figure 1. GDNF expression in area of transplant at disease end stage

Comment 3. Will GDNF expression down regulate? Concerns over long term expression from cells have been addressed previously by showing up to three months expression when the cells are transplanted into the brain of aged primates (Behrstock et al, Gene Therapy, 2006) or the rat model of ALS (Klein et al, Human Gene Therapy, 2005). New data collected since submission of the grant further confirm very robust expression of GDNF from hNPC around dying motor neurons at disease end stage (see Figure 1, left). In the proposal itself we will look at GDNF expression from the cells for 9 months in immune compromised rats.

Comment 4. No mention of cell tracking method in clinical trial. Our pre clinical studies using SPIO for tracking transplanted cells have go/no go milestones. If these are met we will include SPIO in the clinical protocol as per the optimized method. If they are not met we will not use a tracking method in the clinical trial.

Feasibility of the project plan: There was some reviewer concern that (i) *no allowance was made for a potential clinical hold, (ii) clinical site training was insufficient and (iii) there should be patient follow up for longer than 12 months.* In response, we wrote the grant with our best attempts at predicting time lines, and given all our experience and two previous meetings with FDA we do not expect a clinical hold. Of course if this happens we will have to adjust the final time line but it was impossible to write this into the grant without prior knowledge. We felt that we gave an extensive description of training at all sites and are not sure how much more we can add. Finally, primary care physicians will keep monitoring patient disease progression upon CIRM grant completion. However, we will also be applying for continued funding from CIRM and other agencies to extend this study further and perform more complex tests on these patients after the grant is finished.

Principle Investigator and Development Team: Deemed excellent.

Collaborations, Resources and Environment: The reviewers were concerned that there was *no description of intellectual property needed for product development*. We agree that our product has not been developed under a single IP umbrella. Rather it has developed from the science – that led us to the best cell combined with the best growth factor to treat ALS. The current IP landscape for stem cells and GDNF is complex. However, if our trial slows disease progression in the limb we target, we know that many stem cell companies and pharmaceutical companies will be extremely interested in discussing how to move this forward to a commercial product. We feel that at this early stage of development CIRM have a very important role to play in supporting the critical Phase I studies that will lead to commercial interest and development. Our other hope is that once the procedures are standardized, this type of cell therapy for ALS may rapidly become accepted as a specialized hospital (and insurance) based treatment for ALS in the same way that organ transplants are currently performed (without company involvement). Finally, the recent experience of Geron suggests there is a danger in companies becoming too involved at very early stages of pre clinical product development and these complex and expensive clinical trials. We suggest that an academic approach through state funding and Medical Centers that first shows safety and perhaps some Phase II positive results followed by company investment may be an alternative and sustainable model.

Final thoughts: **The case for studies in humans -** Overall, we are confident that we have an extremely strong rationale for moving forward into patients and would like to also mention that we have the full support of the ALS association for these studies (a separate letter has been submitted to CIRM by the ALS association). Furthermore, **we see spinal cord delivery of astrocytes releasing GDNF as a first important step in treating the disease.** Parallel studies in our laboratory and others are actively pursuing stem cell delivery of growth factors to the muscle as well as upper motor neurons that are also affected in ALS. Clearly future combined approaches such as these will enhance any potential effects. However, **the primary goal of the current proposal is to protect patient motor neurons and possibly preserve function. This would be an outstanding achievement and a major step forward for the field.**

We feel that the only way to really test promising therapies that have a strong rationale is to perform careful patient studies. We have designed a novel human stem cell trial that is blinded and powered not only to provide safety data, but also by using a unilateral approach we will be able to see if the cells combined with GDNF release are actually having a functional effect in human patients. Because the cells are releasing GDNF we will also be able to **locate them in patients at post mortem and assess motor neuron survival in the same area.** We agree with the reviewers that this is a diffuse disease and we are not attempting to cure it at this early stage. However, we cannot emphasize enough **how significant to the ALS world it would be to even show that stem cells releasing GDNF can protect motor neurons in a specific spinal cord region and/or delay disease progression in a single limb** which would then provide a clear path toward injections in different regions for a potentially curative effect.

Yours sincerely,

Clive Svendsen, PhD