**MEMORANDUM**

**Date:** July 18, 2012

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

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

**Subject:** Extraordinary Petition for Application DR2-05416

Enclosed is a petition letter from Dr. Alexandra Capela, Dr. Ann Tsukamoto, and Dr. Frank LaFerla of Stem Cells Inc. and University of California Irvine, 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.

We are submitting this extraordinary petition in support of DR2-05416, "Neuroprotection to Treat Alzheimer's: A New Paradigm using Human Central Nervous System Stem Cells," and request that the ICOC consider the following four points given the dire need for therapeutic options faced by the AD community:

**(i) Comments by the grants working group (GWG) were inconsistent with previous guidance provided by CIRM:** While we appreciate the GWG's thoughtful perspectives, a number of points made by the reviewers were inconsistent with previous guidance by CIRM for an Early Translational Grant (ETG) awarded to Dr. LaFerla and the Planning Grant (PG) to facilitate this DT application. Not only did we view this feedback as crucial for a successful DT application, but it greatly reinforced the direction of the planned research. Specifically,

**a. The GWG contradicted CIRM guidance regarding use of animal models**

GWG comments: *(i) Some reviewers commented that the use of only small animal models may not be predictive for humans considering the much smaller ratio of treatment area to brain in the human. (ii) Reviewers were not convinced that in the engrafted animals the level of formation of functional circuits and repair would be predictive of a therapeutic effect in humans. (iii) In general reviewers agreed the preclinical model was appropriate, however questioned how adequate this model would be to perform dose-ranging studies.*

The reviewers did not challenge the validity of the preclinical data submitted with the application, noting that the data showed *"improvements in context recognition and place recognition."* However, questioning the proposed models was contrary to earlier guidance from CIRM. CIRM reviewers acknowledged in the PG, for example, that *"the animal model of AD [used by applicants] has provided proof-of-concept efficacy data."* Similarly, in interactions concerning the ETG, CIRM clearly encouraged the use of small animal studies and de-emphasized large animals and non-human primates (NHPs).

STEM's three clinical trials authorized by the FDA involving neural stem cell transplantation, have all been based on preclinical efficacy and allometric scaling obtained only in small animal models. Similarly, the ongoing thoracic spinal cord injury study authorized by Swissmedic did not require large animal data. One trial in a neurodegenerative disease (PMD) produced evidence of clinical and radiological efficacy, and it is worth noting that this trial was solely based on small animal data. Therefore, the success of our translational approach should extend to advancing a cell therapy for AD.

We acknowledge that animal models, regardless of size, may have limitations for predictability and scaling, but these issues are not overcome with the use of larger animals (Braidy N et al, J Neural Transm 119, 2012) (Oliveira AA, Curr Alz Res 2, 2005). We understand the reviewers question regarding optimal dose calculation, but note that allometric scaling to humans from animals, regardless of size or species, is an accepted and reasonable metric in which to base first-in-human doses. Ultimately, dose escalation is best investigated in the human patient after demonstration of clinical safety. We are unaware of feasible large animal models relevant to AD and the use of NHPs poses significant ethical, financial and experimental challenges, particularly in the setting of human xenotransplantation. It is also unclear whether large animal (canines) or NHP studies increase human predictability or enhance dose scaling enough to offset the above challenges. Ironically, it is evident from our own extensive interaction with the FDA and Dr. LaFerla's exchanges with CIRM, that both agencies are de-emphasizing the use of NHPs. For these reasons, we proposed the replication of the preliminary efficacy results in two separate animal models as critical DT milestones, each with larger cohorts of animals, as well as completion of a dose finding study. The GWG conclusion regarding larger animal models is a departure from previous statements by CIRM and the position of the FDA.

**b. The GWG objected to a clinical approach that was already supported by the CIRM in a successful Early Translational Research Grant and the Planning Grant.**

GWG comments: *(i) A major weakness of this proposal was the lack of a rationale for how a localized injection of hNSCs could treat a diffuse neurological disease. (ii) The optimal location for transplantation of the hNSCs is not established. In the preclinical models the hippocampus area was investigated but no alternatives were discussed. While the applicant presents a good rationale for focusing on the hippocampus, at least one reviewer cautioned that this may be too restrictive of an approach.*

We understand that approaching a diffuse disorder with a localized, albeit bilateral, injection of cells could be interpreted as too restrictive. Highlighting the biological attributes of our cells, we made an effort to explain the scientific and clinical rationale in Sections 4 and 6 of the DT proposal, in which evidence of the migratory properties of the human neural stem cells in both the animal data (pg12) and from post-mortem analyses in human patients (pg15) was provided. Such biological attributes potentially allow a localized dosing of cells to spread and impact regions of the brain well beyond the initial injection site. Indeed, study results recently presented at the Alzheimer's Association International Conference 2012 (Press release link: http://investor.stemcellsinc.com/phoenix.zhtml?c=86230&p=irol-newsArticle&ID=1715297&highlight= ; Poster link http://www.stemcellsinc.com/LiteratureRetrieve.aspx?ID=142864 ) show that transplanting the cells into the hippocampus statistically increased memory in two different animal models relevant to AD. The researchers observed improved memory function and increased synaptic density post-transplantation and the results did not require reduction in beta amyloid burden or tau pathology. These results were discussed in the supporting data and graphically illustrated in Fig. 3 and 4 of the DT application.

CIRM has already documented support of localized injections as the clinical approach. For example, in the feedback of the PG, the reviewers commented *"the rationale for injecting NSCs into the brains of AD patients is reasonable"* and furthermore, *"if successful, NSC transplantation could have a very significant impact on AD therapy."* CIRM has also conveyed continued approval of this approach through the comments received by Dr. LaFerla in the ETG progress meetings, which further served as reassurance for the design of the DT application. Indeed, the focus of the ETG awarded to Dr. LaFerla by CIRM was to explore the potential of producing a cognitive benefit based on dosing of the hippocampus alone, and thus supporting the first clinical paradigm to be investigated in human patients. We were therefore very pleased that our efforts to develop a strategy involving transplantation into a critical location, i.e., the hippocampus, in two different animal models resulted in confirmation of behavioral and histological efficacy. Although a more widespread transplantation scheme in AD patients may have merit for future consideration, multiple transplantation sites is more appropriately entertained once safety and initial clinical proof-of-concept (POC) is achieved with select anatomic targets easily feasible to early clinical investigation. Given that the hippocampus is a pathological focus of AD, establishing clinical POC for hippocampal transplants should justify the risk of pursuing alternative routes, regimens, and sites of cell administration. In summary, the strategy of dosing select, but critical regions, of the brain in AD provides a safe, feasible and incremental approach to exploring neural stem cell transplantation in AD.Notably, some reviewers in GWG acknowledge that we have provided a "*good rationale for focusing on the hippocampus*", but this again seems inconsistent with the criticism concerning "localized injection" in the grant application. This critique of the DT application is inconsistent with the data presented and perspectives voiced by CIRM for the PG and ETG, all of which have stressed the same overall clinical strategy. **Citing the localized delivery as a major weakness in this DTG contradicts previous acceptance of this strategy by CIRM and constitutes a central reason for our appeal to the ICOC.**

**(ii) The GWG did not fully appreciate certain critical aspects within the DT application:**

GWG comment: *Reviewers were concerned about the commercial feasibility of the cell supply since each working cell bank will be sufficient for a very limited number of patients. It was not clear if this calculation took into consideration higher doses that might be required based on clinical trial dose-finding studies.*

Cell manufacturing is a dynamic process that can scale according to commercial needs as resources are added at each appropriate clinical stage. Even though we fail to understand why this point became a consideration in our DT proposal, the stated goal of which is to file an IND, we addressed this specific question in our response to the GWG *ad hoc* request for clarification and clearly stated that there was adequate capacity for an estimated total of 500 patient doses at the current manufacturing capability. Perhaps this explanation was overlooked both in the grant and our ad hoc response.

GWG comment: *Efficacy endpoints described for the clinical trial may be difficult to quantify which may make it difficult to assess preliminary efficacy readout.*

The Phase I/II study will have assessment of safety as the primary objective and assessment of efficacy as the secondary goal. We are pleased that the GWG acknowledged the credentials of our consultants who advised us on efficacy measures and noted that they are *"all excellent and of high-quality."* These consultants have participated in numerous AD trials and indicated that the efficacy endpoints in the protocol synopsis are very appropriate for this stage of clinical research and are being used in current clinical trials for AD (Cummings J et al, Dement Geriatr Cogn Disord 33, 2012) (Tuszynski MH et al, Nat Med 11, 2005) (Bernick C et al, Arch Neurol 69, 2012).

**(iii) Denial or significant delay of funding would have serious consequences to existing animal colonies:** Because AD is an age-related neurodegenerative disease, "appropriately aged" AD relevant mice are required in preclinical studies. Following favorable CIRM reviews on the PG, and to expedite completion of the proposed studies within the four-year funding period, two transgenic mouse colonies with large cohorts of selectively aged mice were generated. These very unique colonies cannot be preserved for future use and would need to be destroyed should this DT not be funded at this time. Re-establishment of these colonies would pose a costly and significant delay in scaling up any future studies in these AD models.

**(iv) Funding of clinical translation for AD is aligned with public health policy:** AD is a growing health crisis that threatens not only our state but the national healthcare system. The complete lack of disease modifying agents and recent late-stage failures of possible treatments, strongly argues in favor of funding the innovative approach offered by neural stem cell transplantation. We believe our application presents the ICOC with a compelling opportunity to advance a therapeutic approach for a disorder with significant unmet medical need, specifically: (i) the potential therapeutic has an established positive safety profile in multiple trials along with preliminary efficacy in at least one neurodegenerative condition (PMD) (no other applicant can point to such clinical success); (ii) the recently presented animal data establishes preclinical POC, i.e., improved memory in a two AD models independent of reduction in beta amyloid and tau; and (iii) the proposed study would represent a successful evolution of research previously funded by the CIRM into the clinic with the aim of treating this devastating disease.

Finally, we note that CIRM now has no other DT focused on Alzheimer's. Our team includes an internationally recognized investigator and a company that is responsible for four clinical trials. We ask that the ICOC reconsider its funding priorities and lead the exploration of stem cell transplantation in the most prevalent neurodegenerative disorder of our time. We hope the ICOC recognizes the depth and skill of our team and respectfully request that we be allowed to continue this important research along its current trajectory.