CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

MEMORANDUM

Date: October 17, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application SP1-06467

Enclosed is a petition letter from Dr. Robert Mays of Athersys, Inc, an applicant for funding under RFA 12-05, CIRM Strategic Partnership Awards. This letter was received at CIRM on October 16, 2012 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

Athersys' Extraordinary Petition for ICOC Consideration to fund Grant Submission SP-06467 to CIRM RFA 12-05: Strategic Partnership Awards.

We have reviewed the Grants Working Group Review Report (RR) for our application and believe that the criticisms raised can be addressed straightforwardly with information that may not have been adequately conveyed at the time or with new information that has since become available. We make this submission to provide such additional information and to petition the ICOC and CIRM staff to reconsider our application for funding.

1. "Significance and Impact" and "Risk / Benefit" Responses (refer to RR)

We believe there is "convincing data" that MultiStem administration can provide benefit to acute CNS injuries via immune modulation. Athersys and collaborators have demonstrated that MultiStem can have significant immunomodulatory effects in a variety of settings, as evidenced by previous publications referenced in the application on traumatic brain injury (TBI) (Walker at al. (2010)), and spinal cord injury (SCI) (Busch et al. 2011)). In addition, we have presented data at relevant conferences (2011 / 2012 Int'l Stroke Conferences (cited, data supplied in the application)), and at more recent conferences, showing the effect of our cells on immune activation in multiple sclerosis (MS) models and new data on SCI. We have direct evidence in multiple animal species and acute stroke models and in pre-clinical models of TBI, SCI and MS, that the IV administration of MultiStem results in a decrease in systemic immune activation and improves outcomes in cell-treated vs. placebo-treated animals.

Two recently published papers provide further substantiation for the benefit of our cell product. (1) Mora-Lee et al., "Therapeutic Effects of hMAPC and hMSC after Stroke in Mice," published in *PLOS One*, August 31st, 2012, demonstrated that transplantation of human MAPC into mice 2 days after stroke significantly decreased brain tissue loss, as determined by quantitative histopathology, and significantly decreased microglial activation in the peri-infarct regions of the cell-treated vs. PBS-treated animals. Other relative benefits for MAPC-treated animals included: increases in angiogenesis, decreases in glial scarring, increases in endogenous neural stem cell activation and endogeneous neuroblast survival. MAPC-treated animals also outperformed MSC-treated animals in each of these outcome measures. (2) Walker et al., "Intravenous MAPC therapy after traumatic brain injury: modulation of the resident microglial population," *J. Neuroinflammation*, e-published September 28, 2012, shows that the intravenous delivery of MAPC after cortical injury increases T regulatory cells in splenocytes and plasma with a related increase in the brain M2/M1 macrophage ratio, adding further evidence of spleen involvement in MAPC-mediated neuroprotection after acute CNS injury.

In line with our hypothesis, translational research from others in the field has increasingly focused on the role that peripheral immune organs (e.g., spleen) and the innate immune response play in secondary damage to at-risk brain tissue after acute CNS injury. (A) Gu et al., from the Gary Steinberg lab, published in *Stroke*, July, 2012, "Distinctive Effects of T Cell Subsets in Neuronal Injury Induced by Cocultured Splenocytes *In Vitro* and *In Vivo* Stroke in Mice", shows that T-cell subsets play critical roles in stroke-induced brain injury and that new stroke treatments may focus on minimizing Th1 (deleterious) cell response and increasing Th2 (beneficial) cell response. (B) Seifert et al. published in *J. of Neuroimmune Pharmacology* in October 2012, "A Transient Decrease in Spleen Size Following Stroke Corresponds to Splenocyte Release into Systemic Circulation," directly demonstrates that after ischemic brain injury, splenocytes enter into systemic circulation and migrate to the brain exacerbating neurodegeneration.

We believe that the risks of IV MultiStem administration to ischemic stroke patients are low and the potential benefits substantially outweigh the risks. As acknowledged in the RR, there have been few SAEs in on-going MultiStem clinical studies. Importantly, recent data from the first part of Athersys' ischemic stroke study confirmed that MultiStem is safe and well tolerated, and the independent safety committee authorized proceeding with high dose administration to patients for the remainder of the trial. While the clinical trial itself is intended to demonstrate proof-of-concept and significant clinical benefit, MultiStem's immunomodulatory and neurotrophic

properties, noted above, suggest that MultiStem cell therapy could provide substantial benefit to ischemic stroke victims. The proposed phase 2 trial is designed to demonstrate a meaningful clinical benefit, as measured by the percentage of moderate to moderate-severe stroke patients who achieve independent living (modified Ranking Score 0-2) following MultiStem cell therapy compared to placebo. This primary endpoint, and the targeted difference between MultiStem and placebo treatment, reflects the same outcome achieved in the tPA treatment trial, and would reflect a clinically meaningful outcome given the tPA trial results. Additionally, our proposed study evaluates other functional improvement measures intended to test our hypothesis.

2. "Design and Feasibility" Responses (Refer to RR)

The clinical study is being conducted in two parts: (1) a safety and dose escalation stage, consisting of two dose cohorts including low dose and placebo and high dose and placebo groups; and (2) a proof-of-concept of efficacy stage. Enrollment of part 1 has been completed, preliminary data has been reviewed, and the independent safety committee has authorized proceeding at the high dose level in part 2. The doses studied in part 1 were within the range of expected efficacy based on the preclinical studies, and a review of the blinded part 1 efficacy data provides a strong basis for establishing proof-of-concept in the 2nd part of the study. (Subsequent dose ranging studies, if desired, could be carried out in a subsequent Phase 2b study.) Part 2 activities are underway with re-initiation of enrollment planned to occur in Q4 2012.

Manufacturing for part 2 product requirements is also underway, utilizing our current manufacturing process and contract manufacturer. A portion of the clinical product for the study has already been produced and manufacturing will be completed in the near future, sufficient to allow us to complete the clinical trial as planned. We have substantial experience with scaled production of cell therapy for clinical use, and have manufactured cell therapy product at a greater scale than nearly any other competitive cell therapy company. To date, we have completed more than 50 production runs, manufacturing more than 400 billion cells. To clarify, manufactured product availability will neither be a constraint, nor a rate limiting factor for completion of the clinical study according to the proposed timeline.

In parallel with, but separate from the phase 2 clinical trial, we have proposed to conduct process development work to further optimize manufacturing to put the company in the best position to supply subsequent phase 3 studies and commercial demand. In short, the company intends to improve the manufacturing scale, product yields and manufacturing productivity, and reduce production costs. This work would be completed over the next 2-3 years, as the phase 2 study proceeds, and will allow for the implementation of changes and the characterization and regulatory work necessary to ensure consistent product performance. Once completed, the validated manufacturing process improvements would be included in our subsequent phase 3 studies ("CMC") and, with trial success and authorization, used for commercial manufacturing.

Improving product configuration (e.g., formulation) and manufacturing is not a trivial undertaking as noted in the RR. For instance, in addition to completing the development work, it will be important to ensure consistent product performance with the improvements implemented. We have already obtained feedback from the FDA with respect to ensuring product consistency and comparability. We are confident of the feasibility of the work because we have already made similar improvements for other clinical applications and manufacturing approaches. We have successfully reformulated the product for on-site use and catheter delivery in the treatment of acute myocardial infarction (heart attack), and have successfully transferred MultiStem product manufacturing to a hollow-fiber bioreactor format. In other words, we have substantial experience with validating and implementing improvements of the nature proposed. Since this work will take place in parallel with the phase 2 trial, there will be no impact on the timeline for completing the phase 2 study. Furthermore, since the work anticipates improvement before subsequent phase 3 trials, we have time to complete the goals of the project within the projected timeline.

As noted in the RR, we have put in place a straightforward phase 2 trial design with a focus on including a homogenous patient population. This reflects feedback from our clinical

investigators, including Dr. Steinberg, as well as feedback from the STAIR Group (Stroke Treatment Academic-Industry Roundtable), which has stated that many stroke trials may have suffered because of the heterogeneity of patient populations. We considered whether including patients receiving other treatment may introduce variability and complicate the design, but decided to include patients who have had tPA treatment or mechanical thrombectomy, and who have not responded to such treatment within 24 hours. Generally, patients respond or not to thrombolytics or thrombectomy within 24 hours, meaning that the stroke progression of the moderate/moderate-severe patients (NIHSS 8-20) included in our study should not be affected by these other treatments given that the patients with ≥4 point improvement in NIHSS in first 24 hours are excluded. Since our inclusion/exclusion criteria eliminate patients benefitted by anti-thrombotic therapies, we feel that non-responders should be included in the study.

The phase 2 trial is designed to demonstrate a meaningful clinical benefit, as measured by the percentage of moderate to moderate-severe stroke patients who achieve independent living (modified Ranking Score 0-2) following MultiStem cell therapy as compared to placebo. This primary endpoint, if achieved, would reflect a clinically meaningful outcome given the tPA experience, as noted above. The underlying targeted improvement used to power the study (10-12 absolute percent above the placebo percentage) represents a high improvement threshold – in other words a "stringent" test. The secondary endpoints will provide additional perspective on the impact of the MultiStem treatment on functional improvement, including functional outcome through range of mRS scores by shift analysis and the proportion of patients achieving mRS 0-1, NIHSS 0-1 and Barthel Index >=95 relative to placebo. While this latter test represents a "higher" functional threshold, MultiStem performance is measured relative to placebo.

An important milestone in the project has already been achieved, the completion of the dose determination part of the clinical study, with the next milestone being the completion of the phase 2 clinical study itself. Regarding process development, we have a number of milestones and decision points regarding the selection and implementation of specific process improvements.

3. "Principal Investigator (PI), Development Team and Leadership Plan" Responses

While the PI does not have clinical development experience beyond Phase 2, Athersys has an in-house development team including several employees with phase 3 clinical development experience, which would be utilized when Athersys moves the program forward into Phase 3 development. Nonetheless, we expect to continue to use third party contractors to assist on certain study aspects, including site management.

4. "Collaborations, Assets, Resources and Environment" Responses

As noted, manufacturing to complete the inventory for the Phase 2 clinical study is well underway utilizing our current process and contract manufacturer; and the capacity and resources are in place to complete manufacturing for this study. Given our previous process development experience and knowledge of our cell type and performance, we intend to manage the process development ourselves, utilizing third parties for specific components and the CMO for implementation of the improvements in the GMP setting. The CMO may do some optimization, but will be responsible principally for implementation, which it is well positioned to handle.

5. "Budget" Responses

We are conducting the phase 2 clinical study at many high volume clinical sites across the U.S., including in California. With respect to the process development work intended to support scaled-up / optimized manufacturing for subsequent phase 3 studies and commercialization, we plan to complete key elements of this work in California, with collaborators such as UC-Davis. We are in the process of building up our California beachhead, and plan that several California-based employees will manage the clinical study, as well as the process development work. Ultimately, success in the phase 2 clinical study and in the process development work would lead to the establishment of a manufacturing plant in California to support later stage development and commercialization in the western half of the U.S. and Asia.