MEMORANDUM

Date: July 18, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR2-05735

Enclosed is a petition letter from Dr. Linda Marban of Capricor, Inc, 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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To the Chairman of the ICOC and the President and Chief Scientific Officer of CIRM:

We hereby respectfully submit an extraordinary petition in reference to application **DR2A-05735 Allogeneic Cardiac-Derived Stem Cells for Patients Following a Myocardial Infarction**. Since the time of the review Capricor has made major advances in both our clinical development program and our management and operational team. We believe that had the reviewers had this information at the time of submission, the score may have been substantially increased. More than 1.3 million Americans suffer heart attack each year and this remains America's most deadly disease. Large heart attacks, even when survived, frequently lead to Congestive Heart Failure (CHF) due to death of muscle cells. The opportunity for CIRM to fund this Phase II clinical trial which is set to begin enrolling patients in early 2013 is an extraordinary opportunity to move a California based cardiac cell therapy product towards commercialization without delay.

Briefly, we would like to share with CIRM the strides we have taken since submission of this proposal:

1. Capricor has completed its pivotal pre-clinical study using CAP-1002. Results from this study were submitted to the FDA.
2. Capricor has FDA approval (IND 15118) to begin this trial immediately. The Phase I portion is funded by the NIH. Phase II should commence in early 2013. Funds from this application would be used to fund the Phase II.
3. Multiple endpoints will be assessed in this trial (ALLSTAR) to determine the best ones for Phase III. The primary endpoint will be infarct size. Ejection fraction will be evaluated as well as it is considered a standard biomarker of cardiac function. In terms of serving as a biomarker for a clinical endpoint, infarct size is considered by the FDA as good as ejection fraction.
4. The trial is no longer multi-national. It will be conducted at approximately 20 sites US, and therefore, the budget is adequate to fund the entire Phase II trial.
5. Capricor has expanded its management team to include (among others) Frank Litvack, M.D. as executive chairman of the board. His role is to to provide experienced operational leadership and to guide the company forward in a strategic manner.
6. Capricor has hired an experienced director of clinical operations and added two clinical operations FTEs to manage the execution of the trial. The CRO who will handle data management is United Biosource Corporation (UBC; http://www.unitedbiosource.com/) and the imaging core will be located at Johns Hopkins University.

The reason it is so important to fund Capricor in this funding cycle is that the clinical trial would have to be halted at the end of Phase I, artificially, until funds for Phase II are secured. As a small California start-up, Capricor does not have the ability to fund this trial without the support of CIRM. The delay in the trial would lead to a loss of momentum and slowing down the path of our ground-breaking therapy for the patients of California and the world.

The goal of our therapy is to regenerate heart muscle and prevent progression to CHF. CIRM previously provided funding for product development through a DT1 award. *In fact, this marks the first IND approval for a DT-supported product*. The Phase I trial CADUCEUS, which tested autologous CDCs showed that the cells were safe and pointed towards efficacy in that an imaging biomarker, infarct size, was decreased in all treated patients. Additionally, for the first time, CDC treated patients had an increase in viable myocardium, suggesting regeneration (the CADUCEUS trial, Makkar, The Lancet, 2012). When the review panel met, data was not yet available that we believe would have led to their recommending funding of Capricor's DT-2 application. ALLSTAR is designed as a Phase I/II clinical trial. The NIH is funding the Phase I portion, and Capricor is asking CIRM to fund the Phase II portion set to commence in Q1 2013. The NIH funding not only covers the cost of the Phase I (14 patients) but also covers the

establishment of the complete ALLSTAR database, programming, case report forms, standard operating procedures and biostatistical planning. This amounts to almost $2M. As such, the CIRM funding is highly leveraged by the NIH monies which are covering many of the upfront and start-up costs. In this case, safety in the Phase I portion is evaluated only one month after treatment, and the ALLSTAR protocol dictates that only Data Safety and Monitoring Board (DSMB) review is needed prior to initiating the next phase of study. *No further FDA consultation is necessary prior to initiating Phase II, pending a recommendation from the DSMB to proceed*. Following completion of the safety patients, the Phase II study, which is double-blinded and randomized will evaluate two cohorts of patients, both recent and chronic MI, to see if Capricor's cells reduce the size of the heart attack, which will likely lead to a better and longer life in patients.

The reviewers on the GWG, accepted the basic scientific premises of our program, liked the product and expressed optimism that CDCs should be further investigated in the clinical trial paradigm. Capricor would like the ICOC to consider the concerns expressed by the GWG and the subsequent remediation of these issues as a foundation for this extraordinary appeal. The main issues raised by GWG reviewers were:

1. The FDA status of the trial was unclear. The ALLSTAR IND was submitted on May 15, 2012 and received FDA approval on June 15, 2012.

2. The trial as presented was multinational in scope. The trial is now US only. Twenty high-volume, experienced centers will participate.

3. The primary endpoint of the trial, infarct size, is one that is not commonly accepted; the reviewers prefer ejection fraction (EF). Infarct size as measured by MRI (magnetic resonance imaging) is considered a better predictor of cardiac-related outcomes than EF. The literature over the past 5 years has described that in detail (Wu, E., J. T. Ortiz, et al. (2008). Heart 94(6): 730-736). That said, ALLSTAR will look at many relevant indicators of cardiac outcome as secondary endpoints (EF included). Infarct size is designated the primary endpoint in the Phase II study, and is one of several endpoints under evaluation that fall within the cardiac structure/function category, which also includes ejection fraction. When cardiac MRI is employed, as will be done in ALLSTAR, infarct size is far and away the best predictor of clinical outcomes (for instance, another MI or death) in an MI patient population. In this way, infarct size is not only a metric of efficacy, but also an indicator of safety. Capricor specifically selected infarct size as the endpoint because it improved significantly in CADUCEUS. Strategically, the most important part of a Phase II trial is to hit the designated primary endpoint which identifies the trial as successful. It is even more important when the selected endpoint is one that points towards a positive clinical outcome giving the FDA as well as investors the idea that this product could hit its designated Phase III clinical endpoint and actually help patients.

4. The reviewers were concerned that the endpoints evaluated during Phase II trial would not adequately support selection of Phase III endpoints: The ALLSTAR Phase II study will evaluate multiple endpoints, including those that fall within the categories of: global function, patient symptoms (e.g. quality-of-life), cardiac structure/function, and safety/clinical outcomes. These will be evaluated alone as well as in combination through a composite endpoint. A single composite endpoint is created from multiple other endpoints by predefining the weights and contributions of the other endpoints to a new, combined measurement. This is a well-accepted approach for studies reviewed by the FDA. The FDA likes a composite endpoint because, if predefined, it serves as a means to deal with and to accept a single endpoint

defined in advance. This helps control the statistical error associated with performing many statistical tests to find one that is significant by chance alone.

5. The trial should focus on the recent MI (myocardial infarction) patient population as the one that is most likely to hit the primary endpoint. The chronic population, while interesting, is not as likely to be effective. The company agrees with the reviewers that the recent MI population is the most likely to hit the primary endpoint. However, given that data from CADUCEUS suggested the product was as effective as far out as 1 year post-MI, Capricor developed a win-win strategy by adding the chronic population. Should only the recent MI group hit its endpoint, Capricor has answered a major question about the window of opportunity in treating MI, without "losing" on the trial. If both groups hit the endpoint, then the company has expanded its indication effectively without conducting a separate trial. If the chronic population hits its endpoint but the recent does not, the trial is still a success. We are confident that this trial design will improve the probability of success and potentially expand the number of patients who may benefit from our 'two shots on goal' approach.

6. The reviewers stated that the company should hire a CRO, and the PIs don't have sufficient experience running large clinical trials. Since the time of submission the company has recruited world class leaders to enhance its management team. The clinical trial will be managed by a highly experienced clinical operations team who will oversee independent and respected CROs. In April 2012, Dr. Frank Litvack agreed to become Executive Chairman of Capricor. Dr. Litvack brings significant managerial, administrative and clinical expertise to the Capricor management team with experience as an interventionalist running large clinical trials and success as CEO of a publicly traded medical device company. In addition, Capricor has selected two nationally-prominent Principal Investigators for ALLSTAR. Dr. Timothy Henry is Director of Research, Minneapolis Heart Institute Foundation and has served as national PI on more than 20 stem cell therapy trials. Dr. Rajendra Makkar is Associate Director of the Cedars-Sinai Heart Institute and an internationally-known clinical investigator. He was also the PI of the CADUCEUS trial. Dr. Anthony DeMaria has agreed to Chair the ALLSTAR Clinical Trial Executive Committee (CTEC). He is Professor of Medicine and the former Chair in Cardiology at UCSD and serves as Editor-in-Chief of the *Journal of the American College of Cardiology*. Dr. DeMaria has extensive experience in administration of large clinical trials.

In order to make sure that ALLSTAR is appropriately directed and managed, Capricor has contracted with two leading and highly regarded CROs, United Biosource Corporation (www.unitedbiosource.com) and Boston Biostatistical Research Foundation to provide the following services: data management and electronic data capture; serious adverse event data collection, coding, follow-up and narrative creation (UBC); statistical design, analysis and reporting (BBRF). Capricor has contracted with Johns Hopkins University as the MRI imaging core lab. Capricor has added several highly experienced and time tested managers in the Operations group responsible for execution of the trial. The CROs will be supervised by Capricor's newly minted clinical operations director, Ms. Frances Kivel, MS, who has been active in clinical program development and trial planning and execution both at large pharma (Pfizer) and in a relevant cell therapy company (Aastrom) for over 25 years.

Capricor respectfully asks CIRM to review the information contained herein and recognize that we have addressed all of the GWG's concerns. Capricor is proud to be a California company with the only stem cell product shown to regenerate the heart.

Submitted by: Linda Marbán, Ph.D., CEO, Capricor, Inc.