CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

M E M O R A N D U M

March 7, 2014

From: Gil Sambrano, Ph.D., Associate Director Review
To: Independent Citizens Oversight Committee (ICOC)
Subject: Consideration of RFA 13-01: Duane Roth Disease Team Therapy Development Awards III, Application DR3-07201

The ICOC considered the recommendations of the GWG for applications submitted in response to the Disease Team Therapy Development III RFA at its meeting held December 12, 2013. Consideration of application DR3-07201 by the ICOC was deferred due to the applicant filing an appeal request based on a conflict of interest allegation on the morning of December 12. The applicant alleged that the GWG review of the proposed project may have been "tainted" by the "perceived lack of objectivity" of one member of the GWG. There was no specific basis to support a financial, professional or personal conflict as defined in the GWG conflict of interest policy. Nevertheless, we examined what influence this reviewer may have had on the scoring and final recommendation of the proposal. We examined notes of the discussion taken by CIRM science officers at the review meeting, examined individual reviewer scores, and written critiques. We also presented the facts of this matter to the GWG review chair. Based on this examination, we found no evidence that the reviewer had any significant influence on the score or the recommendation. The reviewer was not an assigned reviewer and therefore did not contribute a written critique to the panel. Consistent with the recollection of the review chair and CIRM science officers in attendance, the discussion notes suggest that this reviewer did not provide any comment either in favor or against the proposal. The individual score given by the reviewer was very close to the mean score and thus did not contribute to the broad standard deviation. In summary, there is nothing specific or substantive to support a conflict of interest, including no evidence that the reviewer would gain financially, professionally, or personally through a negative review of this project. The appeal request was therefore denied.

The applicant also submitted a request for reconsideration based on material new information. Although the applicant provided some information that is new, it did not directly address the main concern of reviewers and therefore did not provide adequate grounds for reconsideration. The request was denied. Nevertheless, CIRM staff took an additional step of seeking the opinion of two new expert reviewers and the GWG chair to assess the proposal with the new information provided by the applicant. In general, the new expert reviewers raised many of the key concerns about the proposal as the original GWG reviewers and did not find the new information compelling. The experts felt that there were significant weaknesses in clinical trial design including a target population that

was too heterogeneous and as such would impair the ability to get useful data. The experts also felt that the preclinical data did not provide support for an effect on the proposed patient population as the preclinical model used was not representative of the condition existing in the targeted patients. Consistent with the GWG assessment, the additional expert reviewers advised that some evidence of efficacy (in addition to safety) from another trial currently evaluating this same product in a different subgroup of patients should be acquired to better inform the scope and design of trials with additional subgroups, such as that proposed in this application. CIRM staff believes that this new assessment, which considered the new information provided by the applicant, supports the original GWG recommendation to not fund the application.

REVIEW REPORT FOR CIRM RFA 13-01 DISEASE TEAM THERAPY III RESEARCH AWARDS

DR3-07201: DYNAMIC (Dilated cardiomYopathy iNtervention with Allogeneic MyocardIally-regenerative Cells) Trial: A randomized, double-blind, placebo-controlled Phase 1a/b multicenter study of allogeneic human cardiosphere-derived cells in patients with advanced heart failure

GWG Recommendation: Not Recommended for Funding
Final Score: --

Public Abstract (provided by applicant)

The proposed research will set out to demonstrate the safety and feasibility, in patients, of a novel treatment for heart failure based on heart-derived stem cells. The focus is on patients who have been diagnosed with a form of heart failure known as dilated cardiomyopathy (DCM). Currently, DCM is the most common type of heart failure, a disease which affects ~5 million Americans and which is one of the major causes of death and disability; it generally results from coronary atherosclerosis and multiple MIs, but can also be idiopathic in nature. The timing and course of the disease differs between individuals but ultimately the progression of disease leads to chronic heart failure. Medication and mechanical devices can be effective in slowing the progression of heart failure, but there is no known commercial therapy that can reverse the progression of the disease process. The heart remodels (i.e., dilates) to offset the loss of functional heart muscle. The remodeling process is ultimately maladaptive, with profound changes in cardiac structure and function as well as in the underlying molecular and cellular pathways. Conventional therapy relies largely on drugs that block secondary maladaptive signaling pathways; they slow the progression of heart failure, but do not reverse the disease. Once DCM becomes symptomatic, with shortness of breath and limited exercise capacity despite best current therapy, clinical outcomes are dismal. The one-year risk of death or hospitalization in such patients approximates 40%. Cell therapy has the potential to achieve myocardial regeneration and thus to improve, qualitatively, the prospects of these desperately ill patients.

We will perform the DYNAMIC Phase 1 trial of allogeneic cardiosphere-derived cells in patients with DCM. DYNAMIC will study 42 patients (14 controls and 28 cell-treated). Functional testing will include cardiac imaging by echo and PET/CT in order to gain extensive information about perfusion, structure and function and how they may respond to therapy. Clinical events data will also be collected so as to better power follow-on studies seeking to reduce death and hospitalization.

By the end of the project, we expect to have completed a clinical trial of a promising form of cell therapy in a highly-deserving patient population. The data collected will be vital in planning more advanced clinical studies that will determine, definitively, whether the treatment saves lives.

Statement of Benefit to California (provided by applicant)

Cardiomyopathy is a group of heart-related diseases that affects heart muscle. This research focuses on dilated cardiomyopathy, which is the most common form and is typically characterized by the progressive, usually irreversible enlargement of heart muscle. Dilated cardiomyopathy is common, accounting for more than half of the ~5 million cases of heart failure in the USA today. Currently, the only treatment for dilated cardiomyopathy is management through optimal medication and lifestyle changes. Management of the disease focuses on reducing the symptoms and slowing disease progression. There is no known cure for dilated cardiomyopathy nor has there been a proven strategy to stop its progression, or to reverse established disease. This research is aimed at using heart-derived cell therapy, the only known intervention, to date, that has been proven clinically effective in regenerating the human heart. If our research is successful, we may offer a cost-effective way to reduce the tremendous damage to Californians inflicted by this type of heart disease. This in turn may also reduce the economic burden presently borne by taxpayers who support the health care systems in California. In addition to the public health benefits, spinoff technology developed by this disease team will benefit existing California-based biotechnology companies, leading to fuller employment and an enhanced tax base.

Review Summary

This proposal is aimed at developing a treatment for a form of heart failure known as dilated cardiomyopathy (DCM). The applicant proposes to test the safety and feasibility of an allogeneic cell therapy based on cardiac-derived stem cells in patients with established DCM, by conducting a Phase 1a/2b clinical trial which would be completed within the grant award period. The proposed clinical trial would include monitoring of clinical events together with functional testing and cardiac imaging to gain information about cardiac perfusion, structure and function and potential response to the therapy.

Significance and Impact

- Although extremely well written, this proposal had a serious major flaw that significantly impacted the score. The major serious criticism and flaw stems from the fact that the applicant is currently evaluating the same cellular product in a Phase 1/2 trial in a different subgroup of cardiac patients. Since the objectives of the proposed and currently enrolling trials are similar, reviewers agreed that the proposed Phase 1 trial does not add value and should be re-evaluated after completion and analysis of data from the current trial.

- The economics of the proposed therapy for DCM was viewed as favorable given that this is an area of unmet medical need and of high patient care cost.

- The target indication as defined in the TPP is extremely broad and includes a heterogeneous patient population with very diverse etiologies and physiologies. Reviewers commented that the target population should be better defined.

Scientific Rationale and Risk/Benefit

- The high one-year mortality for the target patient population may support a favorable risk/benefit ratio for trial participation.

- Reviewers questioned the plausibility of a mechanism of action that would yield clinical benefit in the target indication. While there is reasonable expectation that the therapy will demonstrate short-term clinical benefit, the product was felt to be unlikely to result in reversal of fibrosis in the chronic fibrotic setting of DCM.

- Although the ongoing trial with the same product candidate is in a different subgroup of cardiac patients and with a different cell delivery method, it was strongly felt by the reviewers that the risk/benefit ratio for the proposed trial would be better assessed following examination of the outcomes from the current trial.

Therapeutic Development Readiness

- This product is already in an early phase clinical trial and, therefore, from that perspective has achieved a level of development readiness for the proposed trial.

- Regulatory issues (supported by preclinical data) were felt to have been sufficiently addressed in the IND filing.

Design and Feasibility

- There were several concerns raised about the trial design, such as the overly broad patient population, which reviewers believed would negatively impact whether meaningful information will be gained. The proposed composite endpoint was felt to be extremely optimistic for the proposed study size.

- The project milestones seem to adequately capture key activities that are reliable indicators of the project's progress. At points throughout the clinical development pathway, clearly defined go/no-go decisions are proposed. The Plan to end-of-phase-2 is reasonable and builds upon the experience gained in phase 1.

- The overall project plan is feasible and the proposed timeline appears to be realistic and achievable.

- The investigators have made a good effort to compute the probability of detecting adverse outcomes. However their estimates may be overly optimistic, given the small sample size.

Principal Investigator (PI), Development Team and Leadership Plan

- The PI and development team appear to be strong. They have a good track record of advancing clinical trials.

- Investigators are well trained with a great deal of scientific and clinical expertise making them well suited to lead the trial.

Budget

- Overall, the trial cost is high. Proposed patient care costs and CMC budget seem reasonable.

Collaborations, Assets, Resources and Environment

- The team is judged to be well positioned both with resources at their site and with external collaborators.

- It was unclear if safety would be handled by an external CRO. Reviewers commented that it is critically important for safety to be handled by an independent safety vendor with access to a validated safety database and robust safety data collection processes.