CALIFORNIA'S STEM CELL AGENCY

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

M E M O R A N D U M

May 5, 2014
From: Patricia Olson, Executive Director, Scientific Activities
To: Independent Citizens Oversight Committee (ICOC)
Subject: Review Summary and Staff Recommendation for ES1-05501 submitted under the Extraordinary Supplement program

---

The purpose of the CIRM Extraordinary Supplement Awards program is to provide a mechanism for those extraordinary opportunities when a CIRM-funded project might achieve a major new scientific or translational development if additional funding were made available. CIRM approved submission of a full application, ES1-05501. The requested funding and this specific supplement placed it in the category of a major supplement requiring Grants Working Group review and a funding decision by the Application Review Subcommittee. The review summary for this application accompanies this cover memo.

CIRM Staff Recommendation
In accordance with Section 7, Article V of the Bylaws of the Scientific and Medical Research Working Group and Section 6, Article VI of the Board's bylaws, both as amended on 3/19/13; the President and the scientific staff, following internal review and consideration, request that the Board consider the following:

Application #: ES1-05501
Type application: Extraordinary Supplement Award (Major)
Tier, Average Score: Tier 2, 73
Disease Target: Stress Urinary Incontinence (SUI)
Approach: Autologous skeletal muscle–derived stem cells
Requested Funding: $ 900,424

Points for Consideration:
- This proposal leverages team expertise and know-how gained in the parent project to address preclinical proof of concept for a second disease target where the number of engrafted cells required for disease modification is low.

- CIRM is currently funding one other project targeting this indication that uses an approach targeting smooth muscle cells, rather than skeletal muscle cells. As both muscle types are impacted in SUI and the contribution of each to the disease pathophysiology is unclear, this would enable a complementary approach.

Staff Recommendation: Fund.

ES1-05501: Local Delivery of Rejuvenated Old Muscle Stem Cells to Increase Strength in Aged Patients

Recommendation: Tier 2 **Final Score:** 73
Total Funds Requested: $900,424

REVIEW SUMMARY
The goal of this application for an Extraordinary Supplement to an existing CIRM award is to evaluate human skeletal muscle stem cells (MuSC) as a potential therapeutic for female Stress Urinary Incontinence (SUI). This proposal would build upon ongoing work to isolate and expand human MuSC for preclinical testing in another indication. The applicant proposes to fully characterize the SUI phenotype in a newly established immunodeficient rodent model of SUI (Aim 1), to test the ability of human MuSC to ameliorate incontinence in that model (Aim 2), and to evaluate methods of isolating human MuSC that will ultimately be compatible with clinical application (Aim 3).

Objective, Rationale and Responsiveness
- Stress Urinary Incontinence is a significant unmet need, as current treatments involving surgeries or injection of bulking agents do not have durable efficacy.

- SUI is well suited to autologous stem cell therapy and is an attractive indication for moving rapidly to a clinical test of the utility of human muscle stem cells. The SUI indication has the advantage that it will need only localized muscle recovery, in contrast to the original indication that might involve treatment of larger muscles.

- Some reviewers felt this project could be transformative and have a significant impact on the treatment of SUI, whereas others were not sure how different this approach is from other cell-based approaches that are being evaluated.

- Some reviewers thought that the proposed supplemental funding was a worthwhile investment, allowing a second indication to be explored with the same cells being developed in the original award, while others questioned the rationale for a supplement, suggesting that the original award could be refocused on SUI instead of on the originally proposed indication.

- If successful, this product might be applicable for other disease areas.

Feasibility and Design
- A major concern was the failure to include other cell types or bulking agents as comparators in the proof of concept studies presented in the preliminary data. It will be critical to compare this new therapeutic approach to approaches that already exist.

- It was pointed out that the preclinical model doesn't match the human condition, in which there is muscle and nerve damage, but not complete nerve transection. However, it was acknowledged that there is not a perfect animal model for SUI, and that many in the field do use this model.

- The progress toward milestones on the parent project is impressive and compelling.

- The preliminary data using the preclinical model are impressive, suggesting the competence of the investigators to use that model.

Team, Collaborations, Resources and Environment, Assets

- The PI is a long-standing leader in the field of muscle stem cell biology and has assembled an appropriate team of urologists and stem cell biologists.

- The available resources and surrounding environment are ideal.