CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

M E M O R A N D U M

August 24, 2012

From: Alan Trounson, President; Patricia Olson, Executive Director, Scientific Activities and the Early Translation team
To: Application Review Subcommittee, Independent Citizens Oversight Committee (ICOC)
Subject: Staff Recommendation re Tier 2 applications submitted under RFA 12-07, Early Translation Research Awards IV

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 would like the Application Review Subcommittee to consider the following.

Application #: TR4 -06666
Type application: Feasibility Award
Tier, Average Score: Tier 2, 70
Title: Human Pluripotent Stem Cell-Derived Photoreceptors for Retinal Degenerative Disorders
Disease Target: Retinal photoreceptor disorders such as retinitis pigmentosa and/or X-linked cone and cone/rod disease
Approach: Allogeneic; either hESC or iPSC-derived photoreceptors
Requested funding: $1,960,790

Points for Consideration:

- CIRM is/will be funding 2 similar approaches to address photoreceptor degenerative disorders so additional investment in an earlier stage project is harder to justify.
    - One approach (DR2A-05729) is an allogeneic approach using retinal progenitor cells derived from tissue stem cells. This project has a goal of IND filing and completion of a Phase 1/2a trial
    - The second approach, recommended by the GWG and up for decision today, is an allogeneic approach utilizing hESC-derived sheets of retinal progenitor cells and retinal epithelial cells. This project has a goal of identifying a development candidate

Staff Recommendation: Do not fund

Application #: TR4 -06823
Type application: Feasibility Award
Tier, Average Score: Tier 2, 69
Title: Beta-Globin Gene Correction of Sickle Cell Disease in Hematopoietic Stem Cells
Disease Target: Sickle Cell Disease
Approach: Autologous hematopoietic stem cells, genetically modified *ex vivo* to correct the mutation in the ß-globin gene
Requested funding: $1,815,308

Points for Consideration:

- Leverages team and know-how gained in a related project; is likely to enable a rapid path to clinic for a relatively low investment.
- Although CIRM is funding another more advanced project targeting sickle cell disease, the approaches are different. The other project is a gene addition of the fetal hemoglobin gene delivered by an integrating lentiviral vector; the approach proposed in this application corrects the mutated adult gene.
- The reviewer's concern about the degree of gene correction can be addressed further with the PI in the context of the milestones, if funded.
- While the project is leveraged by in-kind contribution of essential services, technology and expertise to the project, there is no recognition in the application (other than in the scientific proposal) of the key collaborator who is providing these essential in-kind services and technologies.

Staff Recommendation: Fund with condition (execution of a formalized agreement with key project collaborator to the satisfaction of CIRM staff)

Application #: TR4 -06831
Type application: Feasibility Award
Tier, Average Score: Tier 2, 66
Title: Gene therapy-corrected autologous hepatocyte-like cells from induced pluripotent stem cells for the treatment of pediatric single enzyme disorders
Disease Target: Urea cycle disorder
Approach: Autologous iPSC, genetically modified *ex vivo* to correct mutant enzyme gene, then differentiated to hepatocyte-like cells for transplantation
Requested funding: $1,801,629

Points for Consideration:

- A disease where percentage of engrafted corrected cells required for disease modification is low (~4%).

- CIRM has three projects currently in its translational portfolio. However, they target other liver diseases and seek to generate hepatocyte-like cells from different sources and by different approaches. Successful generation of hepatocyte-like cells would be important to the field. A very recent publication provides increased likelihood that functional liver cells may be developed from iPSC.

Staff Recommendation: Fund