M E M O R A N D U M

January 17, 2014

From: Alan Trounson, President; Patricia Olson, Executive Director, Scientific Activities; Michael Yaffe, Associate Director of Research and the Basic Biology Team
To: Application Review Subcommittee, Independent Citizens Oversight Committee (ICOC)
Subject: Staff Recommendations re Tier 2 applications submitted under RFA 13-02, Basic Biology Awards V

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 #: RB5-06935
Type application: Fundamental Mechanisms Award (Track 1)
Tier, Average Score: Tier 2, 71
Title: Misregulated Mitophagy in Parkinsonian Neurodegeneration.
Requested Funding: $ 1,174,943

Points for Consideration:
- The precise mechanisms linking mitochondrial dysfunction to neuronal death in Parkinson's Disease (PD) remain unclear. Reviewers differed in their opinions about the overall novelty of the proposed research, since it is based on findings that have already been described in animal models. However, the use of diseased human neurons, obtained from patient-derived induced pluripotent stem cells (iPSCs), allows, for the first time, the validation of these studies in a human model of the disease.

- CIRM is currently funding only 3 other iPSC-based PD modeling studies, 2 in the Early Translational portfolio, 1 in Basic Biology. Those studies do not address mitochondrial mechanisms.

- Since the PI, who does have a very good track record, is junior, and has no direct experience with dopaminergic neuron differentiation, CIRM will ensure, if funded, that a contributor mentioned in the application is committed to providing the required expertise.

Staff Recommendation: Fund.

Application #: RB5-07285
Type application: Fundamental Mechanisms Award (Track 1)
Tier, Average Score: Tier 2, 70
Title: A Novel Druggable Mechanism to Safeguard Stem Cell Genome
Requested Funding: $ 1,423,800

Points for Consideration:
- The ability to maintain a stable genome is highly desirable in cells intended for therapeutic applications, and a small molecule to ensure this would be significant. If successful, the findings from this effort might be transformative, i.e. could have broad impact in the field of regenerative medicine, with relevance for many different types of stem cell-derived populations considered for therapy development.

- The proposal addresses an RFA priority for Track 1 but is very high risk, as the preliminary observations from animal studies might not be relevant or reproducible in the human system. To mitigate this risk, CIRM staff will ensure, if funded, that a milestone be included such that the applicant must first demonstrate validity of his/her observations in the human system before expanding mechanistic explorations of these phenomena, as proposed.

Staff Recommendation: Fund.

Application #: RB5-07409
Type application: Fundamental Mechanisms Award (Track 1)
Tier, Average Score: Tier 2, 72
Title: Biophysical Determinants of Early Embryonic Stem Cell Fate Specification
Requested Funding: $1,186,500

Points for Consideration:
- This proposal represents a unique opportunity to investigate cell movements that are critical for early human development, utilizing human pluripotent stem cells (hPSC). There are no similar projects within CIRM's research portfolio.

- This is a high risk / high reward proposal. Risk will be managed, if funded, by implementing appropriate milestones and monitoring of progress toward generation of critical tools.

Staff Recommendation: Fund.

Application #: RB5-07414
Type of Application: Exploratory Concepts Award (Track 2)
Tier, Average Score: Tier 2, 67
Title: Directed Differentiation of Specialized Endothelial Cells
Requested Funding: $476,052

Points for Consideration:

- The application focuses on the differentiation of hESCs into endothelial cells, a critical cell type for regenerative medicine applications. In particular, there is a strong emphasis on specifying arterial subtypes, an important resource for creating vascular grafts. A successful outcome could have major impact on 1) our understanding of endothelial cell biology and angiogenesis and 2) our ability to generate critical endothelial subtypes for vascular therapy and treating disease.

- The proposal addresses two areas that are not represented strongly in CIRM's research portfolio: 1) specification of endothelial cell types from pluripotent stem cells; and 2) The role of cell mechanics/mechanotransduction in differentiation of stem cells.

- The applicant is a current CIRM grantee in the New Faculty II program, whose project to create a cardiac patch with hESC-derived cardiac cells, is nearing the end. This Basic Biology grant would allow the PI to capitalize on the initial investment CIRM has already made on the New Faculty award.

Staff Recommendation: Fund

Application #: RB5-07458
Type application: Exploratory Concepts Award (Track 2)
Tier, Average Score: Tier 2, 70
Title: Non-invasive Live Imaging of Stem Cell Signature Metabolic States
Requested Funding: $540,480

Points for Consideration:

- Development and use of single cell imaging techniques represent the cutting edge of the field, and are not well represented in CIRM's research portfolio.

- The applicant team has pioneered a unique imaging platform that enables single cells to be examined without the need for labeling or other forms of manipulation that can inadvertently impact cell behavior. This proposal tests whether this technique can be successfully applied towards investigating fundamental stem cell behaviors in ways that have not been previously possible.

- While the proposal addresses questions of basic research, a successful outcome could have transformative implications for both basic and translational science.

- Aim 3 focuses on the biology of intestinal stem cells, an area of research that is not well represented in CIRM's research and translational portfolios (2 New Faculty Awards, 1 SEED Grant).

Staff Recommendation: Fund

All Remaining Applications in Tier 2: No staff recommendation to fund.