CALIFORNIA'S STEM CELL AGENCY

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

**M E M O R A N D U M**

**July 15, 2014**
**From:** Patricia Olson, Executive Director, Scientific Activities
**To:** Independent Citizens Oversight Committee (ICOC)
**Subject:** ICOC Agenda Item #12: Review Summary and Staff Recommendation for BF1-01841 submitted under the bridging supplement program

---

The purpose of the CIRM Bridging Supplement Awards program is to accelerate development of stem cell therapies by providing a funding mechanism for the efficient and seamless advancement of promising CIRM-funded translational and development projects towards and through clinical development by "bridging" to further funding. CIRM approved submission of a full application, BF1-01841, for a supplement to a project funded under Early Translation II Awards (RFA 10-01). The application was reviewed and scored by external experts. The Application Review Subcommittee of the Independent Citizens Oversight Committee (ICOC) will make the funding decision based on peer review recommendation, any staff recommendation and a programmatic review by the ICOC. 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 members of the scientific team, following internal review and consideration, request that the Board consider the following:

**Application #:** BF1-01841
**Type application:** Bridging Supplement Award to a project funded under Early Translational II Awards (RFA 10-01)
**Tier, Average Score:** Tier 2, 72
**Disease Target**: Huntington's Disease (HD)
**Approach:** Allogeneic human embryonic stem cell-derived neural stem cells
**Requested Funding:** $ 505,717

**Points for Consideration:**

- Encouraging results achieved to date would be further strengthened by the proposed research that continues studies that further address the scientific and preclinical rationale for the proposed therapeutic development candidate and better position it to move into preclinical development.

- The proposed work includes administration of the target therapeutic into murine models of HD that have a protracted onset of neurodegenerative symptoms, more closely reflecting

the human disease progression. Use of these extended HD models will also allow the team to monitor whether the proposed candidate can provide lasting disease-modifying effects.

- CIRM is currently funding two other projects targeting this indication. One is in preclinical development and uses mesenchymal stem cells (MSC) expressing BDNF (brain-derived neurotrophic factor). The other project is a recently funded Early Translational Feasibility award to identify small molecules, using a screen based on iPSC-derived neurons from HD patients, that could correct the structure of mutant huntingtin protein and thereby potentially reverse its neurotoxicity. The approach proposed in this application for supplemental bridging funding could mediate disease-modifying activity through cell replacement and neurotropic effects and as such represents a complementary approach to modifying this devastating disease.

**Staff Recommendation:** Fund.

**BF1-01841, Tier 2 (Score 72)**
**Total Bridging Funding requested: $505,717**

**EXECUTIVE SUMMARY**
This application requests additional funding to complete studies initiated under a CIRM-funded Early Translational Research Award that had the goal of identifying a cellular therapeutic lead development candidate for addressing Huntington's disease (HD), a neurodegenerative disease for which disease-modifying treatments do not exist. The group has identified a hESC-derived neural stem cell line (hESC-NSC) that improves disease-like symptoms after transplantation in a rapid-onset murine HD model, and they can reliably produce the cells using translationally appropriate methods. The additional funds requested in this Bridging application will support long term studies in two slower onset models of HD, allow optimization of the dosing and administration protocols, and address mechanism of action to inform development of the preclinical and clinical development program. The applicant proposes to begin discussions with the FDA with a pre-pre IND meeting during the period covered by the Bridging Award.

**Objective, Significance and Impact**
- There is a great unmet medical need for disease modifying therapies for HD and, with no obvious competing treatment strategies on the immediate horizon, a successful neural transplantation therapy for HD would have major impact on the disease.

- Reviewers noted that this project is unique for its use of pluripotent hESC-derived cells; however, the TPP is poorly developed and focuses on preclinical data. It does not reflect the clinical goals and clinical safety criteria for the proposed therapeutic.

**Responsiveness**
- Reviewers agreed that the requested supplemental funding would provide the needed resources to continue ongoing work to further support the selection of the proposed candidate as a therapeutic development candidate for HD.

- The activities described in this application for supplemental funding were viewed as scientifically sound and falling within the scope of the parent award and the Early Translational award RFA.

- Reviewers stated that it was not clear from the application how the continuation of the project (towards a clinical trial) will be funded.

**Feasibility and Design**

- The scope of work proposed was viewed as well-defined and their plan for the requested duration of bridging funding support was thought to be appropriate to allow completion of proposed milestones that support the selection of the proposed candidate as a therapeutic development candidate for HD.

- Despite encountering a number of unexpected hurdles that caused delays in the identification and characterization of the therapeutic candidate, reviewers felt that the investigators implemented careful, logical activities to mediate these challenges and have made significant, encouraging progress towards the milestones of the parent award.

- Reviewers stressed that it will be important for the team to clarify the intended mechanisms through which a hESC-NSC transplantation may affect the HD clinical population so that a development plan may be properly tailored to address and validate those mechanisms.

- Reviewers assessed the requested supplemental Bridging funding as appropriate to support the research proposed, although they also noted that the balance between personnel and supply costs may need to be clarified with the applicant.

- While reviewers appreciated the value of examining performance of the therapeutic candidate in both a rapid onset disease model and a long-term disease model, some reviewers questioned the additional value of performing studies in two long-term disease models and extending the work to include transplantation into a second area of the brain.

**Team, Assets, Collaborations, Resources and Environment**

- Reviewers commented that this is a very well integrated, cooperative, highly productive, pioneering group of investigators in the field of HD research who have the resources and expertise to complete the proposed activities to further development of the therapeutic candidate. The requested supplemental funding will allow this team and its ongoing collaborations to remain intact.

- For further preclinical and clinical development of the therapeutic candidate, some reviewers thought that the team could benefit from additional expertise in the areas of stem cell science and brain repair.