CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

August 31, 2012

From: Ellen G. Feigal, M.D., Senior Vice President, Research and Development

To: Independent Citizens Oversight Committee (ICOC)

Re: Pre-read for Agenda Item #8, Additional Analysis recommendations, for discussion at ICOC on September 5, 2012

This pre-read for the ICOC is providing context for the September ICOC discussion on the Additional Analysis recommendations. The document provides a brief summary of the RFA 10-05 Disease Team Development (DTTD) Research Award, a recap of the DTTD approvals from the July 26, 2012 ICOC, a description of the Additional Analysis process, and recommendations from the Additional Analysis review for ICOC consideration at the September ICOC. We look forward to a productive discussion.

Background

The purpose of RFA-10-05 Disease Team Therapy Development Research Awards is to advance preclinical and/or early clinical development of stem cell-based therapies. The goal is to achieve, within the 4 year time frame: the submission to the FDA of a well supported IND for a clinical study and/or completion of a phase 1 or phase 1/2 clinical trial and/or the completion of a phase 2 clinical trial. The therapeutic approach must have been derived from or utilized hESCs, hiPSCs, neural stem cells, neural progenitor cells, or reprogrammed/genetically-modified stem cells; or a small molecule or biologic candidate characterized or generated using stem cells; or a candidate that targets cancer stem cells or endogenous stem cells in vivo; or is an engineered functional tissue candidate for transplantation.

The submitted applications had been reviewed by the Grants Working Group (GWG) based on the following criteria: significance and impact; project rationale; therapeutic development readiness; feasibility of the project plan; principal investigator and development team; collaborations, resources and environment, and any conditions reviewed that were set at the time of the review of planning awards.

The GWG included experts with experience in the following areas: Preclinical studies including preclinical toxicology/safety; chemistry manufacturing and control (CMC); disease/clinical; regulatory, and product development. All applications were evaluated and scored by the scientist members of the GWG, and then were assessed programmatically in a discussion led by the Co-Vice Chair of the GWG. Recommendations from the GWG were brought forward to the ICOC meeting on July 26, 2012.

At the July 26, 2012 ICOC Meeting

GWG recommended 6 proposals for funding for a budget up to $113 M, and 14 were not recommended for funding. The ICOC sought CIRM Management scientific advice on 9 applications, and they advised the ICOC that 2 proposals deserved additional consideration because of new data that potentially addressed some of the key concerns in the GWG recommendations.

The ICOC deliberations were based upon inputs received from the GWG, CIRM, and public comment. They voted to approve 8 proposals for funding (see Table 1), for a budget up to $151 M, and sent another 5 proposals (see Table 2) for Additional Analysis by a subset of the GWG. The Board directed the President and the Co-Vice Chair of the GWG to establish a process for the Additional Analysis. In consultation with the Chair of the ICOC and CIRM scientific staff, the President and the Co-Vice Chair determined that the additional analysis should be conducted by the Review Chair of the GWG, another scientific member of the review panel, and a patient advocate member of the GWG. The additional scientist reviewer was selected based on the expertise necessary to assess the new information. Each of the 3 individuals (chair, scientist, and patient advocate) voted on whether the information changed the funding recommendation by the GWG. A new score was not assigned.

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Table 1 July 2012 ICOC approved awards

App DR2A #	Score	Disease Area	Approach	Goal
05415	87	Huntington's Dis	Allogeneic gene-modif MSC	Phase 1/2 trial
05309	84	Melanoma	Autologous gene-modif HSC	Phase 1 trial
05302	80	Osteoporosis	Small molec	Phase 1 trial
05423	79	Critical Limb Ischemia	Allogeneic gene-modif MSC	Phase 1 trial
05736	79	Cervical spinal cord injury	Allogeneic hNSC	IND
05394	68	End stage heart failure	Allogeneic hESC derived cardiomyocytes	IND
05320	64*	ALS	Gene-modified fetal derive.NSC	Phase 1 trial
05365	53*	SCID	Monoclonal antibody	Phase 1 trial
*ICOC Moved to funding level				
Budget up to a total of $151 M				

Table 2 July 2012 ICOC referred these proposals for Additional Analysis

App DR2A#	Score	Disease Area	Approach	Goal	Budget $ in M
05416	61	Alzheimer's Dis	Fetal derived NSC	IND	20
05739		Retinitis Pigmentosa	Allogeneic hRPCs	Phase 1/2 trial	17.3
05426		Duchenne Musc Dys	Antisense oligonucleotide and small molecule	IND	20
05352		Breast cancer	Monoclonal antibody	Phase 1/2 trial	20
05735		Post MI heart failure	Allog cardiac-derived stem cells	Phase 2 trial	19.8

The Additional Analysis Process

The purpose of the additional analysis was to evaluate specific new information that became available after the GWG review and determine whether the information addressed some of the reviewers' key/primary concerns and would have impacted the overall recommendation by the GWG for funding the award. For each application, the information provided or referenced at the board meeting, and associated specific additional material were requested from the applicant. The new information was evaluated in all cases by the GWG Review Chair as well as one of the originally assigned reviewers and a patient advocate.

Each application was assessed independently and a teleconference was scheduled to discuss each one. The goal was to present results of the additional analysis at the September 5/6 ICOC meeting.

The following information was provided to reviewers for assessment. They also had access to the original application, review critique and extraordinary petition. Information in **bold** was the new material requested beyond what was provided in their extraordinary petition or the original application.

5426

1. Copy of petition
2. Sarepta (AVI Biopharma) press release regarding observed clinical benefit of antisense oligo
3. **Data supporting the claims of the press release (limit 5 pages)**

5735

1. Copy of petition
2. **Biosketches of new personnel including Frank Litvack, Timothy Henry, Rajendra Makkar, Anthony DeMaria and any key clinical personnel responsible for leadership and operations of the clinical trial**
3. **Description of the new US clinical trials sites including experience in conducting clinical trials and principal investigators (limit 2 pages)**
4. **Correspondence from the FDA acknowledging receipt of IND package, IND approval (including any caveats or comments from the FDA on the phase 1/II trial) and FDA comments related to requirements to continue to the phase II component of the trial**
5. **NIH IRB or PRIC approval of the phase I/II clinical trial and any caveats attached to it**
6. **Clinical protocol synopsis of the phase I/II clinical trial (limit 5 pages)**
7. **NIH summary statement and letter acknowledging approval of the grant, award amount, and the approved budget sheets for the phase I trial funding**
8. **Description of the CROs hired to conduct the clinical trial, including experience and qualifications**

5352

1. Copy of petition
2. **New data related to biomarker prevalence in the patient population targeted in the application. This information should describe the development stage of the biomarker, how it was validated or qualified, the methods used, and the specific patient population(s) to be tested and selected**
3. **Clarify on which of the clinical trials described in the application and which patient cohorts are to be supported by CIRM funds (limit 2 pages)**

5739

1. Copy of petition
2. Latest progress report for ET2 grant
3. **Bill of materials (raw materials used for ex vivo culture, source and qualification); flow chart of process with key control points described; tabulation of in-process and final product tests and**

specifications; batch analysis, including certificates of analysis and other data demonstrating the cells made are well characterized and function; a statement from the Head of Manufacturing and/or Quality Assurance from the manufacturing facility certifying that the cells are manufactured in compliance with GMP

5416

1. **Copy of manuscript submitted and accepted for publication related to migration of human neuronal stem cells in vivo**
2. **Copy of letter from the scientific journal that demonstrates acceptance of the manuscript for publication**

Recommendations

The reviewers assessed the specific new pieces of data provided to them, and evaluated whether this new information addressed the key concerns, and would have changed the GWG recommendations. The results are described below:

5735

Changed the GWG recommendations - Recommended for funding, with 2 conditions: 1) ensure the phase 1 component of the phase 1/2 clinical trial has demonstrated adequate safety before proceeding to the phase 2; and 2) investigators should focus the phase 2 component on patients with recent MI.

Reviewers were convinced by the achievement of key milestones since submission that the applicant had addressed key concerns about readiness to proceed to a phase 2 clinical trial e.g., applicant had filed and had an approved IND by the FDA; an NIH grant had been awarded to conduct the phase 1 component; applicant had hired experienced consultants and a contract research organization, limited their trial to the US rather than international, and had engaged the appropriate clinical leadership with defined roles and responsibilities. The reviewers asked CIRM to conduct a formal assessment after phase 1 to ensure safety before allowing the phase 2 component to proceed. The reviewers wanted the applicant to focus their phase 2 on the patient population with the strongest potential benefit - the patients with recent MI. Lack of benefit in this group would likely mean the patients with a longer time after MI would not respond. If recent MI patients benefited, then it would be logical to extend the study to the other group. In addition, CIRM was advised to ensure the revised budget appropriately covers the costs needed to complete the trial. The reviewers expressed a concern that the team may have underestimated their needs.

5739

Changed the GWG recommendations - Recommended for funding , with suggestion for a CIRM Management site visit.

The key concerns from the GWG had primarily been that the applicant was suggesting a two-pronged

approach for development of the therapy, starting first with a GTP level of manufacturing and then changing to GMP. Reviewers were convinced by the data they received that the manufacturing was at a GMP level of development. Reviewers suggested CIRM management do a site visit to gain more in depth details about the manufacturing and research project status.

5426

Modified GWG recommendation - Not recommended for funding as a Disease Team award; However, recommended the applicants be allowed to revise the proposal along the lines of an Early Translation award, with a reduced scope and budget (total budget up to $6 M), and that CIRM fund the revised proposal.

One of the key concerns from the GWG review had focused on the lack of any demonstrable clinical benefit at 24 weeks from the phase 2b trial of the single agent antisense oligonucleotide (AO) in patients with DMD, diminishing the rationale for a combination approach; another key concern had been on the interactions of the applicant with the company, as CIRM was being asked to pay for all of the manufacturing costs of the AO. The reviewers received information contained in the company sponsored press release at the 36 week mark of the phase 2b trial, showing a statistically significant benefit as measured by the 6 minute walk test, of the higher dose of single agent AO. Although promising, the reviewers expressed concern about the controls and methods of analysis (2 patients who rapidly progressed in their disease on the lower dose arm were not included in the analysis), and considered the data preliminary but not compelling. All reviewers felt the data were worthy of further investigation.

The company is proceeding with the single agent - AO - for the DMD indication. The applicant wants to develop a **combination product**, but the reviewers did not feel they had received any compelling preliminary data on dystrophin and whether the small molecule to be used in the combination with AO could increase the levels. The applicant noted the small molecule could potentially require less AO to get the same level of dystrophin. This was felt to be a potentially interesting economic rationale but were not convinced this would have any clinical impact. Another concern from the GWG review had been on the impact on the heart. The small molecule is skeletal muscle specific, but it was not felt to be a rate limiting point. The reviewers agreed that any benefit to respiratory function could have a good impact, and the cardiac concern would be a second order issue.

Overall, the reviewers agreed that the proposal was not ready for a disease team award, but they felt strongly that CIRM should invest in a revised proposal focused on further understanding the combination approach as a potential development candidate. The intent of funding a revised proposal at the level of an early translation award would be to ensure the scientific questions for the combination candidate are adequately addressed and that the applicants are able to get any business relationships appropriately aligned.

5352

Unchanged GWG recommendation - Not recommended for funding.

Key concerns from the GWG review had focused on the lack of compelling data of the approach on breast cancer CSC, lack of a biomarker and no data on the prevalence of activated Notch in the breast cancer population the applicants proposed to conduct the trial. The data sent described the utilization of a polyclonal antibody but no data on a monoclonal antibody. It is the monoclonal antibody that would be needed in a bioassay.

Three key problems were identified 1) preclinal data – are they able to inhibit breast CSCs? No new data was provided. The applicant showed five xenografts, with activity in 3 out of 5 models; 2) biomarker in patients – they still do not have a monoclonal antibody, and this is needed in a clinical assay to identify and select patients; and 3) remained concerned about how many patients would need to be screened to obtain a sufficient number to evaluate in a clinical trial. It was estimated that approximately 800 unselected breast cancer patients would need to be screened, based upon data provided by the applicant, and it was suspected it would take significantly longer to accrue and conduct a clinical trial than the applicant states. There is a need to clarify the budget – additional analysis estimated $5M but application states it is closer to $20M.

5416

Unchanged GWG recommendation - Not recommended for funding.

The key concern from the GWG review was that the applicant is using a local injection for a diffuse disease in the brain. The reviewers did not feel there was compelling data for neuron migration in the submitted manuscript. This is the manuscript specifically referenced at the ICOC meeting that prompted the call for Additional Analysis. The manuscript is not yet accepted, it is “potentially acceptable” but requires “major revisions” according to the Journal editor note. In addition, however, the studies in this manuscript used mouse NSCs, not the human NSCs proposed for the Disease Team award, and although there is some indication that pathology is affected at a distance from the injection site in one of the figures, this is a therapeutic gene-modified mouse NSC, so it is difficult to extrapolate to a non-gene modified human NSC.

Material that the applicant also provided, but was not requested included: a poster from an Alzheimer’s meeting in Vancouver 2012, with figures that were already contained and assessed in the grant application. In addition, the applicant provided unpublished data of 2 graphs and 1 figure, with the figure potentially relevant to the question of hNSC migration in the triple transgenic AD mouse brain, with the cells migrating at least to regions adjacent to the hippocampus and along white matter tracts bordering the hippocampus, but the figure shows only a tiny area of cortex, a site of widespread degeneration in AD, and it does not appear to have any labeled cells in this region. The additional confidential materials submitted to the reviewers were in different disease indications, and involved

different anatomic areas of delivery, and were not felt to be relevant to the disease proposed for study in this application, Alzheimer's Disease.

The reviewers agreed that most researchers will acknowledge NSCs can migrate in the mouse, but there are significant anatomic/spatial issues in moving from a small animal to a human. Can the cells migrate and form new circuitry over several cm? The reviewers felt there was much more plausibility for using these cells in a localized disease/injury, such as spinal cord injury, a more feasible volumetric issue.