CALIFORNIA'S STEM CELL AGENCY

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

M E M O R A N D U M

July 15, 2014

From: Ellen G. Feigal, MD., SVP Research and Development, and
Ingrid Caras, PhD., Senior Science Officer
To: Application Review Subcommittee, Independent Citizens Oversight Committee (ICOC)
Subject: Staff Recommendation for Tier 2 applications submitted under RFA 13-03, Strategic Partnership III (SPIII) Awards

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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 #: SP3A-07526
Type application: Strategic Partnership Award, Phase 2 clinical trial
Tier, Average Score: Tier 2, 74
Title: A Clinical Study of a Small Molecule that Preferentially Inhibits Cancer Stem Cells (CSCs) for Treatment of Women with High-Risk, Early Stage, Triple-Negative Breast Cancer (TNBC) as Neoadjuvant Therapy in Combination With Chemotherapy
Disease Target: A subtype of breast cancer termed Triple-Negative breast cancer
Approach: Small molecule targeting cancer stem cells
Requested funding: $ 9,891,332

Points for Consideration:

- Triple negative breast cancer (TNBC) is associated with worse outcomes than other subtypes of breast cancer and is not susceptible to the targeted therapies that already exist for other subtypes of breast cancer.
- The proposed therapeutic targets a specific population of cells within a tumor [termed cancer stem cells (CSC)] that is associated with poor clinical outcome in TNBC and is thought to be responsible for breast cancer progression and recurrence.
- The proposed clinical trial is designed to directly test the "cancer stem cell hypothesis" which postulates that eliminating the CSC could cure the disease.

- The therapeutic candidate is a small molecule and is therefore likely to have access to alternative funding sources.
- CIRM recently awarded three Disease Team III Awards to fund early clinical trials for novel therapeutics aimed at targeting cancer stem cells:
    - Disease Team DR3-06965 is developing an antibody therapeutic that blocks a "don't eat me" signal on cancer stem cells, enabling macrophages to phagocytose CSC. This project includes the conduct of two Phase 1 trials, one in solid tumors and one in acute myeloid leukemia (AML).
    - Disease Team DR3-07067 is developing a first-in-class cell division inhibitor targeting cancer stem cells in patients with advanced solid tumors, and is being funded by CIRM to conduct a Phase 1 clinical trial.
    - Disease Team DR3-06924 is developing an antibody therapeutic against a target highly expressed on the cell-surface of cancer stem cells in chronic lymphocytic leukemia (CLL), and is being funded by CIRM to conduct a phase 1/2 study in patients with CLL.

Request for Reconsideration: A request for reconsideration on the basis of submission of new information did not alter the GWG score and recommendation.

Staff Recommendation: Weaknesses in the scientific merit of the proposal combined with portfolio considerations led to a staff recommendation NOT to fund.

Translation Portfolio: Cancer Stem Cells

App #	RFA	Goal	Approach	Disease
DR3-07067 Slamon	DTIII	Phase 1 trial	Small Molecule inhibitor targeting CSC	Solid tumors
DR3-06965 Weissman	DTIII	Phase 1 trial	Antibody therapeutic targeting CSC	Solid tumors and acute myeloid leukemia (AML)
DR3-06924 Kipps	DTIII	Phase 1/2 trial	Antibody therapeutic targeting CSC	Chronic lymphocytic leukemia (CLL)
TR4-06867 Reiter	ET	Preclinical	Monoclonal antibody against N-cadherin positive CSC	Prostate cancer
TR2-01789 Jamieson	ET	Preclinical	Small molecule pan BCL-2 inhibitor targeting CSC	CML
TR2-01816 Müschen	ET	Preclinical	Small molecule inhibitor of BCL6 targeting CSC	AML, ALL