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

ORIGINAL REVIEW SUMMARY

From the May Board Meeting

REVIEW REPORT FOR CIRM RFA 13-03: STRATEGIC PARTNERSHIP III AWARDS

SP3A-07526: A Clinical Study of a Focal Adhesion Kinase (FAK) Inhibitor 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

Recommendation: Tier 2 **Final Score:** 74
Total Funds Requested: $9,891,332

PUBLIC ABSTRACT (provided by applicant)

Breast cancer is a global problem, with 1.3 million new cases diagnosed and 430,000 deaths each year worldwide. Breast cancer is generally segregated into subtypes based on the presence of three protein receptors - estrogen, progesterone and HER2. The subtype that lacks all three of these receptors is known as triple-negative breast cancer (TNBC) and comprises ~15% of all breast cancers. TNBC tends to grow faster, has a higher rate of metastases and limited treatment options. Furthermore, TNBC tends to recur more often than other subtypes of breast cancer. Patients with TNBC generally have a poorer prognosis and lower overall survival rate than patients with other types of breast cancer.

Surgery, radiation therapy, and combinations of conventional chemotherapy are often used to treat TNBC. However, these therapies carry significant side effects and frequently do not result in a durable clinical response. Over the last 10 years, multiple studies have shown that giving chemotherapy before surgery (so-called “neoadjuvant setting”) instead of after surgery can result in the same improved long-term outcomes (disease-free and overall survival), and has the potential to allow smaller, less invasive surgery. However, even when cancer treatments appear initially effective in shrinking tumors, highly resistant subpopulations of tumor cells called cancer stem cells often remain. These cancer stem cells can initiate new tumors, leading to disease recurrence. We believe that a key reason for the ultimate failure of many current therapies is the presence of these cancer stem cells. We are developing drugs targeting cancer stem cells that in combination with other cancer treatments can target all of the cells comprising a tumor and, thus, create a durable clinical response.

We have a cancer stem cell-targeting agent that acts through potent inhibition of the enzyme Focal Adhesion Kinase. Recent research has demonstrated that this pathway is critical for the growth and survival of cancer stem cells. While most anti-cancer agents increase the proportion of cancer stem cells, this compound reduces cancer stem cells and inhibits tumor growth and metastasis in models of TNBC. The agent is currently in multiple clinical trials and has been shown to be well tolerated when used in combination with the standard chemotherapeutic, paclitaxel.

This proposal seeks CIRM’s help in conducting a large multi-center clinical trial in TNBC of this novel therapeutic as neoadjuvant therapy in combination with standard chemotherapy. The hypothesis is that a cancer stem cell-targeting agent in combination with standard chemotherapy will eradicate both cancer stem cells and the bulk tumor cells. By addressing both cell populations, this dual targeting may lead to an improvement in meaningful clinical benefit such as increases in disease-free and overall survival. The proposed project has the distinct potential to revolutionize the treatment of TNBC and lead to better patient outcomes.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)
This project will benefit the state of California and its citizens in several significant ways. 180,000 women in the US are diagnosed each year with breast cancer and 25,000 of these diagnoses occur in California. We believe that cancer stem cells are an underlying cause of tumor resistance to chemotherapy, recurrence and ultimate disease progression. Through this study we aim to significantly improve the response to treatment by targeting the cancer stem cells in addition to the bulk tumor. If successful, this study would have a significant positive impact on the women afflicted with breast cancer and their families. In addition to the medical benefits of this project, funds from this grant will create and maintain high quality jobs in the state of California. Our company will spend significant resources in California on this CIRM project including 1) hire a CA-based Contract Research Organization for clinical trial management for the entire four year project; 2) utilize a California-based hub of a major US network of oncology clinical centers at least several clinical sites in California, 3) hire several consultants and employees expressly to support this project working from California. There will likely be additional benefits due to our increased collaboration, exposure and relationships in California. Our company is anxious to expedite multiple compounds through multiple clinical trials to attain FDA approval in as timely a manner as possible, and establishing a highly-functioning team is a key element in the regulatory process. The California-based team and support structures formed for this project may be utilized for additional non-CIRM projects in the future within California. If this study succeeds and this therapy is able to meaningfully improve clinical outcomes we will promptly proceed with the necessary further trials to get the treatment approved. A new therapeutic option may benefit Californians by extending and improving the lives of breast cancer patients. Improving outcomes in early stage breast cancer is far more likely to have an impact pharmacoeconomically (reduced burden on healthcare system due to reduced recurrence and minimized surgery) than treatments that target much later stage disease where there is a low probability for effective treatment or elimination of disease. This is particularly true in this proposal as women with early stage triple negative breast cancer tend to be diagnosed at a younger age and have a higher incidence of mortality. Our therapy could provide a dramatically improved outcome, significant reduction in the lifetime cost of treatment and increased productivity in the future.

REVIEW SUMMARY
The goal of this proposal is to complete a Phase 2 trial evaluating the addition of a small molecule candidate therapeutic to standard neoadjuvant chemotherapy in women with early stage triple negative breast cancer (TNBC). 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 candidate therapeutic is designed to target cancer stem cells (CSC) that are associated with poor clinical outcome in TNBC. The primary endpoint of the proposed trial will be an assessment of the ability of the therapeutic to reduce or eliminate CSC found at the time of surgery. Secondary endpoints in the trial will be pathological complete response (pCR), event free survival (EFS) and overall survival (OS), assessed over two years.

Significance and Impact
- If the applicant is successful in eliminating or decreasing cancer stem cells and that correlates with increased EFS and OS, this compound could be approved for TNBC relatively quickly.

- The primary drug target is not novel and at least one big pharmaceutical company has a competitive compound. However, the compound described in this application is distinguished by the fact that it also inhibits a second target expressed on cancer stem cells.

- There are other candidate therapeutics for TNBC being evaluated in clinical trials. The potential for superiority of this approach was not demonstrated.

Scientific Rationale and Risk/Benefit

- Most of the preclinical data presented in the application is for a different compound than that which is proposed for clinical trial. While there is some data indicating that the compound intended for the clinical trial targets CSC in vitro and is able to decrease the frequency of cancer initiating cells in vivo, the reviewers did not find the data to be compelling.

- The primary target of this compound is considered, within the field, to be a viable target for oncological indications.

- This compound has already been tested in patients for other indications, and appears to have a good safety profile, lowering the overall risk.

Therapeutic Development Readiness
- Manufacturing of tablets is well established since this compound has already been tested clinically.

- Plans for establishing distribution logistics are underway.

Design and Feasibility
- This compound has already been tested in Phase 1 clinical trials, so safety and dosing parameters have already been established.

- Some reviewers felt that the large number of clinical sites proposed for this trial (75) would pose a clinical operations challenge, especially since the clinical operations team will be newly formed for this trial. Other reviewers were less concerned, stating that the team members had good experience managing large trials.

- Reviewers were concerned about potential enrollment issues, citing the anticipated need for 75 sites to enroll 160 patients. The large number of sites planned is indicative of anticipated competition for patients from other clinical investigations.

Principal Investigator (PI), Development Team and Leadership Plan
- The team is excellent, with expertise in business development, research and trial design and execution. They have the relevant experience to execute their aggressive timelines.

Budget
- The proposed budget seems appropriate, well defined and well supported.

Collaborations, Assets, Resources and Environment
- The CRO retained for carrying out the trial is excellent and has the appropriate experience managing oncology trials.

- The applicant has the resources and intentions to carry out this trial regardless of whether CIRM provides funding. However, CIRM funding would accelerate the initiation of this trial.