CIRM STRATEGIC PARTNERSHIP III AWARDS – RFA 013-03

Tier 1 - Recommended for funding = ☐

Tier 2 - Moderate scientific quality or consensus on scientific merit cannot be reached, and may be suitable for programmatic consideration by the ICOC= ☐

Tier 3 - Not recommended for funding at this time = ☐

App #	TITLE	Score	Median	SD	Low	High	Budget	Tier
SP3-07536	A Phase I, Open-Label Study to Assess the Safety, Feasibility and Engraftment of Zinc Finger Nucleases (ZFN) CCR5 Modified Autologous CD34+ Hematopoietic Stem/Progenitor Cells with Escalating Doses of Busulfan in HIV-1 (R5) Infected Subjects with Suboptimal CD4 Levels on cART	**76**	80	7	65	85	$5,583,438	1
SP3-07552	A Phase I/IIa Dose Escalation Safety Study of [REDACTED] in Patients with Cervical Sensorimotor Complete Spinal Cord Injury	**76**	78	5	68	83	$14,323,318	1
SP3-07526	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	**74**	72	10	60	90	$9,891,332	2
SP3-07548	Multicenter Ph2b Trial of [REDACTED] for Dual Cord Blood Transplantation in Patients with Hematological Malignancy or Myelodysplastic Syndrome	**71**	74	5	62	75	$ 9,496,582	2
SP3-07559	Clinical Development of A Cell Therapy for Acute Adult Severe Traumatic Brain Injury	**68**	70	8	55	85	$9,800,000	2
SP3-07529	A Study of Allogeneic Mesenchymal Bone Marrow Cells in Subjects With ST Segment Elevation Myocardial Infarction (STEMI)	**--**	--	--	--	--	$9,348,792	3

M E M O R A N D U M

May 19, 2014

From: Ellen G. Feigal, MD., Senior Vice President, 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

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 are associated with poor clinical outcome in TNBC and are 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.

Staff Recommendation: Staff finds no compelling scientific or programmatic reason to recommend funding /Do not fund

Application #: SP3A-07548
Type application: Strategic Partnership Award, Phase 2 clinical trial
Tier, Average Score: Tier 2, 71
Title: Multicenter Phase 2b Trial of Pharmacologically Modified Cord Blood for Dual Cord Blood Transplantation in Patients with Hematological Malignancy or Myelodysplastic Syndrome
Disease Target: Blood cancers (Hematological Malignancy) requiring a stem cell transplant
Approach: Ex vivo modification of cord blood stem cells
Requested funding: $9,496,582

Points for Consideration:

- Cord blood has a number of advantages over other hematopoietic stem cell sources used for transplantation, but is hampered by delayed recovery.
- There are no other projects in the CIRM portfolio aimed at overcoming barriers to the use of cord blood for hematopoietic stem cell transplantation.
- The proposed project addresses a currently unmet need in the transplant field and the rationale for the approach is compelling.
- Complete data from an ongoing Phase 1 study and a final FDA-approved protocol for the proposed Phase 2 study were not available at the time of the review. This was reflected in the overall score.

Staff Recommendation: Do not fund

Application #: SP3A-07559
Type application: Strategic Partnership Award, Phase 2 clinical trial
Tier, Average Score: Tier 2, 68
Title: Clinical Development of Bone Marrow Derived Progenitor Cells for Acute Adult Severe Traumatic Brain Injury
Disease Target: Traumatic Brain Injury
Approach: Bone Marrow Derived Progenitor Cells
Requested funding: $ 9,800,000

Points for Consideration:

- The scientific rationale and supporting evidence to justify a clinical trial of the proposed approach in Traumatic Brain Injury are not strong.
- The proposed project is premature as key parameters such as the optimal timing to initiate treatment is still being evaluated.
- CIRM is funding an Early Translation project (TR2-01767) aimed at evaluating human embryonic stem cell-derived neural stem cells for use in Traumatic Brain Injury.

Staff Recommendation: Do not fund

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.

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

SP3A-07529: A Study of Allogeneic Mesenchymal Bone Marrow Cells in Subjects With ST Segment Elevation Myocardial Infarction (STEMI)

Recommendation: Not Recommended for Funding **Final Score:** --
Total Funds Requested: $9,348,792

PUBLIC ABSTRACT (provided by applicant)

The proposed project is to conduct a Phase IIa/b clinical trial under a collaborative agreement with pharmaceutical partner for the treatment of Acute Myocardial Infarction using allogeneic ischemic tolerant human mesenchymal stem cells. The proposed trial will be split into two parts, a Phase IIa and Phase IIb. The Company has already received an IND for the Phase IIa portion of the trial, which will commence before the disbursement of funds by CIRM, in Q4 2013. In Phase IIa 50 patients will be treated at 4 sites, and take approximately 2 years to complete. Following the completion of the Phase IIa portion of the trial, the Company will file for an expanded IND to proceed to the Phase IIb portion of the trial which will treat up to 100 patients and take approximately 2 years to complete. The budget for the project will be approximately $18.7 million over 4 years, $9.35 million to be provided by the Company and its collaborative partner and $9.35 million from CIRM.

The proposed therapeutic will advance treatment of AMI by allowing for a post-stent treatment option that may be able to improve the ejection fraction of a damaged heart, decrease the size of the scar resulting from AMI and, as a result, better long-term clinical outcomes. By conducting a Phase II clinical trial, assuming positive results, the Company will be able to move on to a pivotal Phase III trial which could lead to the eventual approval of ischemic tolerant mesenchymal stem cells as a market approved treatment option for post-stent AMI patients. An additional, non-surgical, non-invasive treatment option for AMI could lead to a decrease in the overall direct and indirect costs of AMI, as well as the possibility of a significant increase in quality of life for such patients.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

Our proposed clinical trial will have at least one clinical site in the State of California. This will provide an economic influx of at least five million USD ($5M) into the general state economy, whether through salaries, benefits, contractor services, etc. The full funding of this clinical trial will result in the hiring of up to five additional employees. Furthermore, the treatment is intended to improve quality of life for treated patients, increase economic activity by having an increased ability to perform societally useful work by patients who might otherwise receive disability or be unable to work.

Approximately six percent (6%) of California's population has some form of heart disease, making this project of great benefit to a large group of Californians. Additionally, the completion of a successful Phase II clinical trial for ischemic tolerant mesenchymal stem cells will vastly increase the market value of our company. It will also lead to a much larger Phase III clinical trial, funded by a large pharmaceutical company, most of which will be conducted in California. By providing data that shows the efficacy for MSC treatment of AMI, We stand ready to increase acceptance of California's nascent, but large, stem cell industry as a possible treatment for AMI, as well as other ischemic conditions. Having a definitive FDA approved Phase II clinical trial completed would further the goal of having an approved allogeneic stem cell treatment, which could very well lead to an economic boom in the California regenerative medicine industry in concert with leading regenerative medicine institutions California-wide.

REVIEW SUMMARY
This application describes development of a candidate allogeneic human mesenchymal stem cell (MSC) product for treatment of acute myocardial infarction (AMI). The proposal includes the manufacture of the MSC product, and Phase 2a and Phase 2b clinical trials to assess the safety and preliminary clinical efficacy of the cells.

Significance and Impact
- While there is unmet medical need for effective treatment after AMI, reviewers noted that this is a competitive area of development and other MSC-based therapeutics are under assessment in Phase 2 and Phase 3 clinical trials for AMI.

- The Target Product Profile (TPP) was not well developed and did not adequately reflect the increased availability of current interventional standard of care practices. Reviewers commented that the clinical endpoints and surrogate markers proposed in the TPP would not likely support initiation of Phase 3 clinical trials.

- Some reviewers thought that the intended route of administration could confer a competitive advantage over other cellular therapeutics currently under development for AMI.

Scientific Rationale and Risk/Benefit
- The intended clinical product has been delivered to patients and the applicants report that it has been well tolerated; reviewers interpreted this as suggestive of a manageable risk profile. However, given the results of similar clinical trials in AMI, reviewers also expressed a low expectation for impactful clinical benefit from the proposed therapy.

- The scientific rationale behind the product is reasonable and consistent with putative effects of other MSC-based therapeutics. However, insufficient data were presented to support the applicant's proposal that the candidate MSC product would have increased biological activity compared to other MSC products.

- Limited efficacy data with the intended product in cardiac indications were presented and appear to be unpublished.

Therapeutic Development Readiness
- The applicant has an IND in place to support initiation of the proposed Phase 2a clinical trial.

Design and Feasibility
- Reviewers predicted that enrollment challenges would make it highly unlikely that the proposed clinical studies could be completed within the 4-year project plan timeline.

- Reviewers expressed that the modest clinical efficacy criteria and surrogate markers proposed for the therapy would likely not be sufficient or provide approvable endpoints to support late stage development of the MSC product.

- Reviewers commented that the manufacturing plan was feasible, but noted that plans were not included for assay development and validation that would be required for further clinical development of the MSC product.

- Reviewers stated that insufficient data were presented in the application to allow an adequate assessment of the MSC product characterization.

- The clinical operations plans presented were minimal and lacked detailed risk mitigation strategies.

Principal Investigator (PI), Development Team and Leadership Plan
- Although the PI does not have a background in cardiovascular medicine, the leadership team has successfully brought their product into the clinic in a variety of therapeutic indications.

- The clinical investigators are well experienced in the area and the clinical teams appear qualified to conduct trials in the AMI patient population.

Budget
- Funding was requested for activities that, according to the presented project timeline, should be completed prior to the time that funding could be available under this RFA.

- The overall budget for the proposed clinical studies appears reasonable, but the reviewers questioned the requested funding for additional preclinical studies.

Collaborations, Assets, Resources and Environment
- Proposed clinical sites, contract services and collaborations appear appropriately qualified and able to provide necessary resources to support the described activities.

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

SP3A-07536: A Phase I, Open-Label Study to Assess the Safety, Feasibility and Engraftment of Zinc Finger Nucleases (ZFN) CCR5 Modified Autologous CD34+ Hematopoietic Stem/Progenitor Cells with Escalating Doses of Bulsulfan in HIV-1 (R5) Infected Subjects with Suboptimal CD4 Levels on cART

Recommendation: Recommended for Funding **Final Score:** 76
Total Funds Requested: $5,583,438

PUBLIC ABSTRACT (provided by applicant)

The HIV-1 virus enters cells by binding to a protein called CCR5 on the cell surface. A naturally occurring mutation in CCR5, CCR5d32, has been shown to provide protection from HIV-1 infection and AIDS. All individuals carry two copies of the CCR5 gene, and those with both copies of CCR5 mutated are highly resistant to infection with HIV-1. Those carrying one mutated copy can get infected by HIV-1, but have a delayed progression to AIDS. Media and scientific magazines have discussed widely the case of the “Berlin patient” who was cured of his HIV-1 infection after receiving therapy for his leukemia with a blood stem cell transplant from a donor whose cells had both copies of CCR5 mutated. Other HIV-1 infected patients have not been treated in this way since donors must be a near-perfect tissue match with the patient and also have the double CCR5 mutation, two rare events which almost never happen together.

To mimic the effect of the CCR5 double mutation, we propose to create blood stem cells that have a double mutation in the CCR5 gene and then test this gene therapy method in patients. The patients’ own blood stem cells will be treated in a process that can mutate the CCR5 gene, and then the stem cells will be transplanted back into the individual. These cells will carry the disrupted CCR5 gene and provide a renewable, long-lasting source of HIV-1 resistant immune cells. This novel strategy gets around the need to find a stem cell donor who carries the CCR5 double mutation and, since the stem cells come from the patient, there will be an ideal “perfect match”with no chance for rejection in the patient.

Results from mice transplanted with blood stem cells treated in this way have shown that the modified cells are functional and produce CCR5 mutant (HIV-1 resistant) progeny cells. When infected with HIV-1, these mice have reduced viral loads, and, importantly, the CCR5-disrupted CD4 cells have strong survival advantage. In the proposed clinical trial, HIV-1 infected patients with low levels of CD4 cells and no detectable HIV-1 while on antiviral medications will have their own blood stem cells modified at the CCR5 gene. Modified cells will then be re-infused into the patient after treatment with a chemotherapy agent, busulfan, which makes room for the stem cells to “take hold”in the marrow and generate an immune system with CCR5-mutant, HIV-1 resistant cells.

The applicant institution has worked with collaborating partners to develop this treatment method (a project funded by CIRM). They successfully developed this gene modification method up to the clinical testing phase. With combined expertise in stem cells, gene therapy, transplantation, treatment of HIV-related disease, this Strategic Partnership has the knowledge and skill to achieve all project goals.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

California has the second highest number of persons living with HIV-1/AIDS in the United States. By the end of 2008, there were 100,366 adults and adolescents reported to be living with HIV-1 or AIDS in California (Cf. Scheer S et al, The Open AIDS Journal, 2012, 6(Suppl 1):188). This incidence translates into a medical and fiscal burden larger than any other state, except New York. A study from 2011 reported that public funding accounted for approximately

$1.92 billion in HIV-1/AIDS services in California in the fiscal year 2008, of which the majority (90.4%) supported treatment (Cf. Leibowitz AA et al, J Acquir Immune Defic Syndr 2011;58:e11). In the fiscal year 2007-08, the California AIDS Drug Assistance Program (ADAP) served 32,842 clients and filled over 953,000 prescriptions for these clients. The Governor's current spending plan (2013-14 Budget Act) called for $448.4M to support this program, with sources coming from federal and California state funds.

With these huge costs and HIV-1/AIDS being a life-long infection that requires compliant daily treatment medication for a lifetime, the need for a cure that has the potential to reduce the duration of antiviral therapy is substantial. Most importantly, such a therapy would significantly impact the quality of life of persons with HIV-1/AIDS. If successful, a stem cell-based therapy, though expensive as a single treatment, would significantly reduce the cost burden on the state and federal treatment programs and save money over the lifetime of a patient. The estimated cost of lifelong cART therapy is estimated to be $420,000 -$755,000 USD, with 73% of the cost going to cART drugs (Cf. Sloan CE et al. AIDS 2012, 26, 45). Conversion to generic first line combination cART drugs is estimated to only reduce costs by ~ $42,000/patient (Cf. Walensky R.P et al. Ann Intern Med 2013, 158, 84). Furthermore, not all patients with HIV-1 infection fully respond to the therapy; in fact, about one fifth of patients have an inadequate immune response despite keeping the virus at undetectable levels. These patients are at increased risk of infection and chronic diseases, which also impact the health spending of California.

There is no treatment for such patients and, if successful, the cellular therapy derived from genetically modified blood stem cells proposed here would have a major impact on patient management and outcome. Success of this therapy would establish the safety of a possible future cure for HIV-1/AIDS. Added benefits are: 1) this stem cell-based gene therapy for HIV-1/AIDS will have a positive impact on the overall field of stem cell research with application to other diseases; 2) this demonstrates the progression of new technology supported by CIRM to the clinic, and 3) the technology was derived from California-based industry and success should have a positive economic impact in the state.

REVIEW SUMMARY

This proposal aims to develop a treatment for HIV/AIDS that has the potential to render patients' hematopoietic stem cells (HSCs) permanently resistant to HIV infection. The applicant proposes to use gene editing technology to disrupt the gene encoding a critical HIV co-receptor in patients' HSC. The hypothesis is that the gene-disrupted HSC and progeny cells, which include those cells normally susceptible to HIV infection, will become resistant to HIV infection. The proposed Phase 1 clinical trial will test the gene-edited HSC along with a conditioning regimen in HIV patients on combined antiretroviral therapy (cART) but with suboptimal immune response.

Significance and Impact

- If successful, this approach could have significant impact in that it could alter the course of HIV infection and minimize and potentially eliminate the need for life-long anti-viral chemotherapy with its associated toxicities.

- The Target Product Profile is well thought out and clear metrics have been proposed.

- The proposed approach is competitive with other therapeutic strategies.

Scientific Rationale and Risk/Benefit

- The scientific rationale is extremely strong and the applicant has provided persuasive preclinical evidence for the therapeutic approach.

- There were some concerns regarding the off-target effect of the gene editing technology.

Reviewers felt, however, that clinical data with this gene editing technology and the applicant's proposed risk mitigation strategies would support a favorable benefit/risk justification.

Therapeutic Development Readiness
- Preclinical studies have been completed under a CIRM Disease Team grant.

- The applicant has had extensive interaction with the FDA during the pre-pre- IND and Pre-IND meetings and has also completed Recombinant Advisory Committee (RAC) review.

Design and Feasibility
- Despite some concern about slow enrollment with the proposed target population, the project plan appears feasible and the applicant has articulated risk mitigation strategies.

- The overall plan for the manufacturing is well established given prior experience of the investigators with related cell processing. However, further development and validation of test methods for the release of key reagents for the manufacturing is needed.

- It was noted that the dose escalation design of the study is focused on the conditioning regimen but does not include dose optimization for the gene edited HSC. This issue may mandate an additional phase 2 study, once the conditioning regimen is optimized.

Principal Investigator (PI), Development Team and Leadership Plan
- The PI and team have a strong track record in conducting clinical trials in HIV/ AIDS. The team also has extensive experience in biomanufacturing for early stage clinical trials.

- The corporate collaborator provides valuable experience in the proposed gene editing technology.

Budget
- The overall budget for the proposed studies appears reasonable except for medical monitoring which was thought to be excessive.

Collaborations, Assets. Resources and Environment
- The clinical sites, collaborators, assets and environment are excellent.

- Collaborations are with leading experts in the field.

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

SP3A-07548: Multicenter Ph2b Trial of [REDACTED] for Dual Cord Blood Transplantation in Patients with Hematological Malignancy or Myelodysplastic Syndrome

Recommendation: Tier 2 **Final Score:** 71
Total Funds Requested: $ 9,496,582

PUBLIC ABSTRACT (provided by applicant)

We are a California corporation that has a broad platform technology applicable to all cell therapy and much of regenerative medicine. While other companies concentrate on developing a particular cell type for therapy (what we refer to as the "hardware") Our technology ensures that the cells go where they need to go once they are placed in the body (what we refer to as the "software"). Our product is an enzyme that is used to treat cells before they are placed in the body. The enzyme places a sugar on the surface of the cell that acts like a GPS signal to the body and directs the cells to sites of inflammation, ischemia or tissue damage. Our first clinical indication is for stem cell transplantation in patients with hematological malignancies. This uses adult stem cells obtained from umbilical cord blood. We have safety and preliminary efficacy data from 16 patients as part of an ongoing clinical trial. These results will be presented in December at the American Society for Hematology (ASH) meeting. The purpose of the current proposal is to extend these very promising results to a multicenter trial that includes California clinical sites. If we can repeat our current results in a randomized trial that includes multiple clinical sites then we will have a clinical proof of concept for our platform technology that will allow us to complete corporate partnership deals and launch additional trials for other cell types and disease states.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

The company has been operating in a virtual mode (i.e., operating primarily through subcontractors) in order to mitigate costs until it could begin clinical trials. The lead product is currently in an investigator-sponsored IND for stem cell transplantation in patients with hematological malignancies. This involves treating umbilical cord blood, an adult stem cell source, prior to infusing the cells into the patient. To date, 16 patients have been transplanted with treated cells and safety and strong preliminary data on efficacy have been obtained. The intent of the current proposal is to start a multi-center trial that will include clinical sites in California, one of which has already been recruited.

The potential benefits to the State are both health-related and economic. According to the American Cancer Society, in 2013 there are estimated to be 5,210 cases of leukemia, 7,280 cases of non-Hodgkin's lymphoma, 2,270 cases of myeloma and 990 cases of Hodgkin's lymphoma in California. Our technology has the potential to make stem cell transplants safer and more effective for these patients. Further, if we can confirm our current clinical efficacy data in a multicenter trial, we will have established proof of concept for our technology. This will allow for rapid follow on trials for a variety of cell types and disease states for which we currently have preclinical data. This will allow the company to transit from its virtual mode to a mid-size biopharma company, providing jobs and economic benefit to California.

Approval of our lead compound for stem cell transplantation will allow us to complete deals with major pharmaceutical companies, to grow and expand its technologies, and to extend its relationships with major clinical sites as it matures into an independent biopharma company located in the State of California.

REVIEW SUMMARY

Allogeneic hematopoietic stem cell transplant (HSCT) is a treatment strategy for restoring normal hematopoietic function in patients with select hematologic malignancies after high dose chemotherapy. Umbilical cord blood (UCB) as a source of hematopoietic stem cells (HSC) has a number of advantages compared to other stem cell sources but is hampered by the low cell dose, which results in slower engraftment and an elevated risk of engraftment failure. The objective of this proposal is to further clinical development of a technology to improve engraftment of HSC obtained from umbilical cord blood, for use in patients with hematological malignancies requiring a stem cell transplant. The proposed approach involves ex vivo enzymatic modification of the stem cells prior to transplantation to enhance homing to bone marrow, with the goal of enhancing engraftment and overcoming the reduced time to recovery typically observed with cord blood transplants.

The applicant proposes to conduct a Phase 2b, randomized, multicenter study of the safety and efficacy of the approach in patients with hematologic malignancies or myelodysplastic syndromes receiving dual cord blood transplants. Project-related activities will include production of sufficient quantities of product to complete the multicenter trial.

Significance and Impact

- It would be a significant advancement if cord blood could be used with greater assurance of engraftment; if the delayed HSC engraftment associated with UCB could be overcome; UCB could become the preferred source for HSCT.

- While some reviewers thought that the effect of the proposed approach would be incremental, others disagreed, arguing that any significant improvement in time to engraftment would be clinically meaningful and would be a notable advancement in the field, arguing even that the proposed approach could have a “game-changing” impact on the transplant field and could change the practice of medicine.

- This is a novel approach and it is reasonable to move forward although there are other competing approaches under development.

- The advantage of the proposed technology over other technologies in development is that the other approaches require unique central processing capabilities whereas the proposed technology is very straight forward, practical, and useable.

- The anticipated effects on engraftment could translate into improved patient survival and reduced hospital stay, potentially leading to reduced costs and improved quality of life.

- The TPP is not well done and does not clearly delineate the optimal from minimal product attributes.

- The application of this technology within the continuum of care was viewed as a strength of the approach.

Scientific Rationale and Risk/Benefit

- Strong scientific rationale and a favorable benefit/risk ratio for this stage of development have been adequately demonstrated.

- Data from appropriate and well-designed preclinical proof of concept studies provide a convincing scientific rationale for the approach and for development of the product.

- Preliminary clinical data suggest that the product is safe and may be efficacious. However, key information was missing from the application, which impacted interpretation of the Phase 1/2a data.

Therapeutic Development Readiness
- The IND has received FDA clearance and an initial Phase 1/2a trial is ongoing.

- The FDA has not yet provided feedback regarding the acceptability of the proposed Phase 2 trial.

Design and Feasibility
- A flaw in the design of the Phase 2 clinical study is that the patient preparation regimen as currently defined introduces a confounding variable. The applicant will need to stratify for that confounding variable at the time of randomization.

- The application did not contain a justification of sample sizes; there is no assurance that the study is powered appropriately to demonstrate a clinical meaningful effect.

- Reviewers questioned several aspects of the trial design such as the broad age range of patients to be included in the study. However, they commented that these study design problems are potentially correctable.

- While some reviewers questioned the enrollment assumptions and felt it may be difficult to complete the study in the proposed 4-year time frame, others commented that the timeline seems feasible if anticipated additional sites are initiated early in the development timeline.

- The proposed therapeutic approach is straightforward, practical and usable.

- The regulatory pathway is straightforward and the product has been granted orphan drug status.

- It was acknowledged that many of the criticisms and issues might be addressable in the near future as additional information became available.

- Enthusiasm for the application was dampened by the fact that it was poorly written and contained numerous errors and inconsistencies.

Principal Investigator (PI), Development Team and Leadership Plan
- The lead clinical investigator is an outstanding investigator with strong experience in UCB transplantation and is probably the ideal clinician to lead the proposed Phase 2 clinical trial.

- The applicant has assembled a good team; the development team is experienced in both translation of novel technologies and expert in the current technology.

- The clinical sites involved are all world class with reputable investigators and extensive experience in running trials.

- The study design contained a number of errors and inconsistencies which reduced confidence in the PI.

Budget
- Some aspects of the budget may be low, although other aspects are appropriate.

Collaborations, Assets, Resources and Environment
- No concerns.

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

SP3A-07552: A Phase I/IIa Dose Escalation Safety Study of [REDACTED] in Patients with Cervical Sensorimotor Complete Spinal Cord Injury

Recommendation: Recommended for Funding **Final Score:** 76
Total Funds Requested: $14,323,318

PUBLIC ABSTRACT (provided by applicant)

The proposed project is designed to assess the safety and preliminary activity of escalating doses of human embryonic stem cell derived oligodendrocyte progenitor cells (OPCs) for the treatment of spinal cord injury. OPCs have two important functions: they produce factors which stimulate the survival and growth of nerve cells after injury, and they mature in the spinal cord to produce myelin, the insulation which enables electrical signals to be conducted within the spinal cord.

Clinical testing of this product initiated in 2010 after extensive safety and efficacy testing in more than 20 nonclinical studies. Initial clinical safety testing was conducted in five subjects with neurologically complete thoracic injuries. No safety concerns have been observed after following these five subjects for more than two years. The current project proposes to extend testing to subjects with neurologically complete cervical injuries, the intended population for further clinical development, and the population considered most likely to benefit from the therapy. Initial safety testing will be performed in three subjects at a low dose level, with subsequent groups of five subjects at higher doses bracketing the range believed most likely to result in functional improvements. Subjects will be monitored both for evidence of safety issues and for signs of neurological improvement using a variety of neurological, imaging and laboratory assessments.

By completion of the project, we expect to have accumulated sufficient safety and dosing data to support initiation of an expanded efficacy study of a single selected dose in the intended clinical target population.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

The proposed project has the potential to benefit the state of California by improving medical outcomes for California residents with spinal cord injuries (SCIs), building on California's leadership position in the field of stem cell research, and creating high quality biotechnology jobs for Californians.

Over 12,000 Americans suffer an SCI each year, and approximately 1.3 million people in the United States are estimated to be living with a spinal cord injury. Although specific estimates for the state of California are not available, the majority of SCI result from motor vehicle accidents, falls, acts of violence, and recreational sporting activities, all of which are common in California. Thus, the annual incidence of SCI in California is likely equal to or higher than the 1,400 cases predicted by a purely population-based distribution of the nationwide incidence.

The medical, societal and economic burden of SCI is extraordinarily high. Traumatic SCI most commonly impacts individuals in their 20s and 30s, resulting in a high-level of permanent disability in young and previously healthy individuals. At one year post injury, only 11.8% of SCI patients are employed, and fewer than 35% are employed even at more than twenty years post-injury (NSCISC Spinal Cord Injury Facts and Figures 2013). Life expectancies of SCI patients are significantly below those of similar aged patients with no SCI. Additionally, many patients require help with activities of daily living such as feeding and bathing. As a result, the lifetime

cost of care for SCI patients are enormous; a recent paper (Cao et al 2009) estimated lifetime costs of care for a patient obtaining a cervical SCI (the population to be enrolled in this study) at age 25 at $4.2 million. Even partial correction of any of the debilitating consequences of SCI could enhance activities of daily living, increase employment, and decrease reliance on attendant and medical care, resulting in substantial improvements in both quality of life and cost of care for SCI patients.

California has a history of leadership both in biotechnology and in stem cell research. The product described in this application was invented in California, and has already undergone safety testing in five patients in a clinical study initiated by a California corporation. The applicant, who has licensed this product from its original developer and recruited many of the employees responsible for its previous development, currently employs 17 full-time employees at its California headquarters, with plans to significantly increase in size over the coming years. The successful performance of the proposed project would enable significant additional jobs creation in preparation for pivotal trials and product registration.

REVIEW SUMMARY

This application proposes to use embryonic stem cell-derived neural cells, called oligodendrocyte progenitor cells (OPCs) to treat patients with spinal cord injury (SCI). An initial Phase 1 trial has been conducted in patients with injuries to the thoracic region of the spinal cord. The current proposal is to treat patients with injuries to the cervical region of the spinal cord, which is the patient population considered most likely to benefit from the therapy. The project plan comprises a Phase 1/2a clinical study that will test several increasing dose levels of the candidate therapeutic and assess safety and look for signs of neurological improvement. In addition, the project plan includes manufacturing and assay development activities in preparation for later stage clinical development.

Significance and Impact

- Spinal Cord Injury (SCI) is a devastating medical condition with no available treatment at the present time. If therapeutically effective, the proposed therapy could have a highly significant impact on the treatment of SCI.

- A positive result with the proposed therapy would become a high visibility achievement for the entire field of stem cell-based/regenerative medicine.

- The Target Product Profile is adequate and well-conceived and identifies reasonable goals for the disease indication and the desired activity, efficacy, safety and dosing of the intended therapeutic.

- The high long term costs associated with care of patients with SCI support the development of a treatment that will provide even a modest improvement in patient cost of care.

- The proposal is highly responsive to the RFA, using an embryonic stem cell-derived cell therapy to treat spinal cord injury.

- While there are no approved treatment options for patients with SCI, there are a number of ongoing clinical trials to treat SCI, including some with competing cell therapy products.

Scientific Rationale and Risk/Benefit

- The rationale behind the selection of SCI patients with cervical injuries as the target population is sound. The proposed dose range is also well justified.

- The proposed study builds upon the safety profile demonstrated by an earlier Phase 1 study in

patients with SCI. The availability of clinical data is a strength of the proposal, and there is preliminary evidence for safety in humans.

- Some reviewers questioned the strength of the preclinical efficacy data.

Therapeutic Development Readiness
- Clinical grade material is available that has been used in a previous trial so manufacturing for this phase 1/2a study has already been completed.

- The regulatory path has been identified and the preclinical plan to support the proposed phase 1/2a study has largely been completed.

Design and Feasibility
- The design and feasibility of the proposed clinical study is appropriate with realistic timeframes, achievable milestones, and well defined go/no go decision points.

- The previous clinical experience along with the current availability of sufficient cell therapeutic to support the proposed study make the goal of completing the trial very reasonable.

- Reviewers felt that the choice of patient population is wise as it improves the likelihood of seeing benefit and because there are good outcome measures. The inclusion and exclusion criteria are appropriate.

- The proposed Phase 1/2a study is a key and necessary study in the development of the proposed therapeutic candidate for spinal cord injury.

- The proposal includes plans to make manufacturing changes to support future development during the award period. Reviewers expressed concern regarding the manufacturing plan and strategy to support future development, which they viewed as risky.

Principal Investigator (PI), Development Team and Leadership Plan
- Reviewers praised the quality of the team and the significant expertise and experience represented. It is likely that the project will be carried out effectively and as planned.

- The PI has an excellent track record in the field of stem cell biology.

- The clinical investigators have excellent track records in this field and are highly capable of conducting the proposed trial.

Budget
- Some reviewers felt that the budget is appropriate for the proposed project and activities. Others commented that the CRO/Clinical Management costs in the budget may be high considering the small number of patients to be enrolled in the study.

Collaborations, Assets, Resources and Environment
- Appropriate assets and resources are in place.

- Clinical sites are excellent with track records in SCI, appropriate imaging facilities and clinical center infrastructure.

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

SP3A-07559: Clinical Development of a Cell Therapy for Acute Adult Severe Traumatic Brain Injury

Recommendation: Tier 2 **Final Score:** 68
Total Funds Requested: $9,800,000

PUBLIC ABSTRACT (provided by applicant)

Currently, there are no effective therapies for treating severe traumatic brain injury, and there are no stem cell based treatments for severe traumatic brain injury in the CIRM portfolio. This proposal seeks to use a bone marrow derived adult progenitor cell product to treat severe traumatic brain injury in adults within 48 hours after injury. The proposed clinical trial is a Phase 2 clinical trial, meaning it seeks not only to determine safety, but also to determine if there are meaningful clinical improvements following cell therapy treatment. Additionally, the proposed trial will examine whether the cell therapy infusion after traumatic brain injury preserves specific brain structures that typically atrophy/degenerate in the months after injury. The proposed cell therapy product has been used in humans in multiple other clinical trials, demonstrating an excellent safety profile. Substantial pre-clinical (animal) data suggest that the cell therapy product improves functional outcomes by down-regulating the inflammatory response to the initial traumatic brain injury. The inflammatory response, when uncontrolled, can exacerbate the initial injury-ultimately worsening functional outcomes. Positive findings from this trial would accelerate cellular therapies for traumatic brain injury, and offer patients/families more advanced treatment options than are currently available.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

The development of a novel treatment using cell-based therapy for traumatic brain injury would benefit California and its citizens in four main ways: (1) Californians with acute, severe, traumatic brain injury would benefit from having access to the most advanced and novel treatment for an injury that presently has no reparative therapies; (2) Expertise gained by California sites will establish these trauma centers as leaders in cell based therapy for traumatic brain injury, forming a critical element of the emerging Alpha Stem Cell Clinic infrastructure for stem cell therapies within the state; (3) Establishing the critical, collaborative clinical trial consortium to execute this trial will attract follow-on studies to be performed in California; and (4) Industry expansion in California will occur to support the trial yielding direct and indirect economic benefit.

REVIEW SUMMARY

This application proposes a Phase 2 clinical trial of bone marrow derived progenitor cells for traumatic brain injury (TBI). TBI is relatively common, with outcomes ranging from complete recovery to permanent disability and death. The applicants propose to test their cell product in severely injured patients within 48 hours of the TBI. The clinical trial is designed to assess safety of the transplanted cells as well as efficacy, as measured by a number of clinical and imaging endpoints. The cell product has been tested in early phase clinical trials for other indications. Activities proposed in this application include cell manufacturing, submission of an Investigational New Drug (IND) application with the Food and Drug Administration (FDA), clinical site initiation and training, patient enrollment and completion of a Phase 2 clinical trial.

Significance and Impact

- TBI is a devastating condition with no effective treatment and represents a large unmet medical need.

- The Target Product Profile is generally reasonable but reviewers questioned whether the minimally acceptable criteria would be sufficient for FDA approval.

- The application is responsive to the RFA.

Scientific Rationale and Risk/Benefit
- Reviewers raised significant concerns about the preclinical data supporting efficacy of the cell product in an animal model of TBI. They questioned whether these data are robust enough to justify moving into clinical trial.

- Some reviewers questioned the scientific rationale for the therapeutic approach as well as the proposed mechanism of action. Others suggested that the rationale is supported by preclinical data from the field of stroke.

- The proposed patient population, adults who have suffered severe TBI, is appropriate.

Therapeutic Development Readiness
- The timing to initiate treatment is currently being evaluated in a preclinical animal model to determine the therapeutic window for effective treatment. Reviewers noted that these are critical experiments to complete before designing and embarking on a clinical trial. They felt that funding this application would be premature without the evaluation of data supporting an optimal treatment window.

- The applicants have had appropriate regulatory interactions and demonstrated an acceptable safety profile of their cell product when administered to patients in other clinical trials.

Design and Feasibility
- The current proposed treatment time after injury presents significant logistical challenges and reviewers questioned its feasibility. While preclinical work to support an alternate treatment schedule is ongoing, reviewers noted that data from these studies are not yet available.

- Reviewers were concerned that the primary efficacy endpoints proposed for the clinical trial are surrogates, with cognitive and functional measures included only as secondary endpoints. They noted that a positive result with surrogate endpoints may not enable a pivotal trial and recommended adding patients to power the trial for a primary cognitive or functional endpoint if possible.

- Reviewers would have appreciated more detail about how blinding would be performed to assure that investigators remain unaware of a patient's assigned intervention during product administration and patient evaluation.

- One reviewer suggested some changes to the proposed clinical protocol to exclude patients with hypotension or hypoxia, lower the percent reduction in oxygen partial pressure that would constitute a serious adverse event, and screen for and exclude patients with a patent foramen ovale.

Principal Investigator (PI), Development Team and Leadership Plan
- The leadership team is strong and experienced in all aspects of clinical development.

- The PI has relevant experience and a documented track record translating stem cell therapies into the clinic.

Budget
- The budget is generally appropriate.

- Reviewers raised minor concerns regarding the budgets for investigators meetings, Institutional Review Board fees, and study site training.

Collaborations, Assets, Resources and Environment
- The clinical investigators have excellent track records in the field and are capable of conducting the proposed clinical trial.

- The manufacturing activities are well established and will be conducted by a respected CMO.