**REVIEW REPORT FOR CIRM RFA 12-05: STRATEGIC PARTNERSHIP I AWARDS**

**SP1-06386:** Clinical Development of a Small Molecule Drug Targeting Endogenous Stem Cells to Restore Cartilage and Relieve Pain in Osteoarthritis Patients

**Recommendation:** Not Recommended for Funding **Final Score:** --
**Total Funds Requested:** $9,989,293

**Public Abstract (provided by applicant)**
We propose to develop the first drug therapy to reverse the damage of osteoarthritis (OA) in joints. OA is a serious disease that involves the degeneration of joint cartilage and the underlying bone resulting in joint pain, stiffness and immobility. OA is the leading cause of disability and chronic pain in the world and its impact on patients and its economic burden are rapidly increasing with our aging demographics. The statistics for OA are staggering: 27 million Americans and 3.25 million Californians have moderate to severe OA, 25% of OA patients cannot perform their major daily activities of life and 80% have limitations in movement. Ultimately, the pain and disability caused by OA is so severe that 1 million patients annually opt for painful, and for certain patients life-threatening, joint replacement surgery.

Our proposed therapy is a small molecule drug that will be delivered as a single injection into the affected knee. Once injected, the drug activates the patient's own stem cells that are already in the knee, causing them to change into cells that produce the cartilage tissue that is lacking in OA joints. It's this lack of joint cartilage that leads to most of the debilitating symptoms associated with OA, including joint swelling, pain and immobility. By recruiting the patient's own stem cells and natural repair machinery to fix the cause of OA, our drug can repair the diseased joint and allow the patient the opportunity to return to a normal productive, active lifestyle. The drug itself is only present at appreciable levels in the joint and nowhere else in the body, making it extraordinarily safe.

This drug has proven safe and active in regenerating cartilage tissue in all preclinical models to date and we expect it to begin the clinical trial required by the US Food and Drug Administration in the first quarter of 2013. Depending on the results of those trials, the drug could be broadly available as early as 2017.

**Statement of Benefit to California (provided by applicant)**
The proposed research comprises the clinical development to demonstrate safety and efficacy of an interventional drug to treat Osteoarthritis ("OA") and restore patients to a normal active lifestyle. OA is a serious degenerative disease involving joint cartilage and the underlying bone. It affects 3 million Californians and prevents an estimated 750 thousand Californians from performing their major daily activities of life, and its impact is growing fast with our aging population.

Our drug candidate offers the potential to regenerate cartilage tissue, repair the affected joint and relieve the patient of debilitating pain, thereby restoring many of these patients back to a state of well being, permitting them to return to their normal productive daily activities. Additionally, the economic cost of OA to the state of California is substantial, approximately $7-11 billion per year including direct medical, drug and work loss costs.

Due to the medical impact of OA on patients and its economic burden on our health care system, an approved drug for this disease would be valued highly across the nation and globally and could bring countless new jobs and tax revenue to the citizens and State of California. Furthermore, an early success in regenerative medicine in California would likely generate additional excitement and investment in the stem cell field, generating more jobs and helping to ensure California's leadership in this important new industry.

**Review Summary**
This application proposes to submit an IND, and to conduct and complete both a Phase 1 and Phase 2 clinical trial in osteoarthritis (OA) within the four year project period. Osteoarthritis is a chronic debilitating disease that involves the degeneration of the joint cartilage and bone that leads to disability and chronic pain afflicting over 27 million patients in the US. Standard of care therapy for OA may reduce pain and inflammation but do not affect cartilage and bone destruction. The intended therapy is a small molecule drug that activates a signaling pathway important for healthy bone and tissue maintenance, and will be delivered locally into affected joints. This approach is based on the applicant's premise that the drug

stimulates the patient's endogenous stem cells to produce cartilage and thus repairs the joint damage.

**Significance and Impact**
- Reviewers agreed that there is a significant unmet medical need for treatment of OA. Current treatment options are limited to reduction of pain and inflammation, and ultimately joint replacement. A disease-modifying product for treating OA of the knee would have a large impact on health and quality of life.

- The Target Product Profile (TPP) lacked appropriate detail for the proposed stage of development. The target population, efficacy endpoints, dosing regimen and safety section are all inadequately specified. The safety section was judged to be inadequate.

**Risk/Benefit**
- Reviewers were intrigued by the therapeutic concept to deliver a small molecule locally that could stimulate chondrogenesis.

- The preclinical data presented to support the rationale of using the candidate in OA was judged to be weak; and to date, limited in vivo data support the premise that mobilization of the endogenous stem cells is a primary mechanism of action.

- Although an increase in chondrocytes could lead to symptom relief in patients with knee OA, reviewers cautioned it is possible that this might lead to increased symptoms if there is induction of inflammation or too much cartilage or bone production in the knee.

- Another concern was raised regarding the overstimulation of this target and potential tumorigenesis. The panel recommended long term toxicology studies to determine the risk for oncogenic transformation.

**Design and Feasibility**
- Reviewers judged the timeline to be unrealistic, based on their assessment of additional necessary preclinical work.

- The in vitro preclinical proof-of-concept (POC) efficacy data was judged to be inadequate for a proposed project at this stage of development.

- Reviewers suggested further studies for functional outcome be conducted in large animal models with surgically induced cartilage damage to better understand the impact of the therapeutic on cartilage in weight-bearing conditions. Additionally large animal models were recommended to study the impact of dose and regimen on the balance of cartilage repair versus potential overgrowth.

- Reviewers agreed the amount of preclinical work (including additional necessary studies) and the proposed Phase 1 study was feasible to complete in the 4 year time frame. However the proposed Phase 2 study timeline was not realistic due to the large number of subjects to be enrolled and the longer duration of the study compared to the Phase 1.

**Principal Investigator (PI), Development Team and Leadership Plan**
- The team could benefit from an advisor with small molecule development experience, and regulatory expertise familiar with the CDER division.

**Collaborations, Assets, Resources and Environment**
- Reviewers found the list of collaborations comprehensive but would have liked more detailed description of selection of the Contract Research Organizations.

**Budget**
*Assessment of the budget was conducted separately from the overall scientific evaluation and points or concerns raised in this section did not contribute to the scientific score. This section highlights items that must be addressed should the application be approved for funding.*

No relevant budget concerns were highlighted by reviewers.

**The following scientific working group members had a conflict of interest with this application:**
Joy Cavagnaro

**SP1-06398:** Gene-modified Mesenchymal Stromal Cells for Chronic Focal Traumatic Brain Injury: Phase 1/2a and Phase 2b Clinical Trials

**Recommendation:** Not Recommended for Funding **Final Score:** --
**Total Funds Requested:** $10,000,000

**Public Abstract (provided by applicant)**
Traumatic Brain Injury (TBI) results from a strong blow or concussive force to the head. The injury to the brain can render the patient permanently disabled. TBI is a common injury. Over 1.7 million people seek treatment for a TBI in the United States each year. A number of treatments are being developed to reduce the short-term brain damage caused by TBI, but no therapies, beyond physical rehabilitation, have proven effective in lessening the long term or chronic effects of TBI. These long-term effects can include movement disorders and cognitive impairment.

An adult stem cell product, derived from the bone marrow of healthy donors, has recently been shown to reverse neurological disorders in rodent models of TBI. This same product is currently being tested in a human clinical trial for stroke patients. The FDA required extensive safety and efficacy testing of this product before permitting the stroke trial to proceed.

This project intends to initiate a clinical trial of this cell therapy product for chronic TBI patients. Much of the work required to initiate an FDA-approved clinical trial has already been done in order to be able to initiate the stroke trial. The cells have been produced according to the FDA's exacting standards. The cells have been extensively tested for toxicity or unforeseen side effects in animal models. None were found. Mechanism-of-action studies have been ongoing for several years. An additional benefit of the stroke trial is the generation of preliminary safety data in human subjects.

This recent progress means the TBI clinical trial can be initiated fairly quickly. The goal of this first trial will be to determine the feasibility and safety of administering this cell therapy product in chronic TBI patients (a Phase 1 study). Because actual patients will be tested, preliminary efficacy measurements will also be made.

Based on this first TBI study, a second more extensive study will be undertaken. This study will determine the effective dose and ideal target patient profile. Additional safety and efficacy data will also be collected (a Phase 2 study).

Together, these two studies will set the stage for a definitive test of this product's safety and efficacy for the treatment of chronic TBI (a Phase 3 study). The Phase 3 clinica trial is outside of the scope of this specific proposal and at least several years in the future.

TBI is a complex and as yet unmet medical need. Its effective treatment will most likely require a therapy employing multiple mechanisms. Cell therapy offers a potential solution. The results seen in animal models of TBI are very encouraging. If these results can be translated into human TBI patients, then a true therapeutic option will finally be available.

**Statement of Benefit to California (provided by applicant)**
This project will test the safety and effectiveness of gene-modified stem cells in patients suffering from Traumatic Brain Injury (TBI).

Californians are active people. Californians traverse more freeway miles than the citizens of any other state. Unfortunately, this means Californians suffer a larger number of TBIs. Subsequently, California taxpayers suffer a larger burden paying for the long-term care of permanently disabled TBI patients. No other State stands to benefit as much as California if an effective therapy can be developed for chronic TBI.

This stem cell therapy has been developed at a California-based biotechnology company. The manufacturing processes were developed at a California-based Contract Manufacturing Organization. Initial human safety testing has been led by a major California university. This is a California project supporting many well-paying California jobs and generating significant tax revenue. This trend will

continue and grow.

The first part of this project will take place in California. Two major California universities will serve as clinical sites for the proposed Phase 1/2a clinical trial. As the project progresses, clinical sites outside California will be required, but the "center of gravity" will remain in State.

Finally, if an approved therapeutic results from this project it will be available at reasonable cost to Californians by virtue of the financial agreements established with CIRM.

**Review Summary**
This application proposes two clinical trials of gene-modified mesenchymal stromal cells (MSCs) for chronic, focal, traumatic brain injury (TBI). TBI is a relatively common injury caused by a blow to the head. The outcomes of TBI can range from complete recovery to permanent disability and death. The applicant proposes to test gene-modified MSCs that are currently in clinical trial for stroke in two clinical trials for TBI. The first trial would primarily test safety while the second, larger trial would also test for efficacy. The applicant also proposes scale-up manufacturing activities required to support larger clinical trials.

**Significance and Impact**
- TBI is a significant unmet medical need with no effective treatment other than physical therapy.

- The Target Product Profile (TPP) does not adequately describe biological activity and the proposed efficacy endpoints are not standard for TBI.

**Risk/Benefit**
- There is inadequate preclinical data supporting a potential for benefit for the therapeutic candidate in the proposed indication. The one relevant preclinical study was performed in an acute model of TBI that does not reflect the proposed patient population. In addition, this small study did not include appropriate behavioral tests or controls.

- The risks associated with surgical injection into one of the proposed regions may be too great for a Phase I safety study.

- The rationale for gene-modification of the MSCs is not clearly presented or supported by preclinical data in an animal model of TBI.

**Design and Feasibility**
- Reviewers believed that the proposed patient enrollment is not feasible given the very specific subset of TBI patients targeted by the proposed trials.

- Reviewers noted that the proposed clinical outcome measures may not be the most appropriate for TBI. They recommended adding a trauma neuropsychologist to the team to help revise these measures.

- Reviewers were not convinced that the timeline to enroll and complete both clinical trials is feasible. They recommended inclusion of enrollment tables or registry data from the proposed clinical sites to justify enrollment expectations.

- Reviewers appreciated that the proposed therapy has been evaluated by regulatory bodies and is currently in clinical trial for stroke. However, they were not convinced of the feasibility of the proposed regulatory strategy to leverage the data from this stroke trial. They also cited other regulatory risks that could substantially affect the project timeline.

- The cell manufacturing plan is reasonable and clearly outlined.

**Principal Investigator (PI), Development Team and Leadership Plan**
- Reviewers noted the presence of an experienced clinical lead investigator but did not get the sense that this individual was involved in the design of the clinical study.

- The PI has clinical experience but reviewers were concerned that the proposed level of effort might be unrealistic given his/her position at the company.

**Collaborations, Assets, Resources and Environment**
- The clinical sites are appropriate and include a world-class institution for neurology and neurosurgery.

- The contract manufacturing organization is experienced and appropriate.

**Budget**
*Assessment of the budget was conducted separately from the overall scientific evaluation and points or concerns raised in this section did not contribute to the scientific score. This section highlights items that must be addressed should the application be approved for funding.*

- Large subcontracts to the clinical sites are not well justified.

- Aspects of the manufacturing budget were confusing and poorly justified.

**The following scientific working group members had a conflict of interest with this application:**
None

**SP1-06467:**[REDACTED] Treatment for Patients Suffering an Acute Ischemic Stroke: A Phase II Clinical Study

**Recommendation:** Not Recommended for Funding **Final Score:** 60
**Total Funds Requested:** $8,264,800

**Public Abstract (provided by applicant)**
Stroke is the leading cause of disability and the third leading cause of death in the United States. Recent estimates by the American Heart Association suggest that in 2011, ~800,000 people in the US suffered a stroke, with 80-90% of those strokes being ischemic strokes involving blockage of a blood vessel in the brain, resulting in a lack of oxygen and nutrients to the tissue and subsequent cell death. Calculated costs of stroke on our health care system point to total combined direct and indirect costs of $73.7 Billion dollars annually, with lifetime costs associated with caring for stroke victims approaching $200,000 per survivor.

Despite these statistics, there are few treatment options for people suffering strokes. Drug development efforts have largely focused on stroke prevention, "clot-buster" drugs, or neuroprotectants and have been almost universal failures. Only tPA, a thrombolytic or clot-buster, has received FDA approval for treatment of ischemic stroke, and unfortunately, must be administered within 4.5 hours of the onset of the stroke. As such, only 3-8% of all Americans suffering an acute ischemic stroke who could benefit receive tPA due to the delayed recognition of the symptoms associated with stroke, coupled with the limited window for receiving tPA treatment. This equates to ~650,000 Americans in 2011 who could have benefited from an alternative effective stroke therapy. Other than tPA, the primary standard of care and treatment for stroke victims is hospitalization and rehabilitation, which are clearly not intended to target the primary tissue injury and the associated lasting neurological deficits. The numbers of affected individuals, and costs to facilitate their care and rehabilitation, combined with the lack of current therapies reiterates stroke represents a current unmet medical need of significance.

Our company has been developing an adult stem cell product for treatment of stroke. We have completed extensive preclinical safety and efficacy studies with our stem cell product and have developed an FDA reviewed manufacturing plan for producing the cells for intravenous administration following stroke. We have received FDA authorization of an IND for using the stem cell product to treat patients suffering from an acute stroke in the first 1-2 days after onset, increasing the window of therapeutic intervention for stroke patients. We are currently enrolling patients in a Phase I clinical study evaluating the safety of the cells in ischemic stroke patients. We are submitting this application requesting funds to do process development to improve the formulation of the cell product to allow for administration of the product at all hospitals, as well as funding to test the stem cell product in a larger Phase II study, evaluating both the efficacy and safety of the cells. Funding this study could accelerate a novel cell based therapy for treating stroke patients who would otherwise have no therapeutic options.

**Statement of Benefit to California (provided by applicant)**
The proposed project could benefit the citizens of California in at least four important ways, including: improving clinical outcomes and enhancing patient quality of life for patients that have suffered a stroke; reducing overall healthcare costs, especially those covered by the taxpayers of California; reducing the loss of economic productivity for working age individuals that suffer long term disability after a stroke, and; by creating high quality jobs in the state.

Stroke is a leading cause of death and serious long term disability, and represents a major area of healthcare costs. In 2011 the American Heart Association estimated that approximately 800,000 people suffered a stroke in the U.S. (85 - 90% are ischemic strokes). Roughly half of stroke survivors are disabled or experience permanent weakness on one side of their body. Approximately three-quarters of all stroke victims are over the age of 65, and of these, ~26% require full time institutional care following the stroke, while many others require home care or assistance from family members. According to U.S. Census data, California represents approximately 12% of the national population, which suggests more than 82,000 victims of ischemic stroke annually in California alone (although a 2006 study by the Milken Institute estimated the number of California residents suffering a stroke was more than 240,000 annually). Given the aging demographic profile, and that the risk of stroke increases substantially with age, the

number of Californians affected by stroke is expected to increase significantly in the years ahead.

The economic burden of stroke is enormous. The national impact of stroke was recently estimated at more than $73 billion annually. Although there have been few efforts to precisely measure the economic impact within the state of California alone, the national data suggests that this exceeds $8.7 billion annually. This includes the cost of hospitalization, extended physical therapy and rehabilitation for patients with permanent weakness on one side of their body or more serious disability, long term institutional care or home care, and the loss in economic productivity. By improving clinical outcomes, and achieving a better quality of life for stroke patients, much of the downstream costs that are currently incurred could be minimized or avoided entirely. Given that most strokes occur in the elderly population, much of this economic impact occurs through the Medicare and Medicaid systems, and is born by the taxpayers of California. Over time, the economic benefits of reducing direct costs and improving productivity could be many billions of dollars for the state.

Finally, if CIRM makes the award, it would enable our company to establish a more meaningful commercial presence in the state of California, which could lead to the creation of many high quality jobs over time, such as in research and development, bio-manufacturing, and commercialization.

**Review Summary**
The applicant proposes to use an adult stem cell product to treat stroke. There is currently only one FDA-approved treatment for stroke which must be administered within 4.5 hours of stroke onset, leaving a significant clinical need for other persons experiencing a stroke. This project proposes to use cell therapy to treat patients 24-36 hours after stroke onset. The applicant is currently enrolling a Phase 1 trial to test safety for ischemic stroke patients. The proposal considered here requested funds to conduct process development activities to change the cell therapy formulation and to conduct a Phase 2 clinical trial.

**Significance and Impact**
- Stroke represents a significant unmet clinical need, since the only approved treatment, tissue plasminogen activator (TPA), can only be used within a limited time window of stroke onset.

- Reviewers did not see convincing data that this cell therapy approach, with a proposed mechanism of action of immune modulation, would have an impact on stroke.

**Risk/Benefit**
- Few significant adverse events (SAEs) have been attributed to the cell product in other on-going clinical studies, providing preliminary assurance that the risk may be low; but, potential benefit of this therapeutic candidate for stroke is unclear.

- Potential benefit is suggested by data from just one preclinical study report that was published in a journal of modest impact. Other data cited supporting benefit are unpublished. The lack of quantitative histopathology, considered the gold-standard method of outcomes assessment in this indication, was noted as an important gap.

- Reviewers discussed whether the target treatment benefit in the proposed trial is an acceptable and clinically meaningful outcome.

**Design and Feasibility**
- IND has already been approved, but there was concern about feasibility of the timeline especially with respect to coordinating key manufacturing activities with the clinical program.

- Changing the formulation, as is proposed within this study, is not trivial and may affect project feasibility. Specific concern was expressed about the timeline to complete the necessary stability testing.

- Insufficient detail was provided to demonstrate the ability to scale production of the therapeutic to the capacity required and show comparability within the proposed timeline.

- The trial is a conventional design and feasible with a more homogeneous patient population than has been used in other stroke trials. It was suggested, though, that including patients who have already received other treatment may introduce an additional variable to the study that should be considered in the trial design, perhaps as a stratifying criterion.

- Endpoints were judged to be appropriate. The primary endpoint was not as stringent as has been used in other trials. Secondary endpoints were judged to be more stringent.

- Additional Phase 1 data with stroke patients is strongly advised before moving into the proposed larger Phase 2 study. Additional clinical studies may further illuminate clinical dose since the preclinical data may not have sufficiently narrowed the possible dose range.

- Go/No Go decision points were not clearly identified in the research plan.

**Principal Investigator (PI), Development Team and Leadership Plan**
- The PI does not have development experience beyond Phase 2 so there was concern about reliance on the contractor for product development expertise.

- Clinical sites indicated are satisfactory with appropriate expertise to conduct the proposed study.

**Collaborations, Assets. Resources and Environment**
- The Contract Manufacturing Organization (CMO) identified is a recognized leader but reviewers were unclear whether they have the resources and capacity immediately to scale up this product within the proposed timeline.

- Some considered the plan to have a CMO address the process changes a risk.

**Budget**
*Assessment of the budget was conducted separately from the overall scientific evaluation and points or concerns raised in this section did not contribute to the scientific score. This section highlights items that must be addressed should the application be approved for funding.*

- Reviewers deferred to CIRM to ascertain how much of the proposed budget would actually be spent in California.

**Programmatic Review (if applicable)**
A motion was made to move this application into Tier 3, Not Recommended for Funding. Discussion reiterated concerns related to limited preclinical data, lack of evidence that this therapeutic approach will benefit stroke, and concerns regarding manufacturing within the proposed timeline. Since other trials are ongoing for stroke, reviewers were not convinced of a programmatic reason for CIRM to fund the proposed study as submitted. The motion carried.

**The following scientific working group members had a conflict of interest with this application:**
Charles Cox

**SP1-06477:** A Phase 1/2, Open Label Study Evaluating the Safety and Efficacy of Gene Therapy in Subjects with Beta-Thalassemia by Transplantation of Autologous Hematopoietic Stem Cells [REDACTED]

**Recommendation:** Recommended for Funding **Final Score:** 73
**Total Funds Requested:** $9,363,335

**Public Abstract (provided by applicant)**
[REDACTED] plans to carry out a Phase 1/2 study to evaluate the safety and efficacy of [REDACTED] for the treatment of Beta-Thalassemia Major(BTM). [REDACTED] consists of autologous patient hematopoietic stem cells(HSC) that have been genetically modified ex vivo with a lentiviral vector that encodes a therapeutic form of the Beta-globin gene. [REDACTED] is administered through autologous hematopoietic cell transplant(HCT), with the goal of restoring normal levels of hemoglobin and red blood cell(RBC) production in BTM patients who are dependent on RBC transfusions for survival.

Because they cannot produce functional hemoglobin, BTM patients require lifelong RBC transfusions that cause widespread organ damage from iron overload. While hemosiderosis can be mitigated with chelation therapy, poor compliance, efficacy and tolerability remain key challenges, and a majority BTM patients die in their 3rd-5th decade. The only cure for BTM is allogeneic HCT, which carries a significant risk of mortality and morbidity from immune-incompatibility between the donor and recipient, and is hampered by the limited availability of HLA matched sibling donors.

By stably inserting functional copies of beta-globin into the genome of a patient's own HSC, treatment with [REDACTED] promises to be a one-time transformative therapy for BTM. The beta-globin gene in the [REDACTED] vector carries a single codon mutation [REDACTED] that allows for quantitative monitoring of therapeutic globin production but that does not alter oxygen carrying capacity. Treatment with an earlier version of the vector has been shown to correct beta-thalassemia in mice [REDACTED]. In a clinical trial [REDACTED], 3 BTM patients were treated-one of whom became transfusion independent 1 year after treatment and remains so 4 years later.

Given the prevalence of patients with a common BTM genotype in California, [REDACTED] plans to open at least 2, and up to 4, clinical sites in California. Development activities are on track to initiate the trial in 1H 2013, and to complete the trial with 2 years of follow-up within the award window. [REDACTED] has completed a pre-IND meeting with the FDA and successfully manufactured a GMP lot of [REDACTED] vector that is available for clinical use. The Company expects to complete all IND enabling activities by Q4 2012.

In the last year, the company has made scientific advances that have allowed for a significant improvement in the efficiency of HSC genetic modification that will be help ensure clinical efficacy in BTM. Moreover, through collaborations with contract manufacturers, [REDACTED] is now producing large scale GMP lots of vector, and is on track to qualify a GMP cell processing facility with commercial capabilities prior to study initiation. [REDACTED].

**Statement of Benefit to California (provided by applicant)**
The company expects to spend a major component of its financial resources conducting business within the state of California during the period of this CIRM award. Specifically: 1) we will have at least two clinical sites in California, and more likely up to 4 sites, 2) our viral vector manufacturing will occur in California, 3) our cell processing will occur in California, 4) we will hire several consultants and full-time employees within California to support the program. Overall, several million dollars will be spent employing the services of people, academic institutions, and other companies within the state of California.

Moreover, the disease we aim to treat occurs at a substantially greater rate of in California than other parts of the United States. As such, it is a significant public health concern, for which our therapy could provide a dramatically improved outcome and significant reduction in the lifetime cost of treatment, along with increased productivity. Due to the prevalence of the disease in California, if brought to the market, the pharmacoeconomic and social benefit of our therapy will accrue disproportionately to the state of

California.

**Review Summary**
The goal of this proposal is to develop a gene-modified stem cell therapy for beta-Thalassemia Major (BTM), a severe blood disorder caused by a genetic defect in the beta-globin gene. Because they cannot produce functional hemoglobin, BTM patients require lifelong red blood cell (RBC) transfusions that cause widespread organ damage from iron overload. In the proposed therapeutic approach, a patient's own hematopoietic stem cells (HSC) would be isolated and genetically modified ex vivo with a lentiviral vector encoding a therapeutic form of the beta-globin gene. The modified cells would then be returned to the patient via an autologous bone marrow transplant, with the goal of restoring normal levels of hemoglobin and RBC production in transfusion-dependent patients. Key project activities include filing an Investigational New Drug (IND) application, improving process development for larger scale manufacture, and completing a Phase 1/2 clinical trial to evaluate the safety and efficacy of this gene-modified stem cell therapy for adult BTM patients. Following the initial enrollment of adult patients and the accumulation of adequate safety and efficacy data, the applicant proposes to extend enrollment to a small number of adolescent subjects.

**Significance and Impact**
- Beta-Thalassemia is a widespread and devastating genetic disorder for which current treatment options are limited. The proposed project addresses a critical unmet need and if successful, the clinical competitiveness and impact will be very high.

- Although new therapies are being developed, the proposed approach offers the possibility of a lifetime cure with a single treatment and without the need for an immune matched tissue donor.

- The proposed project represents a potential leap forward for cell and gene therapies and would enhance our knowledge of corrective gene therapy for the treatment of one of the most common and devastating genetic disorders. If successful, the proposed approach could be widely adopted and would have major impact not only on BTM, but also on the development of cures or treatments for other types of genetic disorders. This could be a very important success for cell and gene therapy.

**Risk/Benefit**
- The rationale for the proposed therapeutic is scientifically sound, based on a strong body of preliminary work and an established clinical precedent for curing BTM with allogeneic bone marrow transplant.

- Reviewers believed that the potential benefits of the proposed therapy strongly outweigh the risks, although they cautioned that a patient's genotype and disease severity could influence this calculation, as could an unanticipated clonal expansion within the autograft.

- While the proposed approach does not avoid all risks inherent to bone marrow transplantation procedures, the use of autologous cells should minimize the possibility of graft versus host disease and may potentially reduce graft failure.

- Reviewers noted that the applicant has modified the vector in order to increase potential benefit and reduce potential risk in the proposed trial. However, based on the available data, reviewers were uncertain whether the re-engineered lentiviral vector would indeed prove safer or more efficacious in vivo than the original vector. In addition, there were no convincing data to suggest the product would not be immunogenic.

**Design and Feasibility**
- The overall development plan is well conceived, with appropriate assessment points and clearly defined milestones. A well-described clinical development plan, regulatory plan and quality plan are in place with defined aims and time lines and the clinical trial is well designed. In light of significant technology risk taking, the applicant presents an excellent, thoughtful, stepwise plan that is well-worth funding.

- It is feasible to complete the proposed clinical trial within 4 years, although reviewers cautioned that there could be delays, given the important but addressable issues identified by the Food and Drug Administration (FDA) during a key regulatory review.

- Reviewers considered the timeline for completing the next generation manufacturing process to be underestimated and the proposal did not address a comparability plan to establish comparability between

the current and improved processes.

**Principal Investigator (PI), Development Team and Leadership Plan**
- The PI and applicant team have considerable experience in vector development and gene therapy. Reviewers believed that the PI is well suited to lead this endeavor but emphasized that since he/she has less expertise with process development, it will be critical to identify appropriate personnel for the key positions, including Project Manager.

- The subcontractors are all well qualified. The working relationships between applicant, contractors and clinical sites are clearly specified; appropriate leadership and communication plans are in place.

**Collaborations, Assets, Resources and Environment**
- The applicant has recruited a team of excellent clinical collaborators with large practices, making it highly feasible that sufficient numbers of patients will be enrolled in the planned clinical trial.

- All necessary resources concerning production and testing of the proposed therapeutic are in place, and the applicant holds relevant intellectual property.

**Budget**
*Assessment of the budget was conducted separately from the overall scientific evaluation and points or concerns raised in this section did not contribute to the scientific score. This section highlights items that must be addressed should the application be approved for funding.*

- $1.1M for vector yet application says it is complete. Is this for lentiviral vector, or new manufacturing? Need more details. In addition, $675K for 2 centers TBD - need to identify the centers and budget according to patient accrual.

**Programmatic Review (if applicable)**
Applications were addressed individually during programmatic review. A motion was made to recommend funding this application. The motion passed.

**The following scientific working group members had a conflict of interest with this application:**
Barbara Matthews

**SP1-06505:** A Treatment For Hemoglobinopathies via Fetal Globin Reactivation in Hematopoietic Stem Cells

**Recommendation:** Not Recommended for Funding **Final Score:** --
**Total Funds Requested:** $6,870,620

**Public Abstract (provided by applicant)**
Sickle cell disease (SCD) is an autosomal recessive disease in which a mutation in the beta globin gene results in the sickling of red blood cells. Affected individuals are predisposed to infection, and may present with pain crises, acute chest syndrome, and stroke. Pediatric patients with sickle cell disease (SCD) receive daily hydroxyurea, which controls disease by activating the gamma globin gene (shut down in infancy), thus reducing adverse effects of mutant beta globin. The clinical benefit of this has been shown by the reduction in the incidence of pain or acute chest syndrome, and a reduction in the need for blood transfusions. However, the effects of hydroxyurea are palliative and chronic therapy has been reported to be carcinogenic in isolated cases. Furthermore, most adults will become refractory to hydroxyurea treatment.

Contemporaneous with the development of hydroxyurea, other investigators have been exploring the potential of curing SCD with hematopoietic stem cell (HSC) transplantation. To date, approximately 400 patients have undergone allogeneic HSC transplantation following myeloablative conditioning. However, it is estimated that HLA-compatible HSC transplants are available to less than 20% of affected individuals and long term toxicities are substantial. The latter includes the need for chronic immunosuppression and the development of graft versus host disease (GVHD).

The proposed therapeutic intervention aims to provide a widely available functional cure for SCD and beta-thalassemia. During infancy, gamma-globin-containing fetal hemoglobin protects SCD and beta-thalassemia patients from developing disease symptoms until gamma globin is replaced by adult-type beta globin chains. The proposed approach combines the benefits of activating the gamma globin gene with the curative potential of HSC transplantation while abrogating the toxicities associated with hydroxyurea, chronic immunosuppression and GVHD. We hypothesize that harvesting HSCs from a patient with SCD or beta-thalassemia, using genome editing to permanently activate the gamma globin gene, and returning these edited HSCs to the patient could provide a lifetime of relief from SCD and beta-thalassemia symptoms. The use of a patient's own cells is anticipated to be safer since the conditioning regimen would be nonmyeloablative, there is no need for chronic immunosuppression, and there would be no risk of GVHD. Importantly, this approach addresses all patients with SCD/beta-thalassemia with one treatment.

**Statement of Benefit to California (provided by applicant)**
Our treatment for hemoglobinopathies will benefit the approximately 5,000 SCD patients in the State of California by providing them with a better treatment option for this severe disease with significant unmet medical need (1). SCD is an ongoing health concern in California, with the California Newborn Screening Program detecting approximately 125 cases of SCD each year (2) . In addition to benefitting patients, our proposed curative treatment will also benefit California's State Medicaid Program, Medi-Cal, through significant cost savings. Acute and chronic clinical manifestations of SCD (vaso-occlusive crisis, acute chest syndrome, stroke, etc.) lead to significant healthcare utilization, especially of the emergency department (ED). The majority of SCD Californians visit an ED more than once during the year; ED visits often result in hospital admission lasting 5-6 days on average for SCD patients. Of importance to the State of California, SCD patients are heavily reliant on Medicaid (~46%). The total lifetime health care costs for an average sickle cell patient are approximately $1 million (3). This translates to approximately $2.5 billion in total costs for the ~50% of SCD Californians covered by Medi-Cal. Thus, our proposed treatment has the potential to provide Medi-Cal significant savings by reducing the number of expensive inpatient hospitalizations and Emergency Department visits by SCD Californians.

1. J. A. Wolfson, S. M. Schrager, T. D. Coates, M. D. Kipke, Sickle-cell disease in California: a population-based description of emergency department utilization. Pediatr Blood Cancer 56, 413 (Mar, 2011).

2. California Department of Public Health: California Newborn Screening Program. http://www.cdph.ca.gov/programs/nbs/Pages/NBSSCDProviders.aspx -- accessed on 6/25/2012.

3. S. K. Ballas, The cost of health care for patients with sickle cell disease. Am J Hematol 84, 320 (Jun, 2009).

**Review Summary**
The goal of this proposal is to develop a new cell therapeutic based on genetic modification of the patient's own blood stem cells (hematopoietic stem, progenitor cells, HSPC), for treating sickle cell disease (SCD) and beta-thalassemia (BT), common and debilitating illnesses. The proposed genetic modification would result in knockout of a gene whose product regulates expression of a fetal globin gene, allowing this gene to be expressed. The patient's genetically modified HSPC would be returned to the patient via a bone marrow transplant following a non-ablative conditioning regimen. Following engraftment, the genetically modified cells would give rise to red blood cells that do not sickle. Key project activities include an observational trial in SCD patients, a preclinical safety studies, process development and manufacturing, filing an Investigational New Drug (IND) application and initiation and completion of a Phase 1 clinical trial in sickle cell disease.

**Significance and Impact**
- Sickle cell disease is a widespread and devastating genetic disorder for which current treatment options are limited. If successful, the proposed innovative genetically modified cell therapy would address a critical unmet need.

- Reviewers noted that success of the proposed less toxic non-ablative conditioning regimen in this indication would be a significant development that could make HSPC transplantation more widely utilized in this and similar patient populations.

**Risk/Benefit**
- Reviewers pointed out that the biological effects of disruption of the targeted regulatory gene in HSPC are not well understood and are likely to extend beyond effects on the fetal globin gene.

- While preliminary data on genotoxicity of the gene modification technology is encouraging, reviewers considered that more stringent tests should be performed with the HSPC cell source.

- There have been no discussions with the regulatory agency on the preclinical and clinical plans for the proposed therapeutic candidate. Reviewers considered this a risk given the targeted HSPC population, the gene modification technology and the patient population.

- Reviewers considered the proposal for a non-ablative conditioning regimen to be a key aspect of this project and noted that the risk of the project is increased if there is a switch to an ablative regimen, presented as an option in the application.

**Design and Feasibility**
- The reviewers raised a number of concerns on the overall readiness and feasibility of the proposed project. They considered the project to be too premature for clinical development. They found the preclinical data to be very preliminary and insufficient to fully evaluate the feasibility of the project.

- It is unclear from the application whether a potentially therapeutic level of gene targeting can be reproducibly achieved in adult bone marrow stem cells. Reviewers also commented on the lack of preclinical evidence supporting the feasibility and durability of cell candidate engraftment to therapeutic levels especially in a competitive engraftment setting.

- Reviewers had several concerns with the proposed Phase 1 study including the feasibility of achieving engraftment given the starting conditioning regimen and the number of HSPC proposed for infusion especially in the non-ablative setting.

- Reviewers considered the observational study in SCD patients to be of little value and commented that no criteria were specified for the selection of the subset of patients from that study for the Phase 1 study.

**Principal Investigator (PI), Development Team and Leadership Plan**
- The PI and the applicant team have considerable experience in the development of proposed platform

technology.

- The clinical sites are appropriate for the proposed project with clinical experience in the proposed clinical indication.

**Collaborations, Assets. Resources and Environment**
- Resources for development, manufacturing and clinical work are appropriate

- A collaborator on the biology of targeted gene may be helpful.

- It is not clear if the applicant organization has access to the IP covering the targeted gene

**Budget**
*Assessment of the budget was conducted separately from the overall scientific evaluation and points or concerns raised in this section did not contribute to the scientific score. This section highlights items that must be addressed should the application be approved for funding.*

- The reviewers considered the per patient cost as high considering that the first year of the study is observational requiring data management only

- The reviewers commented that certain GMP manufacturing costs appear to be underestimated.

**The following scientific working group members had a conflict of interest with this application:**
None

**SP1-06513:** Preclinical and clinical testing of a stem cell-based combination product for insulin-dependent diabetes

**Recommendation:** Recommended for Funding **Final Score:** 88
**Total Funds Requested:** $10,075,070

**Public Abstract (provided by applicant)**
Diabetes exacts a tremendous toll on patients, their families, and society. Autoimmune Type 1 diabetes, often called juvenile-onset diabetes, is caused by a person's own immune system mistakenly destroying their insulin-producing cells in the pancreas, known as beta cells. When those beta cells are lost, the ability to produce insulin in response to consumed carbohydrates is lost, and blood sugar can increase to toxic levels. Although not due to autoimmunity, Type 2 diabetics often lose their ability to produce insulin as well. While pharmaceutical insulin is commonly used to control both types of diabetes, it is difficult to self-administer optimally, does not sufficiently replace beta cells, and the adverse short- and long-term effects of diabetes and risks associated with insulin usage remain, including potentially fatal hypoglycemic episodes, nerve damage, blindness, kidney failure, foot ulcers / amputations, and heart disease.

Ideally, one would like to replace lost beta cells, and attempts to do so have included the use of pancreas transplants, beta cell (islet) transplants, and transplants of animal cells. Unfortunately, those approaches are hindered by 1) a limited amount of donor tissue, and 2) issues regarding immunological incompatibility between donors and recipients. To solve the first problem, the group applying for this CIRM award has developed methods to make replacement beta cells from human embryonic stem cells (hESC), which can be reliably grown in large-scale batches. The hESC-derived beta cells have been shown to cure experimental diabetes in mice and rats. Regarding the issue of donor-recipient compatibility, the group has found that the cells can be administered under the skin in a simple device, essentially an envelope made of semi-permeable membrane, which is intended to protect the implanted cells from the patient's immune system. Upon implant, the cell-loaded device, which also keeps the implanted cells in place, acquires its own dedicated circulation. This blood supply provides oxygen and nutrients to the implanted cells, and also allows them to respond to blood sugar by releasing pancreatic hormones such as insulin into the circulation. Thus, the implanted cell-loaded device in essence represents a "replacement endocrine pancreas" with its own protection from autoimmunity. This product could return a patient's blood sugar regulation to normal and alleviate both the day-to-day and long-term issues of diabetes.

The group has made tremendous progress in moving the product from concept through years of research and development. At this point an array of detailed work on the exact format to be tested in humans needs to be completed and submitted to the FDA on the way to clinical trials. The proposed award would provide critical funding, including potentially triggering matching funding from a large corporate partner, to advance the product through the first-in-human testing which will be very informative.

**Statement of Benefit to California (provided by applicant)**
Diabetes mellitus currently afflicts approximately 350 million people worldwide, with projections of over 500 million by the year 2030 (sources: World Health Organization; International Diabetes Federation). In the year 2000 there were an estimated 2,089,657 cases of diabetes in California (diagnosed + undiagnosed; source: Diabetes Control Program, California Department of Health Services). Further, the disease disproportionately affects certain minority groups and the elderly. Despite the use of insulin and advances in its delivery, the human cost of diabetes is underscored by the financial costs to society: tens of billions of dollars each year in California alone. The primary cause of Type 1 diabetes, and contributing significantly to Type 2 diabetes as well, is the loss of insulin-producing pancreatic beta cells. The proposed Partnership will develop a beta cell replacement therapy for insulin-dependent diabetes. If successful, the therapy will go beyond insulin function, and will perform the full array of normal beta cell functions, including responding in a more physiological manner than manual or mechanized insulin administration. Because they will be more physiological, the replacement cells should also reduce the long-term effects of diabetes. Moreover, the cell therapy will alleviate patients of the constant monitoring of blood glucose and painful insulin injections. For these reasons, it is possible that the product could transform the diabetes treatment landscape dramatically and even replace pharmaceutical insulin in the market. This product will be available in California first, through clinical testing, and if approved by the

FDA for commercial production, will eventually help hundreds of thousands of Californians with diabetes. The product will substantially increase quality of life for patients and their families while significantly reducing the health care burden in the state. The proposed Partnership will employ Californian doctors and scientists, and success will generate accolades and notoriety for the state. Lastly, once commercially marketed, the product will yield additional jobs in manufacturing, sales, and related industries, and generate revenue for California. Given the market need and the clear feasibility, the product could become the most significant stem cell-based medical treatment of the coming decade, and that will be a great achievement for California, its taxpayers, and CIRM.

**Review Summary**
This program aims to complete early clinical development of a therapy for type I insulin dependent diabetes (T1D). The therapeutic candidate consists of a pancreatic progenitor population derived from human embryonic stem cells (hESC) encapsulated in a device to both contain the cells and protect them from immune rejection. Following subcutaneous implantation, the cells mature in vivo to beta cells that secrete insulin in response to blood glucose. This combination product candidate is intended to replace the beta cells that are lost in T1D and restore glucose regulation. During the four-year award period, the applicant and the biopharmaceutical partner plan to complete IND enabling studies, file an IND and initiate and complete a Phase 1/2 clinical trial. The primary endpoint of the trial is safety, with a secondary efficacy endpoint. The applicant and the partner also plan to conduct process scale up and perform preclinical and clinical comparability studies to support a larger scale pivotal clinical trial (Phase 3).

**Significance and Impact**
- Reviewers characterized the goal of the proposed therapy as the "holy grail" of diabetes treatments. The product candidate could have a transformative impact if successfully developed.

- The proposed program is a direct outgrowth of CIRM funded work. It has attracted a biopharmaceutical partner who will co-fund and, assuming success, conduct the pivotal trial and commercialize the product. This program is an excellent fit for both the RFA and CIRM's overall goals.

- The approach is highly clinically competitive. Direct glucose sensing and insulin secretion offers an advantage over therapies such as insulin injection and frequent glucose monitoring, insulin pumps, and new closed loop and continuous glucose monitoring technologies. Encapsulation could obviate the immune rejection that plagues islet transplants; the hESC source for the pancreatic progenitor population eliminates supply issues.

- The TPP is appropriate and achievable.

**Risk/Benefit**
- Containment of the cells in a removable device minimizes risk to patients. Benefit is readily determined and could be dramatic, although it may only be seen in the higher dose cohorts of the early stage trial.

- Reviewers noted the extensive cell, device and combination product characterization and testing which contributes to risk reduction.

- Reviewers raised questions about the potential number of cell-containing devices required for implantation to achieve insulin independence, the frequency of replacement and the kinetics of insulin release but agreed that the proposed clinical protocol would provide important data addressing these points.

**Design and Feasibility**
- The project plan is well conceived, includes appropriate Go/No-Go decision points and delineates program risks and solutions. All components, including preclinical, manufacturing, engineering, regulatory and clinical, are well developed. Reviewers further commented that the program would provide insight regarding safety, preliminary clinical efficacy and mechanism of action of the candidate therapeutic in humans and pave the way for pivotal studies and commercialization.

- While additional scale up must be performed to support a Phase 3 trial, the applicants' strength in bioengineering and the "off the shelf" nature of the cells used in the candidate therapeutic, including their scalability and ability to be cryopreserved, strengthen the manufacturing strategy.

- The class of this proposed therapy for this indication is novel to the FDA, and the agency may request

additional studies that could delay the timeline. However, this risk has been mitigated by the applicant's proactive, forthright and constructive engagement with the agency.

- Preclinical data are impressive. However, the inability to model allogeneic immune responses to the candidate therapeutic in large animals limits assessment of in vivo durability of the device and immune responses to the therapy. These will be addressed in the Phase 1/2 study but constitutes a risk.

- Reviewers agreed that the technology was at a point where it should be tested in humans and that the proposal was a solid plan to do that.

**Principal Investigator (PI), Development Team and Leadership Plan**
- The team is appropriate, has demonstrated a long-term focus on the candidate diabetes treatment and has made excellent progress to date.

- Clinical investigators and sites are highly qualified and possess the appropriate experience to execute the proposed Phase 1/2 trial.

**Collaborations, Assets, Resources and Environment**
- Collaborators, resources and environment are excellent. Productive relationships with contractors are already established; however, some personnel remain to be named.

- Applicant reports a broad patent portfolio.

**Budget**
*Assessment of the budget was conducted separately from the overall scientific evaluation and points or concerns raised in this section did not contribute to the scientific score. This section highlights items that must be addressed should the application be approved for funding.*

- The budget appears reasonable and appropriate.

**Programmatic Review (if applicable)**
Applications were addressed individually during programmatic review. A motion was made to recommend funding this application and a panelist highlighted that the project meets all the programmatic criteria of the RFA. The motion passed.

**The following scientific working group members had a conflict of interest with this application:**
Olle Korsgren