CIRM STRATEGIC PARTNERSHIP II AWARDS – RFA 012-09

Tier 1: Recommended for funding = ☐ Tier 3: Not recommended for funding at this time = ☐

Application #	Title	SCORE	Median	SD	Low	High	BUDGET	TIER	Area of Focus	Approach	Stage
SP2-06902	A Treatment For Beta-thalassemia via High-Efficiency Targeted Genome Editing of Hematopoietic Stem Cells	**80**	80	3	75	85	$6,374,150	1	beta-thalassemia	gene/cell therapy	Preclinical/ Phase 1
SP2-06906	Mesenchymal Stem Cells and an Advanced Synthetic Bio-textured Scaffold for the Restoration and Repair of Bone Defects	**55**	55	11	40	70	$10,121,275	3	Spinal fusion	cell therapy	Preclinical/ Phase 1/2

REVIEW REPORT FOR CIRM RFA 12-09 STRATEGIC PARTNERSHIP AWARDS II

SP2-06902: A Treatment For Beta-thalassemia via High-Efficiency Targeted Genome Editing of Hematopoietic Stem Cells

Recommendation: Recommended for Funding **Final Score:** 80
Total Funds Requested: $6,374,150

Public Abstract (provided by applicant)
Beta-thalassemia is a genetic disease caused by diverse mutations of the beta-globin gene that lead to profoundly reduced red blood cell (RBC) development. The unmet medical need in transfusion-dependent beta-thalassemia is significant, with life expectancy of only ~30-50 years despite standard of care treatment of chronic blood transfusions and iron chelation therapy. Cardiomyopathy due to iron overload is the major cause of mortality, but iron-overload induced multiorgan dysfunction, blood-borne infections, and other disease complications impose a significant physical, psychosocial and economic impact on patients and families. An allogeneic bone marrow transplant (BMT) is curative. However, this therapy is limited due to the scarcity of HLA-matched related donors (<20%) combined with the significant risk of graft-versus-host disease (GvHD) after successful transplantation of allogeneic cells.

During infancy, gamma-globin-containing fetal hemoglobin protects beta-thalassemia patients from developing disease symptoms until gamma globin is replaced by adult-type beta-globin chains. The proposed therapeutic intervention combines the benefits of re-activating the gamma globin gene with the curative potential of BMT, but without the toxicities associated with acute and chronic immunosuppression and GvHD. We hypothesize that harvesting hematopoietic stem and progenitor cells (HSPCs) from a patient with beta-thalassemia, using genome editing to permanently re-activate the gamma globin gene, and returning these edited HSPCs to the patient could provide transfusion independence or greatly reduce the need for chronic blood transfusions, thus decreasing the morbidity and mortality associated with iron overload. The use of a patient's own cells avoids the need for acute and chronic immunosuppression, as there would be no risk of GvHD. Moreover, due to the self-renewing capacity of HSPCs, we anticipate a lifelong correction of this severe monogenic disease.

Statement of Benefit to California (provided by applicant)
Our proposed treatment for transfusion dependent beta-thalassemia will benefit patients in the state by offering them a significant improvement over current standard of care. Beta-thalassemia is a genetic disease caused by diverse mutations of the beta-globin gene that lead to profoundly reduced red blood cell (RBC) development and survival resulting in the need for chronic lifelong blood transfusions, iron chelation therapy, and important pathological sequelae (e.g., endocrinopathies, cardiomyopathies, multiorgan dysfunction, bloodborne infections, and psychosocial/economic impact). Incidence is estimated at 1 in 100,000 in the US, but is more common in the state of California (incidence estimated at 1 in 55,000 births) due to immigration patterns within the State. While there are estimated to be about 1,000-2,000 beta-thalassemia patients in the US, one of our proposed clinical trial sites has the largest beta-thalassemia program in the Western United States, with a population approaching 300 patients. Thus, the state of California stands to benefit disproportionately compared to other states from our proposed treatment for transfusion dependent -thalassemia.

An allogeneic bone marrow transplant (BMT) is curative for beta-thalassemia, but limited by the scarcity of HLA-matched related donors (<20%) combined with the significant risk of graft-versus-host disease (GvHD) after successful transplantation of allogeneic cells. Our approach is to genetically engineer the patient's own stem cells and thus (i) solve the logistical challenge

of finding an appropriate donor, as the patient now becomes his/her own donor; and (ii) make use of autologous cells abrogating the risk of GvHD and need for acute and chronic immunosuppression.

Our approach offers a compelling pharmacoeconomic benefit to the State of California and its citizens. A lifetime of chronic blood transfusions and iron chelation therapy leads to a significant cost burden; despite this, the prognosis for a transfusion dependent beta-thalassemia patient is still dire, with life expectancy of only ~30-50 years. Our proposed one-time treatment aims to reduce or eliminate the need for costly chronic blood transfusions and iron chelation therapy, while potentially improving the clinical benefit to patients, including the morbidity and mortality associated with transfusion-induced iron overload.

Review Summary
The goal of this proposal is to develop a therapy for beta-thalassemia, a genetic disease caused by mutations in the beta-globin gene, leading to impaired production of hemoglobin and a lifelong dependence on red blood cell (RBC) transfusions for survival. During infancy, gamma-globin containing fetal hemoglobin protects beta-thalassemia patients from developing disease symptoms. However, during normal development, the gamma-globin gene is inactivated and gamma-globin is replaced by the adult-type beta-globin chains that are defective in beta-thalassemia patients.

The proposed approach will use a novel gene-editing technology to permanently re-activate fetal gamma-globin expression in hematopoietic stem cells (HSC) isolated from patients in order to restore fetal hemoglobin production. The modified cells will then be returned to the patient via an autologous bone marrow transplant, with the goal of achieving normal hemoglobin levels and RBC production, thereby obviating or greatly reducing the need for chronic blood transfusions.

The proposed 4-year project plan includes preclinical work leading to the filing of an Investigational New Drug (IND) application as well as completion of a Phase 1 clinical trial in transfusion-dependent beta-thalassemia patients.

Significance and Impact
- The proposed therapy could have a great impact not only on beta-thalassemia, but also in related hemoglobinopathies.

- This proposal has great merit and the impact could be extraordinary.

- The proposed approach is competitive with other therapeutic strategies in development including viral mediated gene therapy, and there are significant advantages over current therapies should this approach prove efficacious.

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

Scientific Rationale and Risk/Benefit
- The scientific rationale is extremely strong and the applicant has provided good preclinical evidence for the therapeutic approach.

- Reviewers expressed enthusiasm for the proposal with comments such as: "I am highly enthusiastic; this is a study that should be done; this is a trial we would want to do at our center."

- Some questions relating to long-term stability and dose need to be answered to balance the risk/benefit ratio in favor of benefit.

- Two potential risks that are not addressed completely, are a potential effect on long term hematopoietic stem cell (HSC) activity and on the T-cell lineage and immune reconstitution; the applicants have not demonstrated that T-cell activity is not altered.

- Although the data on long-term reconstitution are encouraging and suggest stable modification, they are not definitive since serial transplantation has not been done and it is still an open question whether this will be a life-long treatment.

Design and Feasibility

- The development plan is well thought out and considers both the potential upside and downside.

- The project plan appears feasible and the applicant has articulated risk mitigation strategies at each step.

- The clinical plan is straightforward and feasible.

- Consistency of the manufacturing process is a concern; the manufacturing process may need refinement to obtain a consistent product with well defined specifications and predictable long term engraftment potential. The effect of genotype on stem cell mobilization and variability needs to be considered.

Principal Investigator (PI), Development Team and Leadership Plan

- There are no concerns about the team and collaborators - all are excellent.

- The budget is reasonable.

Collaborations, Assets. Resources and Environment

- The clinical sites, collaborators, assets and environment are excellent.

- Collaborations are with leading experts in the field.

- The applicant has identified appropriate, experienced contractors to manufacture reagents and cell products.

RECOMMENDATIONS

- Reviewers agreed that while this is an excellent proposal, there are some questions relating to risk versus benefit that should be addressed to strengthen the IND submission. Reviewers had the following recommendations:

- Long-term persistence of the gene modified HSC in vivo should be evaluated in serial transplantation experiments in an animal model to clearly demonstrate that long term reconstituting cells are not impaired by the manufacturing process; transplanted cells should be derived from the target patient population and transplant recipients should be followed for longer periods of time.

- Stem cell dose is critical. The applicant needs to evaluate the impact of the manufacturing process on the survival and potency of the HSC and demonstrate that what will be delivered to patients is an effective dose and that it can be reproducibly produced from genotypically diverse patients. Careful titration of the engraftment potential of shipped, frozen and thawed, control and gene modified HSC in an animal model would add confidence that dosing will be adequate.

REVIEW REPORT FOR CIRM RFA 12-09 STRATEGIC PARTNERSHIP AWARDS II

SP2-06906: Mesenchymal Stem Cells and an Advanced Synthetic Bio-textured Scaffold for the Restoration and Repair of Bone Defects

Recommendation: Not Recommended for Funding **Final Score:** --
Total Funds Requested: $10,121,275

Public Abstract (provided by applicant)
This work is directly relevant to stem-cell derived therapy that will advance the treatment of a serious injury in humans. This research and product development will provide a novel method for bone graft to address the needs of spinal fusion patients. We will do translational studies to develop bone remodeling therapies.

More than 400,000 Americans require surgery every year for debilitating spinal conditions at an annual cost of more than $3 billion. Spinal fusion surgery is often the only effective procedure for treating pathologic spinal conditions such as scoliosis, degenerative disc disease, spondylolisthesis, or spinal instability, which can cause severe pain by compressing spinal nerves.

The traditional method is to remove the pathology compressing the spinal nerves, and then fuse the spine by removing the disc material and inserting a "cage" between the vertebrae. The current "gold standard" for spine bone replacement is the use of autologous bone harvested from the same patients' hip. But the patient must undergo two surgeries, one for the hip and one for the spine. Bone chips are harvested from the patient's hip and inserted into the cage. The bone eventually causes the vertebrae to fuse, which stabilizes the spine. Limitations of harvesting the bone graft from the patient include longer recovery time, increased blood loss, pain and co-morbidities associated with bone harvest from the hip. Patients may be relieved of their spinal conditions, but many end up with chronic hip pain.

With the advancement of minimally invasive surgical techniques the opportunity to identify autograft bone replacements is imperative. The company's new biomaterial is a synthetic bone graft alternative, which has been shown to stimulate differentiation of stem cells into bone forming osteoblasts. However, the major limitation is that it relies on the patient's own cells to form new bone. Often, these patients are elderly or have co-morbidities such as diabetes or obesity that has a detrimental effect on their own regenerative potential. Higher yields of bone reformation could be achieved therapeutically by combining human bone marrow-derived stromal cells (hBMSCs) with the synthetic biomaterial. We have shown that stimulation of hBMSCs and differentiation to osteoblasts followed by attachment to the biomaterial enhances the efficacy of this approach. We will clinically evaluate a bone remodeling therapy utilizing a classic tissue-engineering approach that combines sources of cells, signaling factors, and a biomaterial scaffold. The novel cellular bone graft will be elaborated through this work without the need for autologous bone. In the long run this will improve the health of individuals with debilitating spinal conditions.

Statement of Benefit to California (provided by applicant)
An estimated 10 million adults suffer from chronic back pain annually, making back pain the number 1 cause of healthcare expenditures in the U.S. with a direct cost of more than $50 billion annually for diagnosis, treatment and rehabilitation. The majority of patients suffer spine problems related to degenerative conditions. These degenerative conditions can result in instability and intrusion into the spinal cord and surrounding nerves, causing back pain and/or radiating pain in the arms or legs. The State of California has approximately 12% of the US

population which translates to 1.2 million chronic spine pain individuals with a direct cost of more than $6 billion annually for diagnosis, treatment and rehabilitation. Even for patients that had successful spinal surgery, other problems are associated with bone collection procedures and post-surgical scenarios. Accordingly, an urgent need for a less invasive, more efficient means of doing spinal fusion is needed.

Tissue engineering of bone is important because it has a huge impact on the economy and patient welfare. With an aging population, the needs for improved grafting options that remove the collection of the patient's own hip bone is necessary to address. Most currently available bone grafts require the patient's own cells to enter the graft and form bone. Often, these patients are elderly or have co-morbidities such as diabetes or obesity that has a detrimental effect on their own cellular regenerative potential.

Cell implants are a superior alternative for bone repair, particularly for spinal fusion where the endogenous source of progenitor cells is not present in sufficient quantities. This strategy has been brought to clinical trials using stimulated human bone-marrow derived stromal cells (hBMSCs) that have been expanded in cell culture to adopt an osteogenic lineage. By combining novel cell-stimulating technology and FDA-approved hBMSCs and matrix, a robust product will be created. An estimated 5% of the Californian population is expected to be personally impacted with a serious spinal condition at some point in their lives. Of these, 48,000 will be indicated for spinal fusion surgery each year. As such, spinal conditions are one of the most prevalent conditions faced by Californians, and this is only expected to increase as the population continues to age. An estimate of annual revenues for this product is in the $200-$800 million range within the first few years of full commercial launch. Thus, successful completion of this work will not only provide citizens of California much needed advances in bone healing technology of relevance to spinal conditions and improvement in health care but it will also provide high paying jobs and significant tax revenue. This product may also be significantly cheaper to produce than current state of the art technologies, which will result in lower costs to the health care system and increased profitability for the California-based companies.

Review Summary
The applicant proposes to develop a combination product that can improve on the current methods for spinal column fusion, which often involve a pre-collection of bone tissue from the hip of the patient (an autograft). The proposed combination product consists of a synthetic bone graft alternative that will be combined with human bone marrow-derived stromal cells (hBMSC) that have been stimulated to differentiate into cells that can form new bone. The product would be implanted during lumbar spinal column stabilization surgery and would replace the need for an autograft. The applicant expects spinal column fusion surgery using this combination product to be suitable for a broad range of patients with degenerative disc disease and that it will eliminate some of the risks of the current treatment procedures. The proposed work under the grant would begin with preclinical studies, include submission of an IND, and proceed through initiation and completion of a Phase 1/2 clinical trial.

Significance and Impact
- Reviewers commented that the overall approach of this type of combination product (hBMSC plus a synthetic bone matrix) was not very novel, although they appreciated that pre-stimulating the hBMSC to differentiate to bone forming cells was a distinctive component.

- While reviewers agreed that eliminating the need for an autograft by developing a standardized therapeutic product would likely broaden the patient pool eligible for a lumbar spinal fusion surgery, insufficient data were presented to assess the stated benefits of the proposed combination product.

- Reviewers were enthusiastic about development of a combination product consisting of bone-forming cells and a synthetic scaffold and predicted that it could address unmet orthopedic medical needs. However, some felt the application overstated the potential impact and clinical competitiveness of the combination product for the intended patient population.

Scientific Rationale and Risk/Benefit

- The application contained inadequate information to assess the activity of the fully formulated combination product.

- As the current methods of spinal column fusion are largely successful, reviewers were not convinced that the proposed combination product would provide sufficient additional benefit to outweigh potential product risks, which have not yet been described.

- Reviewers expressed concern that plans were insufficient for monitoring ectopic osteogenesis in trial participants.

- Convincing evidence was provided that effective methods had been developed to pre-stimulate the hBMSC to differentiate towards forming bone cells. However, the safety profile of these stimulated cells was not sufficiently described.

Design and Feasibility

- Preliminary data were lacking from studies using the fully formulated combination product in preclinical models. The team needs to describe the phenotype, immunogenicity and distribution of osteogenic-stimulated hBMSC in the synthetic bone matrix after delivery in a clinically relevant animal model.

- The design of the proposed preclinical studies was considered insufficient to inform clinical dose and assure the safety of the therapeutic combination product in the proposed clinical indication.

- Reviewers described the proposed methods for manufacturing the combination product as quite complex and insufficient data were presented to assess the feasibility of manufacturing and delivering a combination product that maintains the activity of the bone-forming cells. More extensive characterization of the osteogenic-stimulated hBMSC, both before and after formulation for delivery with the synthetic bone matrix, is needed.

- Reviewers assessed the proposed design of the Phase 1/2 clinical trial as unlikely to provide a meaningful data set that would be sufficient for evaluation of product safety and therapeutic efficacy.

Principal Investigator (PI), Development Team and Leadership Plan

- The PI and members of the development team are experts in the advancement of medical devices for spinal applications; however, reviewers described the team as lacking in the specific knowledge required for manufacturing a combination product that includes human cells in a medical device.

Collaborations, Assets, Resources and Environment

- The team is skilled, has experience in developing orthopedic medical devices and is predicted to collaborate well.