REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05272: hESC-derived NPCs Programmed with MEF2C for Cell Transplantation in Parkinson's Disease

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $19,964,300

Public Abstract (provided by applicant)
We proposes to use human embryonic stem cells (hESCs) differentiated into neural progenitor/stem cells (NPCs), but modified by stably programming the cells with the transcription factor MEF2C to drive them more specifically towards dopaminergic (DA) neurons, those lost in Parkinson's disease. We will select Parkinson's patients that no longer respond to L-DOPA and related therapy for our study, because no alternative treatment is currently available. The transplantation of cells that become DA neurons in the brain will create a population of cells that secrete dopamine, which may stop or slow the progression of the disease. In this way, moderate-to-severely affected Parkinson's patients will benefit.

The impact of development of a successful cell-based therapy for late-stage Parkinson's patients would be very significant. There are approximately one million people in the United States with Parkinson's disease (PD) and about ten million worldwide. Though L-DOPA therapy controls symptoms in many patients for a period of time, most reach a point where they fail to respond to this treatment. This is a very devastating time for sufferers and their families as the symptoms then become much worse. A cell-based therapy that restores production of dopamine and/or the ability to effectively use L-DOPA would greatly improve the lives of these patients. Because of our extensive preclinical experience and the clinical acumen of our Disease Team, we will be able to quickly adapt our procedures to human patients and be able to seek FDA approval within four years.

Statement of Benefit to California (provided by applicant)
It is estimated that the cost per year for a Parkinson's patient averages over $10,000 in direct costs and over $21,000 in total cost to society (in 2007 dollars). With nearly 40 million people in California and with one in 500 estimated to have Parkinson's (1.5-2% of the population over 60 years of age), there are approximately 80,000 people in California with Parkinson's disease. Thus, Parkinson's disease is a significant burden to California, not to mention the devastating effect on those who have the disease and their families. A therapy that could halt the progression or reverse Parkinson's disease would be of great benefit to the state and its residents. It would be particularly advantageous if the disease could be halted or reversed to an early stage, since the most severe symptoms and highest costs of care are associated with the late stages of the disease. Cell-based therapies offer the hope of achieving this goal.

Review Summary
The objective of this project is to complete preclinical studies and file an Investigational New Drug (IND) application for a cell therapy treatment for Parkinson's Disease (PD) in patients who no longer respond to dopamine replacement therapy. Currently, medications, surgery, and multidisciplinary management can relieve symptoms in PD. Cell transplantation has been explored in PD clinical trials with mixed results. The proposed approach uses human embryonic stem cells (hESCs) that have been genetically modified to express an active form of the transcription factor Myocyte Enhancer Factor 2C (MEF2C) and subsequently differentiated into neural progenitor cells (NPCs) for transplantation. The applicant asserts that MEF2C-overexpression will drive differentiation of neural stem cells more specifically towards dopaminergic neurons, which are the population that is lost in PD. Proposed project milestones include completing the manufacturing, preclinical, and regulatory activities required to file an IND with the Food and Drug Administration (FDA) within four years.

Significance and Impact
- The proposed therapeutic addresses a highly unmet medical need, especially considering that the approach is intended for patients who have become unresponsive to dopamine replacement therapy.

- Some reviewers saw this approach as not significantly novel and therefore of limited potential impact over other therapeutic approaches under development.

- The potential impact of this approach is unclear, as reviewers were not able to discern whether the proposed therapy would avoid the adverse side effects that have been observed in other cell transplantation studies for PD.

- Important details regarding the implementation and duration of the immune suppression strategy are not elaborated in the Target Product Profile.

Project Rationale
- The rationale for cell therapy to provide dopamine is clear and well established; however, no convincing data are provided to demonstrate why MEF2C expression is a better approach than the best available method for deriving dopamine-producing cells.

- The preliminary data provided for efficacy were not convincing. Data were shown for only one of the two behavioral study models. Only modest improvements were seen in vivo which barely reached a statistically significant difference from the control.

- A reviewer noted that the preclinical behavioral experimental data provided were difficult to interpret, as it was unclear whether the described improvements were due to the effects of transplanted cells or from sprouting of residual fibers that may not have been completely lesioned.

-Reviewers noted that data from several recent publications raise the possibility that serotonin modulation could be contributing to some of the observed effects, which was not discussed by the applicant.

Therapeutic Development Readiness
-The applicant has not shown definitive proof of concept linking dopamine production by transplanted cells with an improved outcome in vivo.

- Reviewers were concerned about the purity of the proposed development candidate and the poor characterization of other cell types in the population. The application lacked detailed cell characterization.

- Reviewers felt the project is at an early stage of therapeutic development readiness.

- Research scale feasibility data is shown but the master cell bank has not yet been developed which must then be qualified and tested.

- One lot of cells appears to be sufficient to treat only a single patient. Production methods may be adequate to get to an IND filing and conduct safety studies but the ability to scale up to conduct later phase clinical trials is unclear.

- Reviewers felt it was premature to conduct studies using a clinically relevant animal model.

Furthermore, the panel disagreed with the applicant statement that two preclinical models would necessarily be required by the FDA.

Feasibility of the Project Plan
-Feasibility of the project plan was questioned in light of the limited characterization of the product. There was no discussion of product heterogeneity, transgene copy number, and other important aspects of the cell population.

-The application lacked data demonstrating duration of MEF2C transgene expression in vivo. Furthermore, the proposal did not address the possibility of gene silencing in vivo and resulting loss of efficacy.

- One reviewer disagreed with the method proposed to determine the dose for the clinically relevant animal model. It was suggested to perform the lesion and then dose to see an effect rather than extrapolating the dose from other preclinical models.

-If the transplanted cells exert their effect through a neurotrophic mechanism, then it would be important to consider this in the clinical trial design.

Principal Investigator (PI) and Development Team
- Reviewers agreed that the PI is an established and qualified researcher in neurodegenerative disease; however some reviewers were concerned about the PI's lack of experience in developing a cell therapy product for clinical transplantation.

- Although reviewers were impressed by the quality of consultants engaged, it was unclear what role some of those identified would play in the project.

Collaborations, Resources and Environment
- The designated Good Manufacturing Practices (GMP) production facility was viewed favorably for being a highly qualified and capable contractor.

- The intellectual property status and whether the applicant would have freedom to operate with the proposed cell line and/or the viral vector used was not fully addressed. Although this was not judged to be a barrier to the ability to conduct the proposed studies, this would need to be clarified for further product development.

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 felt the budget for the proposed Good Laboratory Practice (GLP) rodent studies and for the clinically relevant studies was excessive.

Conditions Applied by the Planning Award Grants Working Group
- The Planning Award GWG set a condition that "to be eligible for the Disease Team Therapy Development Research Award competition, the applicant must provide at the time of Full Application convincing preclinical evidence for the identity and survival of hESC-derived A9 dopaminergic neurons in the striatum, with histological data showing robust neurite outgrowth (3-5 mm from graft, volumetric evaluation) and synaptic connections with the host brain".

- Reviewers did not find the histological data provided in response to the conditions of the Planning Award to be convincing. However, the GWG felt that condition had been addressed sufficiently to permit eligibility and scoring of the application.

Programmatic Review (if applicable)
A motion was made to move the proposal to Tier 1 (recommended for funding). Reviewers reiterated the concerns with the proposal, including the low percentage of therapeutic candidate cell, poorly characterized cell population, and unconvincing preliminary data. It was pointed out that many medical innovations have been made without having understood mechanism of action and whether expectations should be set differently for a patient population in greater need. One reviewer noted that the scores across the reviewers were fairly consistent and in a range that is typically not considered fundable. It was pointed out that there are currently three other projects in CIRM's translational portfolio related to PD. In light of increasing and evolving research activity in PD and this being viewed as premature for a translational award, this proposal was not viewed as worthy of such a large investment.

The motion failed.

The following Scientific Working Group members had a conflict of interest with this application:
Lonser, Pepperl, Weber

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05288: Genetically Engineered Mesenchymal Stem Cells for the Treatment of Vertebral Compression Fractures.

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $19,996,735

Public Abstract (provided by applicant)
Approximately 10 million people in the United States currently have osteoporosis, and an additional 34 million people are at risk for osteoporosis. Osteoporotic vertebral compression fractures (VCFs) are the most common fragility fractures in the US; there are approximately 700,000 such injuries each year, twice the rate of hip fractures. Approximately 70,000 VCFs result in hospitalization each year, consuming enormous amounts of health care resources. Currently, treatment is focused primarily on prevention. When fractures occur in patients with osteoporosis, treatment options are limited because open surgery with implants often fails. In recent years, new therapies involving injection of cement into the fractured vertebra (such as vertebroplasty) have been developed. Unfortunately, these procedures do not regenerate bone tissue and carry risks of cement leakage and emboli. Recent publications in a leading medical journal question the effectiveness of those procedures. Based on these studies the American Academy of Orthopaedic Surgeons issued a set of new guidelines and recommended against the use of vertebroplasty.

We need a new biological treatment that will promote repair of such fractures in a safe and efficient manner. Our plan is to develop a therapy that uses adult mesenchymal stem cells (MSCs) that are genetically engineered to express a bone-forming gene, bone morphogenetic protein 6 (BMP6). These cells have been shown to promote bone formation and fracture repair in numerous studies. Specifically, we intend to use allogeneic ("off the shelf") human MSCs. These cells will be genetically engineered with BMP6 DNA in a virus-free method, using technology currently approved for clinical use. BMP6-engineered MSCs not only secrete BMP6 protein and promote bone formation but also differentiate into bone-forming cells themselves. This combined effect leads to fast and robust bone formation, which could be an attractive therapy for a variety of clinical conditions involving bone loss. An image-guided injection of BMP6-overexpressing MSCs into a fractured vertebra could lead to rapid fracture repair and shortened hospitalization time. We propose to use allogeneic, off-the-shelf, MSCs, which do not require the patient to undergo additional medical procedures such as bone marrow aspiration. Whereas use of autologous cells is limited by the number of cells that can be obtained from the patient, use of allogeneic cells is not limited by cell number. If successful, this therapeutic strategy could revolutionize the treatment of patients with VFCs, offering a minimally invasive biological solution. We plan to analyze aspects of efficiency and safety of use of the proposed therapy in a pre-clinical model, which will enable us to submit an approvable Investigational New Drug application (IND) to the Food and Drug Administration (FDA) by the end of the 4-year project.

Statement of Benefit to California (provided by applicant)
Approximately 10 million people in the United States have osteoporosis, while an additional 34 million have low bone mass. The lifetime incidence of fragility fractures secondary to osteoporosis in women older than 50 years of age is approximately 1 in 2, and that in men of the same age is 1 in 4. Osteoporosis-related vertebral compression fractures (VCFs) are the most common fragility fractures in the United States, accounting for approximately 700,000 injuries per year, twice the rate of hip fractures. Approximately 70,000 VCFs result in hospitalization each year, with an average hospital stay per patient of 8 days. Fragility fractures due to osteoporosis also place a severe financial strain on the health care industry. Estimates show there were approximately 1.5 million osteoporosis-related fractures in the United States in 2001, the care for which cost about $17 billion. Moreover, as the number of individuals over the age of 50 continues to increase, costs are predicted to rise to an estimated $60 billion per year by 2030. VCFs previously received limited attention from the spine care community. This oversight may be a result of the perception that VCFs are benign, self-limited disorders or that treatment options are limited. However, it has become clear that VCFs are associated with significant functional impairment and increased mortality, even in patients not presenting for medical evaluation at the time of fracture. Current treatment of osteoporotic patients is mostly focused on prevention of VCFs. There are few treatment options when VCFs actually occur. Since open surgery involves morbidity and implant failure in the

osteoporotic patient population, nonoperative management, including medications and bracing, is usually recommended for the vast majority of patients. Unfortunately, large numbers of patients report intractable pain and an inability to return to activities. Currently there is no efficient biological solution for the treatment of VCFs. In the proposed study we will continue to develop a biological therapy to accelerate repair of VCFs. This treatment will rely on adult stem cells that have been genetically engineered to overexpress an osteogenic gene, BMP6, by using a nonviral technique that is clinically approved. It will also involve an injection of these cells into the fracture site, instead of a percutaneous injection of a polymer, which does not restore lost bone tissue. Data generated from this study could potentially revolutionize the treatment of vertebral fractures and other complex fractures in patients suffering from osteoporosis. This will benefit the citizens of California by reducing loss of workdays, duration of hospital stays, and operative costs, and by improving quality of life for Californians with osteoporosis, who are at risk for VCFs.

Review Summary
This proposal is focused on the preclinical development of allogeneic mesenchymal stem cells (MSCs) to treat vertebral compression fractures (VCF). VCF are deformities of the vertebral bodies of the spine, and are a common manifestation of osteoporosis. VCF may be asymptomatic, or may cause pain and other neurological symptoms. Treatment of vertebral compression fractures has evolved over the last decade. Several preventive measures and procedure-based treatments have been introduced during this period. Outcomes have varied. The candidate MSCs will be genetically modified using a non-viral technique to overexpress a bone-forming gene, bone morphogenetic protein 6 (BMP6). The concept is based on the applicant's preclinical observations that MSCs secrete BMP protein and promote formation of new bone in several models of bone loss. The key objective of this proposal is to complete the preclinical, manufacturing, regulatory and clinical activities required to submit and Investigational New Drug (IND) application to the FDA within the four-year timeframe.

Significance and Impact
- One reviewer commented that the magnitude of the problem is overstated in the application. Many osteoporosis-related VCFs are asymptomatic, and often symptoms improve over time.

- VCF as a first indication is too high risk; the major risk is potential for bony overgrowth, which could be catastrophic in the spinal column.

-The Target Product Profile (TPP) needs to aim for a specific clinical indication within VCF (e.g. symptomatic osteoporotic or traumatic VCF; acute or chronic).

- The TPP should describe a desired clinical outcome in terms of the benefit to the patient, and all benefits should be compared to a control treatment.

- Several reviewers concurred that the TPP described a goal for a threshold clinical outcome that was below what would be a meaningful clinical benefit.

- The TPP does not address the possibility that a patient might need multiple injections to treat multiple fractures. This has implications for the safety profile that are not addressed in the program.

- It is unclear from the application how this proposed therapeutic candidate will have a better safety profile compared to other clinical interventions.

Project Rationale
- The data do not provide adequate evidence that injection of the therapeutic candidate into the vertebra will restore normal architecture. Several reviewers thought this was critical to achieve the desired clinical outcomes.

- The rationale that MSCs modified to overexpress BMP6 will induce bone formation is valid.

- Utilizing MSCs to produce BMP6 is a good approach and could overcome the manufacturing challenges of producing recombinant BMPs as a therapeutic.

- The therapeutic candidate would better address bone healing in non-union fracture or other bony defects.

Therapeutic Development Readiness
- The program does not yet appear ready to begin preclinical development; the therapeutic candidate has not been finalized (i.e. final plasmid not chosen or produced) and the preliminary proof of concept that normal vertebral architecture can be restored has not been demonstrated.

- Although MSCs may be immunomodulatory, the panel was not convinced that the gene-modified cells would be non-immunogenic.

- Reviewers noted that utilizing a clinically approved source for cells and techniques/processes to produce this candidate was a good strategy to shorten the timeline to IND.

- A cross-reference to the drug master file (DMF) of the original cells will not suffice for safety data in this gene-modified approach using a novel delivery mechanism.

Feasibility of the Project Plan
- The team needs to select and justify a preclinical model that best replicates the human condition and test the candidate in such a model.

- Stabilization of the vertebral body by new bone formation and restoration of the architecture need to be assessed independently and correlated to clinical outcomes.

- Preclinical models can address bone formation; but whether pain is reduced and quality of life is improved will require clinical studies.

- The plan is straightforward, and in the right indication could achieve an IND within the four-year timeframe.

- The plan lacked important details regarding the sensitivity of methods to detect migrating cells in biodistribution studies.

- Immunogenicity was not addressed and is a concern, especially if multiple rounds of injections are given.

- Preclinical toxicology studies will need to be conducted with the final therapeutic candidate and the intended delivery system for this indication.

- Tumorigenicity studies seemed inadequate, given that the cells will be gene-modified and have associated risks.

Principal Investigator (PI) and Development Team
- PI has been working on BMP-modified MSC for bone repair since late 1990s and is a leader in the field with a strong publication record.

- The Co-PI brings expertise in preclinical testing. An additional team member adds expertise with assessing bone biomechanics.

- The team is supported by good product development, manufacturing, and regulatory expertise.

Collaborations, Resources and Environment
- Contract manufacturing for both the plasmid and the cell transduction and banking is supported by solid contractors; as well as preclinical studies.

- The contract research organization that will perform the preclinical studies is qualified to perform the proposed work.

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.)
- CMC costs of $6.8 M were judged to be excessive given commercially available cell source.

- Many consultants to the project were listed as employees.

Programmatic Review (if applicable)
A motion was made to move the application to Tier 3, Not Recommended for Funding. Competitiveness for this complicated potential therapeutic was not judged to be strong against current simple preventive measures under development and on the market. Key preclinical data that vertebral architecture can be restored was missing, and therefore the chance for a meaningful clinical benefit is low. The panel agreed that no model or study in the plan addresses this deficiency.

The following Scientific Working Group members had a conflict of interest with this application:
Mills, Pepperl, Weber

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05298: Airways for Children

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $16,464,856

Public Abstract (provided by applicant)
The primary goal is to bring a safe and effective therapy to children with severe large airway disease. Our intent is to implement all of the necessary steps for a successful new stem/progenitor cell-derived airway transplant for clinical trials in children within 4 years. Our team builds on first-in-human surgical successes with stem cell-based tissue engineered airway implants in compassionate use cases in a young adult and in a child. To this end, we will perform the necessary preclinical studies to support a successful FDA IND application within 3 years. We propose to use stem/progenitor cells from the patient to treat an extraordinarily difficult to manage health problem in children, namely large airway disease. In children this leads to collapse of tracheal cartilage causing severe airway obstruction that is life-threatening. It occurs in approximately 200 children in California each year and the morbidity and mortality associated with this disease are very high. Approximately 25% of these young patients die if not successfully treated. Treatment costs for these children are very high, and the familial and societal investments are substantially higher, although outcomes are consistently poor. The endpoint desired is normal airway and lung function and an improved quality of life. Our team aims to eliminate the need for repeated surgical interventions which are not necessarily successful, presently the standard of care for children with large airway obstruction. Bioengineered airway transplants that use the cells of the patients could be used in humans of all age groups and would not require lifelong harmful anti-rejection medications.

In 2008/2010, we used stem cell-based, engineered tracheal implants to successfully save a young woman's and a child's life. The child has now returned to school and has grown 4 inches in a year. These first-in-human studies emphasize that our goal is realistic and paves the way for clinical trials in children after carefully designed safety studies. Stem/progenitor cell-derived airway transplants that use the patients' cells have the clinical advantage of not requiring anti-rejection medications. Our experience, to date, indicates such medication is not needed and this finding represents a scientific and clinical breakthrough in organ transplantation. While clear medical benefit was demonstrated in these two preliminary patients, there is substantial work that must be done before such transplants can be considered routine for pediatric and adult patients. We address this challenge with our team approach and emphasize the synergism that occurs when linking team members with expertise in a variety of scientific and medical disciplines to address this critical need. This new therapeutic approach could offer a tremendous benefit to children and patients in other age groups who are in desperate need of new treatment options.

Statement of Benefit to California (provided by applicant)
The citizens of California have generously invested in stem cell research and a return on their investment will include breakthroughs in medical treatments for diseases where there are currently limited options. Stem/progenitor cell-derived airway transplantation is a leading example of translational research in regenerative medicine that can be used for a host of diseases. Through this team effort scientists and physicians will lead the early promise of airway transplantation to clinical trials in California and beyond.

This research team proposes to use stem and progenitor cells to cure an extraordinarily difficult to manage and life-threatening health problem in children. Severe airway obstruction occurs in approximately 200 children in California each year. The morbidity and mortality associated with this disease is very high; approximately 25% of patients will die if not successfully treated. The knowledge gained from the tissue engineering and preclinical studies proposed will provide a new technology that can be applied to other disorders in California. We foresee that our stem cell-derived airway transplant could also be applied to treat an important subpopulation of adults with severe chronic obstructive pulmonary disease (COPD) and the large number of children and adults with severe subglottic stenoses that have proven refractory to standard surgical interventions, and patients with debilitating laryngeal scarring. Given that the prevalence rate of COPD for California citizens greater than 65 years of age approaches 10%, if even 0.1% of COPD patients in California were candidates, specifically those with

associated tracheobronchomalacia, then greater than 3,000 patients might benefit from this treatment. The methods and technology developed from this project can also be used as the basis for other similar health needs including esophageal, bladder, and bowel replacements for disorders where present treatments are very limited and impair quality of life.

Review Summary
This proposal focuses on the preclinical and initial clinical development of an engineered stem-cell based airway transplant for children with large airway disease. The proposed approach utilizes a biological scaffold with two different autologous cell types, and builds on experience with two first-in-human compassionate use cases. The applicant proposes to optimize production and characterization of the therapeutic candidate and to conduct preclinical studies including IND-enabling studies within the first three years of the project. During the fourth and final year of the project the applicant proposes to conduct a Phase 1 clinical trial in severe pediatric cases. The applicant states that the first trial would provide information on safety and efficacy, as well as allow refinement of technical aspects of the procedure and outcome measures. Data from this trial would inform future clinical trials, including early clinical studies in additional clinical settings.

Significance and Impact
- The panel characterized this proposal as a high risk / high reward project. In certain clinical scenarios proposed, the proposed treatment could be curative; however, failure could be catastrophic to the patients.

- Several reviewers judged that the magnitude of the problem (i.e. the cases for which this treatment is clinically applicable) was overstated in the application. Some cases could be treated satisfactorily with alternative surgical approaches.

- Initial results have been achieved in two human cases in which the PI has been involved.

- The project is important for the field as a demonstration of bioengineering concepts.

Project Rationale
- At this early stage of technology development, the choice of the pediatric patient population was not justified. The panel felt strongly that a staged development plan first in adults would be more appropriate.

- The panel acknowledged the proof-of-concept data in two patient cases as demonstration that the technique could work.

- The applicants present preclinical data justifying the use of each of the candidate components, both the scaffold and cells.

Therapeutic Development Readiness
- Preclinical data in the application demonstrates feasibility of the approach in a large animal model.

- Adjustment of the transplanted construct to the growth of the patient, a key safety parameter for growing pediatric patients, has not yet been demonstrated preclinically. However, a key experiment is planned as part of this proposal.

- The human proof-of-concept data in the application includes a computerized tomography scan (CT scan) and a ventilation/perfusion scan. One reviewer expected data from pulmonary function tests to be included in the application as convincing evidence that the airway could be patent during the full respiratory cycle.

- Parameters for qualification and quality control for the decellularized scaffolds were insufficient in the proposal. References describe old techniques.

- No description was provided for what would be planned for discussion at a key early regulatory meeting.

Feasibility of the Project Plan
- Reviewers were not convinced that the team could complete the IND enabling studies, the IND filing, and a Phase 1 study within the four-year timeframe.

- Specifically, the panel questioned the feasibility of completing a Phase 1 study as planned in the proposal, given the aggressive enrollment plan and no allotment for a 12-month follow up period, which the panel felt to be standard regulatory practice at this time.

- The panel felt the preclinical plan was generally adequate to be IND-enabling; however, success criteria were not clearly defined for key functional parameters.

- The clinical plan was judged to have major flaws. Two examples provided were the use of subjective clinical descriptors for study entry and the proposed stopping rules.

- The reviewers were divided on the need to study the proposed human product in preclinical models. Several reviewers felt that the studies could be accomplished with analogous constructs in the preclinical models, and that this could be discussed with the FDA prior to initiating key studies.

Principal Investigator (PI) and Development Team
- The PI was recognized as a leader in this cutting-edge technology, and his/her participation in the early case studies was acknowledged.

- The preclinical team is comprised of strong partners who can deliver the non-clinical aspects of the project.

- Participation by a pediatric surgeon with expertise in tracheal reconstruction who is credentialed at the home institution is critical to the project. At the time of the application, an individual had not yet been named.

Collaborations, Resources and Environment
- The applicant institution has excellent stem cell biology and tissue engineering capabilities, and possesses a unique asset to perform the preclinical studies.

- The panel felt that the resources necessary to complete the proposed studies are in place in the applicant institution.

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.)
- There appears to be a calculation error, since "the average cost per visit is $2.9M" which does not make sense. Other costs appear reasonable.

The following Scientific Working Group members had a conflict of interest with this application:
None

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05302: Treatment of osteoporosis with endogenous Mesenchymal stem cells

Recommendation: Recommended for Funding **Final Score:** 80
Total Funds Requested: $19,999,867

Public Abstract (provided by applicant)
Although most individuals are aware that osteoporosis is disease of increased bone fragility that results from estrogen deficiency and aging, most are unaware of the high risk and cost of the disorder. It is estimated that close to 30% of the fractures that occur in the United States each year are due to osteoporosis (Schwartz & Kagan 2002). California, with one of the largest over-age-65 populations, is expected to double the fracture rate from 1995 to 2015 (Schwartz & Kagan 2002). Current treatment of osteoporosis is focused on anti-resorptive agents that prevent further bone loss. These agents and are effective in reducing new vertebral fractures but less effective for the prevention of hip fractures, and the duration of use of one anti-resorptive class, the bisphosphonates, is limited due to a concern about weakening of the cortical bone with longterm use. The only bone growing agent that is approved by FDA is the protein, hPTH 1-34, which requires two years of daily injections, is only approved by the FDA for one course of treatment, is only effective in about 60% of treated individuals for reduction of vertebral fractures, and has not been shown to be effective in reducing new hip fractures. This leaves an unmet medical need for an anabolic or agent that stimulates bone formation for millions of elderly Californians that suffer or will suffer from this disease.

We have developed a small molecule, LLP2A-Ale that directs endogenous mesenchymal stem cells (MSCs), the cells that have the potential to grow bone tissue, to the bone surface to form new bone. We propose a development plan for this small molecule, LLP2A-Ale for the treatment of osteoporosis in both postmenopausal women and men.

Yrs. 1-2: These 2 years will be spent with optimizing the manufacturing and packaging of the small molecule, obtaining information about the efficacy and toxicity in preclinical models, and preparing documents for an FDA meeting when the preclinical studies are completed to provide comment on the proposed Phase I clinical trials.

Yrs. 3-4. We plan perform a Phase I study with two parts. Part I will study postmenopausal women with osteopenia and a fracture risk (3% for hip fracture and 20% for major nonvertebral fractures over the next 10 years). After the initial Phase I study in postmenopausal women we will perform Part 2 and study both postmenopausal women and men with similar inclusion and exclusion criteria. The primary endpoint of these studies will be change in biochemical markers of bone turnover (PINP, BSAP, osteocalcin), and secondary endpoints will be bone mineral density of the lumbar spine measured by DXA and trabecular bone volume measured by QCT. The Phase I trials will also include required pharmacokinetic and pharmacodynamic measures to obtain information about the action of this small molecule and to inform us for Phase II clinical studies in the future.

Statement of Benefit to California (provided by applicant)
Osteoporosis is a disease of the elderly that results from a process of age related bone loss that renders the bone fragile. Current osteoporosis treatments have relatively good efficacy in reducing incident fractures. However these agents (anti-resorptive agents or the anabolic agent rhPTH (1-34) only reduce the risk of vertebral fractures about 60%, and hip fractures only 40%, and these agents require years of treatment to be effective. The goal of this project is to increase bone homing of the endogenous MSCs with a small molecule (LLP2A-Ale) to form new bone as a novel treatment for osteoporosis that could cure osteoporosis with only 3-4 injections by mobilizing the endogenous MSCs to build bone. Our molecule would be highly competitive in this market as the efficacy of increasing bone mass and bone strength would be high and the risks in a very acceptable range.

The market potential for bone tissue regeneration is large as it is estimated that close to 1/3 of fractures that occur in the US each year are due to osteoporosis (Schwartz & Kagan (2002). California, with one of the largest over-age-65 populations, is expected to double the fracture rate from 1995 to 2015 (Schwartz & Kagan 2002). One study places the cost per year in osteoporotic fractures at 2.4 billion dollars

(Schwartz & Kagan 2002), establishing it as one of the highest health care costs for older individuals. The prevalence of osteoporosis is projected to increase with increasing lifespan globally both from age related bone loss and from secondary causes of bone loss including inflammatory diseases and cancer. The market potential for bone tissue regeneration is large, an estimated 2 million fractures and $19 billion in costs annually. By 2025, experts predict that osteoporosis will be responsible for approximately 3 million fractures and $25.3 billion in costs each year (publication from National Osteoporosis Foundation). The osteoporotic patients spend about $10 a month for the generic version of Fosamax, at the lower end, to about $80 a month for brand-name Fosamax or Actonel to $900 or more a month for Forteo (rhPTH (1-34).

Therefore, once validated in osteoporosis patients, this form of tissue regeneration would be effective in patients with primary osteoporosis, in patients with secondary osteoporosis due to long term glucocorticoid treatment or after chemotherapy in both men and women and to augment peak bone mass in children in whom current osteoporosis medications are contraindicated, in individuals who have had radiation to their skeletons in whom rhPTH (1-34) is contraindicated and to augment fracture healing in the elderly. Our agent would have the potential to save the State of California millions of dollars in health care and would allow these osteoporotic individuals to live longer and be independent longer.

Review Summary
This application proposes to develop a small molecule that promotes new bone growth for the treatment of osteoporosis through the clinical proof of concept. The molecule, LLP2A-Ale, is designed to direct endogenous mesenchymal stem cells (MSC) to the bone surface and promote their differentiation into bone forming cells (osteoblasts). Osteoporosis affects over 75 million people worldwide, and in the US 40% of women over 50 and 13% of men will experience an osteoporotic fracture in their lifetime. The applicants plan to develop assays, perform preclinical safety and efficacy studies in relevant animal models, perform the IND-enabling studies required by the FDA, complete scale up of cGMP manufacturing of drug substance, and initiate and complete Phase I/II clinical studies in osteoporotic subjects.

Significance and Impact
-It is currently estimated that the number of Americans with osteoporosis is predicted to increase to 61.4 million by the year 2020. This growing burden to patients, their families and the economy is only partially addressed with available therapies.

-There are several approved therapeutics for osteoporosis that increase bone mass by reducing bone turnover, but these do not stimulate bone remodeling or form new bone. The only currently approved treatment that actually increases bone formation requires costly, inconvenient daily subcutaneous injections for 2 years and is limited to one course of therapy. If successfully developed, the proposed therapeutic would build bone, only require occasional intravenous dosing and thereby have a huge positive impact upon both disease and quality of life.

Project Rationale
-Reviewers appreciated that this novel small molecule drug was specifically designed to mobilize endogenous MSCs to the bone surface and to direct their differentiation to osteoblasts which will promote new bone growth.

-Reviewers agreed with the applicants' rationale for clinical development of the proposed therapeutic in osteoporotic subjects and found it to be strongly supported by peer reviewed publications as well as numerous in vitro and in vivo studies.

Therapeutic Development Readiness
-This team has conducted preliminary discussions with the FDA and have incorporated the regulators' suggestions into their development plan.

-Reviewers found in vivo data showing increased bone mass in a mouse model of osteoporosis to be compelling and supportive of the program's readiness.

-The panel also appreciated strong, in vitro data showing that LLP2A-Ale increased MSC migration and osteoblastic differentiation, consistent with the proposed mechanism of action.

-The milestones were well described, and the majority of the reviewers agreed that a 4-year timeframe is

reasonable for completion of the study.

-The team has identified potential toxicities and has appropriately addressed these issues in their preclinical models and trial monitoring plans.

Feasibility of the Project Plan
-The fact this team has already had positive discussions with the FDA buoyed reviewer confidence that this project was feasible in the 4 year time frame.

-Reviewers appreciated the completeness of the applicants' preclinical plans (well defined toxicology models, relevant preclinical model for dose ranging, etc) to support a successful IND filing.

-The group noted that significant work remains to be done to enable successful IND submission including characterization of raw material purity, assay development and scale up of LPP2-Ale production.

Principal Investigator (PI) and Development Team
-PI is a renowned leader in the field and has extensive research and clinical experience in osteoporosis; however, the PI's experience in leading a small molecule drug development program appears limited.

-The Co-PI has extensive experience and publications in preclinical animal models of bone disease/injury. However, reviewers expressed concern about whether the Co-PI had sufficient development experience to supervise the GMP manufacturing and non-GLP pivotal safety studies. The panel further noted that the team would benefit from a professional project manager with product development experience.

Collaborations, Resources and Environment
-This molecular entity was discovered by the PI and team; intellectual property is held by the applicant institution.

-The research team has selected a successful, experienced consulting agency to provide input on technical support and management of the IND-enabling studies. Additionally, they using a toxicology lab that has specific expertise in bone toxicology.

-Additionally, the team has identified appropriate resources for production and analysis of custom cGMP grade peptides.

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 major issues raised.

The following Scientific Working Group members had a conflict of interest with this application:
Cavagnaro, Pepperl

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05309: Genetic Re-programming of Stem Cells to Fight Cancer

Recommendation: Recommended for Funding **Final Score:** 84
Total Funds Requested: $19,999,563

Public Abstract (provided by applicant)
Science has made great progress in the treatment of certain cancers with targeted and combination therapies, yet prolonged remissions or cures are rare because most cancer therapies only inhibit cell growth and/or reduce such growth but do not stop the cancer.

The study investigators propose to develop an Investigational New Drug (IND) and fully enroll a phase I clinical trial within the grant period to genetically redirect the patient's immune response to specifically attack the cancer starting from hematopoietic (blood) stem cells (HSC) in patients with advanced forms of the aggressive skin cancer malignant melanoma. Evaluation of immune system reconstitution, effectiveness and immune response during treatment will use imaging with Positron Emission Tomography (PET) scans.

The HSC treatment approach has been validated in extensive studies in the laboratory. The investigators of this grant have recently initiated a clinical trial where adult immune cells obtained from blood are genetically modified to become specific killer cells for melanoma. These cells are administered back to patients. The early data from this study is encouraging in terms of the ability to generate these cells, safely administer them to patients leading to beneficial early clinical effects. However, the adult immune cells genetically redirected to attack cancer slowly decrease over time and lose their killer activity, mainly because they do not have the ability to self-renew.

The advantage of the proposed HSC method over adult blood cells is that the genetically modified HSC will continuously generate melanoma-targeted immune killer cells, hopefully providing prolonged protection against the cancer. The IND filing with the FDA will use the modified HSC in advanced stage melanoma patients. By the end of year 4, we will have fully accrued this phase 1 clinical trial and assessed the value of genetic modification of HSCs to provide a stable reconstitution of a cancer-fighting immune system. The therapeutic principles and procedures we develop will be applicable to a wide range of cancers and transferrable to other centers that perform bone marrow and HSC transplants.

The aggressive milestone-driven IND timeline is based on our:

1) Research that led to the selection and development of a blood cell gene for clinical use in collaboration with the leading experts in the field,

2) Wealth of investigator-initiated cell-based clinical research and the Human Gene Medicine Program (largest in the world with 5% of all patients worldwide),

3) Experience filing a combined 15 investigator initiated INDs for research with 157 patients enrolled in phase I and II trials, and

4) Ability to have leveraged significant institutional resources of on-going HSC laboratory and clinical research contributed ~$2M of non-CIRM funds to pursue the proposed research goals, including the resulting clinical trial.

Statement of Benefit to California (provided by applicant)
Cancer is the leading cause of death in the US and melanoma incidence is increasing fastest (~69K new cases/year). Treatment of metastatic melanoma is an unmet local and national medical need (~9K deaths/year) striking adults in their prime (20-60 years old). Melanoma is the second greatest cancer cause of lost productive years given its incidence early in life and its high mortality once it metastasizes. The problem is severe in California, with large populations with skin types sensitive to the increased exposure to ultraviolet light. Most frequently seen in young urban Caucasians, melanoma also strikes other ethnicities, i.e., steady increases of acral melanoma in Latinos and African-Americans over the past

decades.

Although great progress has been made in the treatment of certain leukemias and lymphomas with targeted and combination therapies, few options exist for the definitive treatment of late stage solid tumors. When cancers like lung, breast, prostate, pancreas, and melanoma metastasize beyond surgical boundaries, prolonged remissions or cures are rare and most cancer therapies only inhibit cell growth and/or reduce such growth but do not stop the cancer.

Our proposal, the filing of an IND and the conduct of a phase 1 clinical trial using genetically modified autologous hematopoietic stem cells (HSC) for the immunotherapy of advanced stage melanoma allowing sustained production of cancer-reactive immune cells, has the potential to address a significant and serious unmet clinical need for the treatment of melanoma and other cancers, increase patient survival and productivity, and decrease cancer-related health care costs.

The advantage of the proposed HSC methodology over our current work with peripheral blood cells is that genetically modified stem cells will continuously generate melanoma-targeted immune cells in the patient's body providing prolonged protection against the cancer. The therapeutic principles and procedures developed here will be applicable to a wide range of cancers. Good Manufacturing Practices (GMP) reagents and clinical protocols developed by our team will be transferable to other centers where bone marrow and peripheral blood stem cell transplantation procedures are done.

Review Summary
The goal of this proposal is to file an Investigational New Drug (IND) application with the Food and Drug Administration (FDA) for a stem cell gene therapy for treating metastatic melanoma and to conduct a phase I clinical trial. The disease team proposes to redirect the patient's immune response to specifically attack the cancer by delivering genetically modified antigen-specific mature lymphocytes and hematopoietic stem cells (HSC) to patients with advanced forms of the aggressive skin cancer malignant melanoma. Genetic modifications will include a reporter such that the investigators can evaluate immune system reconstitution, effectiveness and immune response during treatment with Positron Emission Tomography (PET) scans. The applicant hypothesizes that since HSCs have the ability to self-renew, a sustained, high frequency anti-tumor cellular immune response will provide a benefit to these melanoma patients, for whom there are currently limited therapeutic options.

Significance and Impact
-The targeted patient population has few alternatives and represents a population with a clear and significant unmet medical need. All current therapies for malignant melanoma have significant limitations.

-The proposed therapeutic approach builds on prior experience, incorporates lessons learned from clinical research using mature T cells to target melanoma and will likely benefit the subset of melanoma patients eligible for this therapy.

-Impact may be limited due to complexity of the proposed approach as it may not be easily exportable to clinical sites on a wider scale. However, given the great unmet medical need in this patient population, a commercially viable product may be pursued in the event the therapy is efficacious.

-Although autologous cell based therapies are a difficult business model, the proposed approach offers a pathway to commercialization through a business entity founded by the PI.

Project Rationale
-The strong scientific rational is based upon previous clinical studies.

-The use of HSCs is innovative and represents an efficient and potentially long-term solution to the limitations of adult immune system cells based immunotherapies. The applicants are uniquely positioned to inform the field as to whether one can achieve long-term engraftment and expression using this approach.

-Reviewers were concerned about the choice of the tumor antigen, which is also expressed to a lesser extant on some normal cells, and thought another tumor-specific antigen might be better.

-Reviewers pointed out the possibility that, since the proposed antigen is expressed on some normal tissue, engineered T cells may undergo negative selection in the thymus and be eliminated.

Therapeutic Development Readiness
-The preclinical studies are appropriate and support the project plan.

-The gene therapy vector required for the proposed studies has been produced at research scale.

-The proposed timelines for IND-enabling studies and a Phase I clinical study are achievable.

Feasibility of the Project Plan
-Project plan is feasible and likely to be achievable according to the proposed timelines. Though the plan depends on successful completion of IND-enabling studies, it is likely that those studies will be completed in the indicated timeframe. Reviewers noted that the proposed patient enrollment plan might make completion of the clinical study, with all the proposed patients and by the target date, a challenge.

-The team's clinical experience in measuring objective responses to immunotherapy of melanoma as well as ex vivo immune assays to monitor surrogate end points supports the feasibility of the clinical plan.

-Reviewers appreciated the use of non-invasive imaging for in vivo monitoring and, if necessary, elimination of genetically modified immune system cells. There were, however, a lack of details on how imaging will be performed and limited evaluation of the readiness of the technology in the proposed setting. Reviewers cautioned that, depending on the expression of the transgene and sensitivity of the assay, imaging might be difficult to implement.

-Enthusiasm of some reviewers was dampened because of the complexity of combining two separate gene modified cells in the proposed study. It might be difficult to know if any efficacy or toxicity seen is from gene modified HSC or adult cell transplant.

-It will be challenging to define an appropriate conditioning regimen for the patient population, considering the known toxicities associated with the proposed myeloablative regimen.

Principal Investigator (PI) and Development Team
-The team was considered extraordinary and possesses stem cell experience and other essential attributes that should enable accomplishment of the proposed goals.

-The PI is an established translational investigator and a clinical expert in melanoma biology and clinical care.

-The development team includes a number of distinguished clinicians and scientists.

-The team is committed to advancing a stem cell based immunotherapy approach for melanoma and has a demonstrated track record for translating scientific discoveries into clinical development.

Collaborations, Resources and Environment
-Resources and environment were considered outstanding.

-The applicant institution has committed funds to support this proposal should it get approved for funding by CIRM.

-The IP position for this approach and antigen requires clarification.

-Details of collaboration with the NIH on specific memory immune cells and alternative suicide gene is not well described and was considered by some reviewers as a distraction from the primary goals and directions of the application.

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.)
- Costs associated with preparation of the regulatory packages (which includes pre IND, RAC, IRB and FDA IND) have significant overlap and are excessive.

- Costs associated with manufacturing of the gene therapy vector were assessed to be excessive.

- Estimated per patient cost for the clinical studies was assessed to be excessive.

The following Scientific Working Group members had a conflict of interest with this application:
Dropulic

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05320: Progenitor Cells Secreting GDNF for the Treatment of ALS

Recommendation: Not Recommended for Funding **Final Score:** 64
Total Funds Requested: $17,842,617

Public Abstract (provided by applicant)
This project aims to use a powerful combined neural progenitor cell and growth factor approach to treat patients with amyotrophic lateral sclerosis (ALS or Lou Gehrig's Disease). ALS is a devastating disease for which there is no treatment or cure. Progression from early muscle twitches to complete paralysis and death usually happens within 4 years. Every 90 minutes someone is diagnosed with ALS in the USA, and every 90 minutes someone dies from ALS. In California the death rate is one person every one and a half days. Human neural progenitor cells found early in brain development can be isolated and expanded in culture to large banks of billions of cell. When transplanted into animal models of ALS they have been shown to mature into support cells for dying motor neurons called astrocytes. In other studies, growth factors such as glial cell line-derived growth factor (or GDNF) have been shown to protect motor neurons from damage in a number of different animal models including ALS. However, delivering GDNF to the spinal cord has been almost impossible as it does not cross from the blood to the tissue of the spinal cord. The idea behind the current proposal is to modify human neural progenitor cells to produce GDNF and then transplant these cells into patients. There they act as "Trojan horses", arriving at sick motor neurons and delivering the drug exactly where it is needed. A number of advances in human neural progenitor cell biology along with new surgical approaches have allowed us to create this disease team approach.

The focus of the proposal will be to perform essential preclinical studies in relevant preclinical animal models that will establish optimal doses and safe procedures for translating this progenitor cell and growth factor therapy into human patients. The Phase 1/2a clinical study will inject the cells into one side of the lumbar spinal cord (that supplies the legs with neural impulses) of 12 ALS patients from the state of California. The progression in the treated leg vs. the non treated leg will be compared to see if the cells slow down progression of the disease. This is the first time a combined progenitor cell and growth factor treatment has been explored for patients with ALS.

Statement of Benefit to California (provided by applicant)
ALS is a devastating disease, and also puts a large burden on state resources through the need of full time care givers and hospital equipment. It is estimated that the cost of caring for an ALS patient in the late stage of disease while on a respiration is $200,000-300,000 per year. While primarily a humanitarian effort to avoid suffering, this project will also ease the cost of caring for ALS patients in California if ultimately successful. As the first trial in the world to combine progenitor cell and gene transfer of a growth factor, it will make California a center of excellence for these types of studies. This in turn will attract scientists, clinicians, and companies interested in this area of medicine to the state of California thus increasing state revenue and state prestige in the rapidly growing field of Regenerative Medicine.

Review Summary
This applicant proposes to develop and test Glial cell-Derived Neurotrophic Factor (GDNF)-expressing human neural progenitor cells (hNPC) as a therapy for Amyotrophic Lateral Sclerosis (ALS). ALS is a lethal disease that is characterized by severe loss of brain and spinal cord motor neurons and their associated support cells, called astrocytes. This cell loss leads to muscle weakness, paralysis, respiratory failure and death, usually within four years. The rationale behind this combination therapy is that the hNPC will differentiate to replace degenerating astrocytes, while expression of the growth factor will have a neuroprotective effect. The goals of this proposal are to perform preclinical safety and efficacy studies in relevant animal models, and to carry out Phase 1 clinical studies in ALS patients to establish safety and feasibility of this therapeutic.

Significance and Impact
- There are approximately 5,600 new cases of ALS in the USA each year and as many as 30,000 Americans may currently be affected by ALS.

- Currently, there is only one approved therapy for ALS and it has limited efficacy. If successful, this proposed therapy could have a ground-breaking impact on the treatment of ALS.

- Reviewers noted a similar study being carried out in ALS patients by another group. However, differences include the fact that the other group's cells are not engineered to secrete GDNF, and they differentiate into neurons rather than astrocytes after transplantation.

Project Rationale
- Some reviewers questioned the potential therapeutic efficacy of GDNF, referring to previous clinical trial data. One key issue is that GDNF appears only important in early stages of disease onset.

- Reviewers commented that ALS is a diffuse disease and questioned whether this focal therapy would actually impact the disease.

Therapeutic Development Readiness
- Reviewers were concerned about the lack of convincing preclinical data. In the figure measuring a functional endpoint (BBB score) there was minimal difference between the GDNF and non-GDNF groups.

- The investigators have not fully described the potential immunogenicity of allogeneic hNPCs in the context of the suggested immunosuppressive regimen. There was no significant description how this immunosuppressive regimen compares with the animal studies.

- GDNF expression was confirmed in vitro for up to 14 weeks of expansion but there are inadequate data addressing in vivo expression levels or whether gene silencing occurs in vivo.

- The applicants discuss development of a tracking method, however this was not detailed in the proposed clinical trial synopsis.

- The investigators conducted a pre-pre IND meeting with FDA in 2005 and a pre IND meeting in February of 2011 resulting in detailed suggestions for pivotal IND-enabling studies.

Feasibility of the Project Plan
- Reviewers expressed concerns about the aggressive timelines, noting that there is very little time built in between the pivotal nonclinical studies and the start of the clinical trial, thus not allowing any time should the FDA impose a clinical hold.

- There was concern about the lack of information on how the clinical sites would be trained, and how the variability between sites would be addressed. For example, there was no mention of a standardized assay for assessing cell viability prior to administering to patients.

- It was suggested that the patient follow up be longer than 12 months to look for potential tumorigenicity, immunogenicity and other safety issues.

- The use of the proposed tracer was questioned as it is taken up by host cells when transplanted cells die.

Principal Investigator (PI) and Development Team
- The PI is ideally suited to lead this effort, and has the required experience in translational neuroscience that is focused on cell and growth factor therapy.

- The team is excellent. The clinical trial physicians are outstanding members with direct clinical expertise and experience in ALS clinical trials.

Collaborations, Resources and Environment
- The investigators have not fully described how they will access Intellectual Property needed for product development.

- The preclinical CRO is well established and will do the mixed GLP/non-GLP tox studies.

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.)

- It was felt that a budget of close to $300K per patient for the clinical sites was high, and that it should be closer to $50,000 - $80,000 per patient.

Programmatic Review (if applicable)
A motion was made to move this application into Tier 3, Not Recommended for Funding. Reviewers felt the applicant failed to show behavioral efficacy data, and that it was premature to move this therapy into the clinic. It was suggested that there are well-known animal models that could be used for further testing to better develop the product. The motion carried.

The following Scientific Working Group members had a conflict of interest with this application:
Lonser

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05327: Stem Cell Gene Therapy for HIV in AIDS Lymphoma Patients

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $11,711,561

Public Abstract (provided by applicant)
The Human Immunodeficiency Virus (HIV) is still a major health problem. In both developed and underdeveloped nations, millions of people are infected with this virus. HIV infects cells of the immune system, becomes part of the cells' genetic information, stays there for the rest of the life of these cells, and uses these cells as a factory to make more HIV. In this process, the immune cells get destroyed. Soon a condition called AIDS, the Acquired Immunodeficiency Syndrome sets in where the immune system cannot fight common infections. If left untreated, death from severe infections occurs within 8 to 10 years. Although advances in treatment using small molecule drugs have extended the life span of HIV infected individuals, neither a cure for HIV infection nor a well working vaccine has as yet been developed. Drug treatment is currently the only option to keep HIV infected individuals alive. Patients have to take a combination of drugs daily and reliably for the rest of their lives. If not taken regularly, HIV becomes resistant to the drugs and continues to destroy immune cells. What makes this situation even more complicated is the fact that many patients cannot take these drugs due to severe side effects.

Stem cell gene therapy for HIV may offer an alternative treatment. Blood forming stem cells, also called bone marrow stem cells make all blood cells of the body, including immune system cells such as T cells and macrophages that HIV destroys. If "anti-HIV genes" were inserted into the genetic information of bone marrow stem cells, these genes would be passed on to all new immune cells and make them resistant to HIV. Anti-HIV gene containing immune cells can now multiply in the presence of HIV and fight the virus. In most of the previous stem cell gene therapy clinical trials for HIV, only one anti-HIV gene was used. Our approach, however, will use a combination of three anti-HIV genes which are much more potent. They will not only prevent HIV from entering an immune cell but will also prevent HIV from mutating, since it would have to escape the anti-HIV effect of three genes, similar to triple combination anti-HIV drug therapy. To demonstrate safety and effectiveness of our treatment, we will perform a clinical trial in HIV lymphoma patients. In such patients, the destruction of the immune system by HIV led to the development of a type of leukemia called "B cell lymphoma." High dose chemotherapy together with the transplantation of the patient's own bone marrow stem cells cures B cell lymphoma. We will insert anti-HIV genes in the patient's bone marrow stem cells and then transplant these gene containing cells into the HIV infected lymphoma patient. The gene containing bone marrow stem cells will produce a new immune system and the newly arising immune cells will be resistant to HIV. In this case, we have not only cured the patient's leukemia but have also given the patient an HIV resistant immune system which will be able to fight HIV.

Statement of Benefit to California (provided by applicant)
As of September 30, 2010, over 198,883 cumulative HIV/AIDS cases were reported in California. Before 2006, another 40,000 un-named cases of HIV were also reported, although some of them may be duplicates of the named HIV cases. Patients living with HIV/AIDS totaled 108,986 at the end of September 2010. These numbers continue to grow since new cases of HIV and AIDS are being reported on a daily basis and patients now live much longer. In fact, after New York, California has the second highest number of HIV cases in the nation. Although the current and improved anti-retroviral small molecule drugs have prolonged the life of HIV infected individuals, these patients, their partners, friends and relatives still have to deal with the emotional, financial, and medical consequences of the disease. The fear of side effects and the potential generation of drug resistant strains of HIV is a constant struggle that these patients have to live with for the rest of their lives. Furthermore, not every patient with HIV responds to treatment, and not every complication of HIV dissipates upon starting a drug regimen. In fact, the risk of some AIDS-related cancers still remains high despite the ongoing drug therapy. Additionally, in the current economic crisis, the financial burden of the long term treatment of these patients on California taxpayers is even more obvious. Recently, the lifetime cost of taking care of an HIV patient was calculated to be about $1.5 million. Most of this was related to the medication cost. With the introduction of new HIV medications that have a substantially higher price and with the increase in the survival of HIV/AIDS patients, the cost of taking care of these patients can be estimated to be very high.

The proposed budget cuts and projected shortfall in the California AIDS assistant programs such as ADAP will make the situation worse and could result in catastrophic consequences for patients who desperately need this kind of support. Consequently, improved therapeutic approaches and the focus on developing a cure for HIV infected patients are issues of great importance to the people of California.

Our proposed anti-HIV stem cell gene therapy strategy comprises the modification of autologous hematopoietic blood forming stem cells with a triple combination of potent anti-HIV genes delivered by a single lentiviral vector construct. This approach would engineer a patient's immune cells to become resistant to HIV infection. By transplanting these anti-HIV gene expressing stem cells back into an HIV infected patient, the ability of HIV to further replicate and destroy the patient's immune system would be diminished. The prospect of such a stem cell based therapy which may require only a single treatment (at a cost of $100,000) to functionally cure an HIV infected patient, lasting for the life of the individual, without having to take drugs would be especially compelling to the HIV community and the people of California.

Review Summary
The goal of this proposal is to demonstrate safety and effectiveness of a novel therapeutic against human immunodeficiency virus (HIV) infection in patients with relapsed/refractory B cell lymphoma. The treatment will consist of autologous bone marrow transplantation using a patient's own hematopoietic stem cells (HSC) that have been genetically modified to express three independent anti-HIV genes. The applicants hypothesize that since HSC have the ability to self-renew, these cells will allow subsequent repopulation of the patient's immune system with derivatives that are resistant to HIV. Proposed activities include completion of investigational new drug (IND)-enabling studies, filing of an IND and appropriate regulatory approvals, and initiation and completion of a Phase I/II clinical trial.

Significance and Impact
- The proposed target product profile is reasonable. However, similar protocols for HIV patients have been implemented previously with modest success. The competitiveness of the present approach hinges on achieving better gene transfer and better protection against HIV.

- If successful, the clinical impact of the approach could be significant; however, the overall impact of this approach on HIV standard-of-care is uncertain. Autologous cell-based approaches face many impediments that make this approach unlikely to benefit patients in less developed parts of the world.

- In the Target Product Profile, reviewers did not think that the proposed minimum acceptance criteria set for anti-HIV gene expression in immune system cells in vivo will be sufficient to provide clinical efficacy.

Project Rationale
- The biologic rationale to genetically induce HIV-resistant hematopoietic stem cells and the clinical rationale to take advantage of the autologous bone marrow transplantation to treat lymphoma are sound and based on data from a recent case study demonstrating a functional cure in a single HIV+ patient.

- The reviewers acknowledged that the proposed project offers a compelling opportunity to help HIV+ patients develop immunity to HIV infection, as well as to cure their lymphoma. However, they caution that treatment effectiveness faces many unsolved technical hurdles. This proposal does not plan to address those bottlenecks.

Therapeutic Development Readiness
- Some reviewers indicated that although this is a sound idea that should be brought to the clinic, additional preclinical work is required to demonstrate that proposed transduction, expression, and engraftment efficiencies will be sufficient to reduce viral load and provide the described clinical benefit. It was suggested that this project is not ready for the clinic and would be better funded as a preclinical rather than clinical project.

- Reviewers were impressed with the presented preclinical studies but were unconvinced that all the necessary proof-of-concept, safety, and product development studies have been or would be completed to allow initiation and completion of the proposed clinical studies.

- The team has proposed unrealistic timelines to produce cGMP grade reagents and to perform product qualification studies before initiating the proposed clinical studies.

- The team has underestimated the importance, challenges, and time to complete the toxicology studies required for the proposed gene modified stem cell therapeutic candidate.

Feasibility of the Project Plan
- Feasibility of the project plan was considered to be the major weakness of this proposal. The project plan has not taken into consideration a number of preclinical studies including optimization of vector transduction efficiency across multiple batches of HSC, stability of transgene expression, potential selection of resistant virus, and inclusion of tumorigenicity studies.

- Reviewers commented that the study design was not yet sufficiently evaluated and not well thought out. It is unlikely that the time for treatment interruption proposed in the study will be sufficient to evaluate the efficacy of the therapeutic candidate. Reviewers were also not convinced that the proposed clinical sites would be able to enroll the number of patients with intended clinical indication in the proposed time frame.

- Reviewers would have liked to see additional information indicating expected engraftment and demonstrating that engraftment level will be sufficient to confer clinical benefit.

Principal Investigator (PI) and Development Team
- While the PI and Co-PI have considerable experience in bone marrow transplantation and HIV research, reviewers were concerned by their lack of suitable experience in cell therapy product development.

- A reviewer commented on the lack of prior experience of the team in the manufacture of clinical grade lentiviral vector, a process that is known to be technically challenging.

Collaborations, Resources and Environment
- There is limited experience in transplanting HIV-infected patients at the applicant institution. The secondary institution is outstanding with a large HIV population but their participation in transplant-related HIV trials is also limited.

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.)
- Cost estimates for the manufacture of the clinical grade lentivirus were considered to be low.

- Transplantation costs for HIV patient was considered to be excessive.

The following Scientific Working Group members had a conflict of interest with this application:
Dropulic, Pepperl, Weber

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05352: A New Therapeutic to Reduce CSC Frequency in Breast Cancer

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $20,087,303

Public Abstract (provided by applicant)
An important benefit of the tremendous progress in stem cell research has been the recognition that stem cell pathways are frequently re-activated in cancer cells conferring stem cell-like properties on a subset of tumor cells. This understanding is the basis for the emerging field of cancer stem cell (CSC) research.

The cancer stem cell paradigm is a new approach in cancer research that has profound implications for new anti-cancer drug development. It is now widely understood that tumors are comprised of different cell types. Experimental evidence has accumulated from many laboratories indicating that different tumor cells vary dramatically in their ability to grow a new tumor. The tumor cells capable of re-growing a new tumor are the CSCs, whereas the bulk of the tumor cells lack this capacity. This property of seeding new tumor growth is analogous to the growth of distant metastases that is a major cause of mortality in cancer patients. The highly tumorigenic CSCs share certain properties with normal stem cells, but have accumulated cancer causing mutations clearly making them abnormal. It is now widely appreciated that many current therapies fail to effectively target the CSC population, and thus the CSCs mediate recurrence of disease after treatment. New drugs that target CSCs to kill them or cause them to differentiate into less dangerous, non-tumorigenic cells have the potential to provide significant benefit to patients and to dramatically improve cancer treatment.

This project is focused on developing a new anti-cancer drug with an exciting strategy to rapidly identify the specific tumor types that would most benefit and accelerate the process of evaluation and approval in breast cancer. Our drug has been shown to effectively block CSC self renewal in a variety of common types of cancer. New therapeutic agents that are effective in targeting cancer stem cells may reduce metastases and relapse after treatment thus providing a chance for improved long term survival of cancer patients. In the first phase of the project, we will complete the manufacturing of the drug for subsequent use in clinical trials and also execute safety studies that are necessary before initiating clinical trials. Next, we will test the safety of the drug in Phase 1 clinical trials. Lastly, we will determine the efficacy in breast cancer patients in Phase 2 trials. This project will utilize innovative clinical trial designs to identify the patient populations most likely to benefit from treatment with our new drug. We intend to focus our clinical testing on an important subset of women with breast cancer for whom effective therapies are currently lacking. Our project is a unique partnership of industry and academic researchers and clinicians dedicated to bringing new medicines to treat patients most in need of effective therapy. This program is designed with input from the FDA to potentially support efficient regulatory approval.

Statement of Benefit to California (provided by applicant)
Although tremendous advances have been made in the treatment of breast cancer, this disease remains a significant public health problem and is a leading cause of death in women ages 20-59. Recent research has led to the understanding that breast cancer is a heterogeneous set of diseases that can have very different prognoses. For example, the basal and triple negative subtypes of breast cancer have been found to be relatively resistant to current therapies and frequently spread to distant sites in the body. This project is focused on developing and testing a new therapeutic which targets a key pathway shown to play a significant role in these difficult to treat forms of breast cancer. We are developing unique strategies and technologies for the early detection of breast cancer in patients with poor prognoses and who would benefit from this therapy. Furthermore, our work has provided unique insights into identifying the individual patients who have the highest likelihood of responding to this therapy and is a clear example how "personalized medicine" is becoming a reality in cancer research and drug discovery.

This treatment attacks cancer stem cells, the subset of tumor cells that mediate resistance to conventional cancer therapies such as chemotherapy and radiation that results in disease recurrence after treatment. Thus, this project will provide funds for creation of a new medicine that will target women in need of new therapeutic options. Cancer stem cells are also thought to mediate disease progression and the spread of metastasis. Our new agent reduces cancer stem cell frequency, tumor recurrence and

the spread of metastatic disease in pre-clinical cancer models. Patients with advanced, metastatic cancer typically require lengthy, expensive hospitalization. This drug may reduce the incidence and relapse of metastatic cancer, thus reducing hospitalization and associated specialized care for advanced cancer patients.

In addition to the medical benefits derived from the development of a new therapeutic agent, funding this project will create and maintain high quality jobs in the state of California both in the private and public sectors. Our California-based team includes expertise in drug development, stem cell biology, early and late stage clinical trials, and is a synergistic partnership among researchers in industry, academia and community medicine within California. Funds from this project will support research efforts and clinical testing at several sites throughout the state.

Review Summary
The goal of this proposal is to develop a new anti-cancer drug that targets a signaling pathway to block cancer stem cell self-renewal in breast cancer. The applicants intend to complete IND-enabling studies for the new drug and then to carry out Phase 1 and Phase 2 clinical trials. The Phase 1 trials will test safety of the drug in patients with solid tumors, while the Phase 2 trials will study efficacy in breast cancer patients and will be designed to identify subsets of those patients that are most likely to benefit from the treatment.

Significance and Impact
- Reviewers felt that targeting this molecular pathway for cancer is a highly competitive area and were unsure what advantages this product would provide over others targeting this pathway.

Project Rationale
- Reviewers were skeptical of the choice of this indication given that the targeted pathway is known to be activated frequently in other cancers and the limited data for breast cancer suggest low frequency pathway activation.

- Reviewers were not convinced by the limited preliminary data presented that cancer stem cells in breast tumors were frequently dependent upon the targeted signaling pathway and would have liked to see data on a wider number of primary breast tumor isolates.

Therapeutic Development Readiness
- The project is well into IND enabling development. The process for drug manufacture has been developed.

Feasibility of the Project Plan
- Some reviewers felt that the timelines were reasonable and that the manufacturing, preclinical, and clinical trial logistics were well planned. Others felt that it would be difficult to complete the Phase 1 studies within two years.

- Reviewers questioned the feasibility of the post neoadjuvant Phase 2 trial because of the potential difficulty in developing the needed screening test as well as their doubts that the targeted pathway would be activated at a high enough frequency to conduct the trial.

Principal Investigator (PI) and Development Team
- This collaboration between industry and academic researchers and clinicians appears to be ideally suited to such a project and the team is fully able to implement this study.

- It is notable that the clinical investigator has interacted/published on novel trial design teams along with FDA CDER chief medical officers.

- The leadership plan is good; the team is solid with diverse and complimentary skills.

Collaborations, Resources and Environment
- Different companies have IP positions in this area. This aspect requires further diligence.

- The contract research organizations and consultants are experienced and have good track records.

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 contract research organization costs for fill, finish and label of the vialed product seem very high, as do the costs for GMP manufacture of the drug.

- The matching funds should have been applied against expenses within the scope of the application, which is the breast cancer indication.

The following Scientific Working Group members had a conflict of interest with this application:

None

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05365: A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $20,000,000

Public Abstract (provided by applicant)
Successful stem cell therapy requires the replacement of diseased or dysfunctional stem cells with healthy ones. These healthy stem cells can come from either a donor or can be stem cells that are modified by gene therapy techniques. One important step in this process of repair and replacement is to eliminate the existing diseased cells so that physical space is created for the healthy ones, and competition for environmental factors that nurture and support the stem cells are removed.

The oldest and most commonly used form of stem cell therapy is bone marrow transplantation (BMT). Thousands of patients undergo BMT yearly to treat cancers or disorders of blood formation. Bone marrow contains mixtures of cells, but only a minority are the blood forming stem cells, which are critically important as only stem cells can permanently generate new blood and immune cells. In a BMT, stem cells from a donor replace the recipient's diseased stem cells. Currently, the only way to eliminate the patient's own blood forming stem cells is to treat the recipient to accept donor cells with toxic agents such as radiation and chemotherapy.

Our team will focus on the treatment of a disorder in children called severe combined immune deficiency (SCID). SCID children are born without a functional immune system and are therefore extraordinarily susceptible to serious infections. If children with SCID are not treated, most die by the age of two. BMT is the only established cure for this disease. Unfortunately, the likelihood of successful cure is reduced by the way transplants are currently performed, using toxic treatments to prepare the children to accept the donor cells.

We will test an antibody (a type of protein) that recognizes a molecule called CD117 present on blood forming stem cells and leads to their elimination. When used in mice, this treatment enabled excellent donor stem cell engraftment and cured mice with a condition equivalent to human SCID with minimal side effects. We propose to test an antibody that targets human CD117 to safely prepare children with SCID to accept blood forming stem cells from a donor. Based on the animal studies we expect this antibody will allow engraftment of stem cells at high levels, rapidly replacing diseased blood cells with healthy blood cells. Such a result would mean safer and better outcomes for these patients.

Success in this study would have impact far beyond a superior treatment for SCID. If the antibody treatment results in a stronger blood system originating from a donor in SCID patients, this result would prove that the antibody could be used to optimize engraftment of gene-therapy modified cells and could be applied to the treatment of many other diseases that need a BMT. These diseases include, but are not limited to sickle cell anemia, thalassemia, and Fanconi's anemia; autoimmune diseases like diabetes and multiple sclerosis; and cancers that originate from the blood system such as leukemias and lymphomas.

Statement of Benefit to California (provided by applicant)
Diseases of the blood and the immune system plague thousands of Californians and millions of people world-wide. These diseases are quite diverse, ranging from blood diseases such as sickle cell anemia and beta thalassemia, to immune diseases such as severe combined immunodeficiency, HIV, and autoimmune disease including type I diabetes and multiple sclerosis. Current therapies do not fully control the symptoms of these diseases, leaving severe morbidity and early mortality as ongoing consequences. For the health of the citizens of California, both physical and financial, we need to develop cures, rather than marginally effective treatments, for a variety of these devastating blood and immune illnesses.

Hematopoietic stem cell (HSC) transplantation possesses the ability to provide a life-long cure for all of these diverse diseases, as it allows for the replacement of defective HSC. Although effective, the use of this form of treatment is severely limited because of the current need to administer chemotherapy or radiation prior to the transplant to permit engraftment of donor stem cells. The transplant procedure itself

carries a risk of death for ~10-20% of patients, and there are long-term toxicities associated with chemoradiation such as infertility, secondary malignancies, endocrine dysfunction, organ damage, and in children, mental and physical growth impairment.

By developing a novel, non-toxic antibody-based conditioning method, HSC transplants could be expanded to the treatment of non-life threatening yet debilitating diseases that are currently not transplanted due to the associated toxicities. We have achieved this goal with an antibody in mice and have identified a similar agent for use in patients. We aim to begin safely treating patients that suffer from severe combined immunodeficiency (SCID), a diverse disorder that is caused by defects in HSCs. While the incidence of SCID has been thought to be rare, preliminary results of newborn screening in California suggest the incidence is 1/30,000 newborns. In addition, a number of previously treated patients with SCID who did not engraft with donor stem cells are now developing immune failure. The clinical trial to be performed will treat immunodeficient patients from across the state of California through the network of institutions incorporated into this disease team of world-renowned stem cell and transplantation experts.

After successfully treating patients with SCID, we plan to expand this conditioning technique to other diseases, and hopefully pave the way for safe transplantation of genetically modified HSC, thereby expanding stem cell transplantation in California tremendously. We hope this novel conditioning regimen will result in a direct benefit to patients who suffer from blood and immune diseases, as well as create definitive treatments that will lead to a reduction of the massive health care burden these diseases inflict on patients and their families in California.

Review Summary
The goal of this proposal is to develop a novel antibody based approach for the treatment of severe combined immune deficiency (SCID). The therapeutic candidate is a humanized monoclonal antibody (mAb) that recognizes and depletes endogenous hematopoietic stem cells (HSC) from a patient's bone marrow. The applicants hypothesize that such an antibody would provide a safe and effective alternative to the toxic agents, such as radiation and chemotherapy, that are currently used to clear this niche and facilitate engraftment of donor HSCs. Proposed activities comprise pre-clinical and Investigational New Drug (IND)-enabling studies including pharmacological, toxicological and dose ranging studies in relevant animal models. Following acquisition of IND and appropriate regulatory approvals, the applicants propose to initiate a Phase I/II clinical study to test the therapeutic candidate in two different pediatric SCID indications.

Significance and Impact
- The proposed approach addresses an important medical need, as SCID patients are largely precluded from potentially curative allogeneic bone marrow transplants due to the toxic nature of current methods for myeloablation.

- By reducing potential risk of regimen related toxicity, the proposed approach may find broader applicability for hematopoietic transplantation in other non-malignant disorders.

Project Rationale
-The rationale for developing a less toxic conditioning regimen that could enable long term, multilineage engraftment in SCID patients is well supported.

Therapeutic Development Readiness
- The status of this project is sufficiently mature that the proposed objectives could be achieved within 4 years of project start date, provided the applicants have unfettered access to the candidate mAb.

Feasibility of the Project Plan
- Major concerns were raised about the overall feasibility of this project. Existing supplies of the candidate mAb are set to expire prior to completion of the proposed clinical trial, and no clear path has been secured to ensure the applicant has continued and necessary access to this resource, especially in the long term. Reviewers considered these issues to be show-stoppers.

- The supporting antibodies and methodology for selecting and sorting donor HSC are in a preliminary state of development. Manufacturing of these reagents to cGMP grade for the clinical trials will require substantial effort, time, costs, and potentially separate regulatory approval, none of which has been adequately addressed in the proposal.

- To improve the product development strategy, reviewers recommended an earlier pre-IND discussion with the Food and Drug Administration (FDA) to obtain feedback on the proposed toxicology studies prior to their initiation.

- The project design lacks alternate plans should the investigational mAb fail to support engraftment in the patients and also interfere with, or multiply the risks of proceeding with standard of care.

- The half life of the investigational mAb needs to be sufficiently short so as not to interfere with bone marrow engraftment, an issue that has not been well-addressed in the proposal

- The proposal lacks adequate description of the manufacturing process and analytical methods used to test, characterize, release and demonstrate the stability of the investigational mAb.

Principal Investigator (PI) and Development Team
- While the PI and Co-PI have commendable track records in hematopoiesis and bone marrow transplantation, reviewers were concerned by their lack of suitable experience with biologics product development.

Collaborations, Resources and Environment
- Resources and environment are outstanding, and collaborations were considered to be excellent.

- License and access agreements for the investigational therapeutic candidate have not been finalized and remain to be negotiated.

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 concerns were highlighted by reviewers under this review criterion.

The following Scientific Working Group members had a conflict of interest with this application:
Cavagnaro, Chopra, Cox

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05368: Development of a Targeted Therapy to Repair Osteoporosis-Related Hip Fractures

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $24,668,071

Public Abstract (provided by applicant)
We propose the development of a stem cell-targeted drug therapy to improve and accelerate bone healing in patients with osteoporotic hip fractures. Hip fractures are a devastating consequence of osteoporosis striking 1.5 million Americans and 180,000 Californians annually. Among these patients, approximately 375,000 patients in the US and 45,000 patients in California die within one year of their injury. This debilitating and potentially deadly disease-related injury currently has no effective treatment. Current treatment is typically orthopedic surgery to attempt to join the bones, 1-2 weeks of hospitalization followed by extensive rehabilitation and commonly, admission to a nursing home. Current treatment is painful, does nothing to stimulate bone regeneration, often fails, and incurs significant risks of mortality and morbidity. Standard of care leaves large numbers of hip fracture patients in intractable pain, unable to return to normal activities and at significant risk for recurrent fractures. If fracture union is not achieved, the patient may suffer long-term disability. The unmet clinical need for the population of osteoporosis patients with debilitating fracture is enormous and growing with our aging demographics.

Bone is often thought of as a permanent substance that does not change after childhood. However, bone is alive, dynamic and constantly being renewed though a process of the breakdown of old bone and the formation of new bone. As we age, more bone is lost than generated which can lead to osteoporosis, a disease of the bone that greatly increases the bone's fragility. Upon successful development of this project, the drug will drive the patient's own stem cells at the site of the injury to change into bone forming cells that will build and strengthen the affected bone to speed the healing process and reduce the risk of future fractures.

This project will take an already identified compound that is currently under manufacture, through non-clinical and clinical safety studies as well as preliminary efficacy studies as required by the Food and Drug Administration (FDA). This includes supporting data for filing an investigational new drug (IND) application to enter clinical studies and Phase I/II safety and efficacy clinical trials in patients within this grant's time frame of four years. The goal of this project is to significantly advance development of a medication that will be administered when a patient has incurred a fracture and is undergoing the current standard of care, orthopedic surgery. Utilizing the body's own cellular machinery, by inducing stem cells to build localized bone at the point of fracture, is a therapeutic strategy with a high likelihood of success with a low probability of side effects. This proposal offers a therapy that will significantly improve hip fracture patient's post-surgical prognosis, revolutionizing the treatment of hip fractures.

Statement of Benefit to California (provided by applicant)
The aim of this project is to advance the clinical development of a stem cell targeted therapy to improve and accelerate bone healing in osteoporotic hip fracture patients through Phase I/II clinical trials. Osteoporosis is a disease of the bone that increases bone fragility and the possibility of fracture. Hip fractures are a devastating consequence of osteoporosis striking approximately 180,000 Californians annually at an estimated cost of approximately $2 billion. Of these patients, an estimated 45,000 Californians die within one year of their injury. There is no approved drug to treat this scourge of California's aging population.

Current hip fracture treatment is typically orthopedic surgery to attempt to join the bones, 1-2 weeks of hospitalization followed by extensive rehabilitation and commonly, admission to a nursing home. Current treatment is painful, does nothing to stimulate bone regeneration, often fails, and incurs significant risks of mortality and morbidity. Standard of care leaves large numbers of hip fracture patients in intractable pain, unable to return to normal activities and at significant risk for recurrent fractures. If fracture union is not achieved, the patient may suffer long-term disability. The clinical unmet need for the population of California's osteoporosis patients with debilitating fracture is enormous and growing with the aging demographics of our society.

This project will advance development of a compound that is already identified and currently under manufacture, through non-clinical and clinical safety studies as well as preliminary efficacy studies as required by the Food and Drug Administration (FDA). The drug will be administered at the time of fracture when a patient is undergoing the current standard of care, orthopedic surgery. Successful development of this therapy will revolutionize the treatment of osteoporotic hip fractures; not only saving lives, but also significantly improving thousands of Californian's lives every year after sustaining a hip fracture. This therapy will also contribute to a substantial cost savings for the State of California's healthcare budget.

Review Summary
The goal of this proposal is to advance a small molecule drug for accelerating bone repair following osteoporotic hip fracture. The proposed therapy would be administered at the same time as a patient undergoes standard-of-care orthopedic surgery. The applicant claims that the treatment would drive the patient's own stem cells to become bone-forming cells, thereby speeding the healing process and potentially preventing future fractures. The applicant proposes to complete Investigational New Drug (IND)-enabling studies and conduct a Phase I/II trial within four years.

Significance and Impact
- Reviewers agreed that there is a clinical need for bone regenerative strategies, particularly for patients with osteoporosis. However, they were not convinced that this approach would have major impact, as there are currently other treatment options available for hip fracture, and outcomes are significantly improving with time.

- Reviewers found the Target Product Profile (TPP) to be somewhat lacking in details, particularly those relating to optimal indication and specifics of the biologic activity. With so little information provided regarding the identity of the compound and therefore mode of action, reviewers found it difficult to assess the competitiveness of this approach against other drugs/biologics that promote bone formation, such as parathyroid hormone and various bone morphogenetic proteins (BMPs).

- Only circumstantial evidence was provided to indicate that the proposed therapeutic specifically targets an endogenous human stem cell, as required in the RFA. Most reviewers found the proposal to be technically responsive, however, as the targeted pathway is a well-known player in stem cell biology and osteogenesis.

Project Rationale
- The scientific rationale for the project is strong. The proposed therapeutic targets a pathway that is well-known to be involved in bone repair and remodeling.

- Although extensive preliminary data were provided to document the in vitro and in vivo effects of the proposed therapeutic using rodent cells, there were no data provided to confirm that similar effects would be observed with human bone progenitor cells.

- Preliminary data indicate that the proposed therapeutic performs comparably, but not better, than a clinically approved bone growth factor.

- The potential for off-target effects of the therapeutic was not adequately considered in the application. Even with minimal systemic exposure, reviewers questioned whether the gastrointestinal tract and other organ systems might be particularly vulnerable.

- No evidence of an in vivo dose response was provided.

Therapeutic Development Readiness
-The applicant provided a well-defined set of milestones.

- Reviewers expressed concern at the premature status of the toxicology studies, noting that many therapeutic candidates fail in development due to poor toxicology results. No GLP study data were provided, and it was not clear from the application whether all of the necessary studies had been considered.

- Reviewers disagreed about whether the preclinical data provided were compelling. While preclinical efficacy data were viewed as a strength of the application, some reviewers were concerned that key

preclinical large animal studies simulating the human disease had not been completed.

- The in vitro studies performed to characterize the proposed drug delivery approach are not likely to reflect the clinical scenario. While some in vivo data were provided, reviewers believed that a more thorough analysis would be necessary.

Feasibility of the Project Plan
-Some reviewers found their ability to fully assess the project plan feasibility was limited by lack of information about the therapeutic molecule itself and possible safety considerations that might arise.

- Reviewers strongly questioned the feasibility of the proposed timeline, especially when considering the additional preclinical studies requested by the regulatory agency.

- The project plan does not account for dose ranging studies or allow sufficient time for the overall nonclinical program, which usually takes approximately 1 year to complete prior to IND preparation and submission.

- The technical and regulatory challenges associated with the proposed localized delivery method were not adequately addressed or discussed.

Principal Investigator (PI) and Development Team
- Reviewers did not feel this was a strong team. In particular, they noted that many key hires were not yet made and individuals to fill those positions had not been identified.

- The apparent view of the applicants that they could have multiple pre-IND meetings with the regulatory agency suggests a relative lack of experience with the regulatory process.

- Concern was expressed that the applicants may not have the requisite nonclinical expertise on hand to fully anticipate the needs of the nonclinical program or assess the regulatory requirements for IND-enabling studies in this indication.

-Based on the information provided, it was not clear whether the project would be sufficiently staffed and with the appropriate expertise to manage the proposed clinical trial.

Collaborations, Resources and Environment
- Reviewers were concerned that many of the potential clinical sites identified are not affiliated with a university or research institution.

-Little information on collaborators was provided, so reviewers could not adequately determine whether these collaborators would play a significant role and whether they were appropriately qualified.

- Intellectual property position appears reasonable.

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 commented that the overall budget needs refining, particularly after revising project plans in accordance with regulatory advice.

- Reviewers believed the costs of the toxicology studies are likely underestimated, whereas the costs for the proposed bone defect study were viewed as excessive.

- Reviewers noted that the matching funds offered by the applicant did not meet the suggested minimum that was defined in the RFA.

The following Scientific Working Group members had a conflict of interest with this application:
None

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05373: Recombinant Bispecific Antibody Targeting Cancer Stem Cells for the Therapy of Glioblastoma

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $19,999,347

Public Abstract (provided by applicant)
Glioblastoma is the most common and aggressive type of brain cancer in adults. Its treatment presents particular challenges-surgery to remove the tumor can cause collateral damage to healthy brain structures, the tumor often quickly re-grows after radiation and chemotherapy, and it tends to become resistant to treatment despite aggressive management. Standard therapies, which typically include a combination of surgery, radiation and chemotherapy often result in serious side effects and are ineffective long term. Unfortunately, most patients with glioblastoma survive an average of 14 months once diagnosed.

Our research has the potential to dramatically extend the long-term survival rates of patients with this type of tumor using a highly targeted yet systemic and safe approach. It focuses on an exciting new theory that brain cancer cells begin and are maintained by a small fraction of all tumor cells with stem cell properties. The theory proposes that if this small subset of cancer stem cells could be inactivated, the tumor would stop growing.

In our studies, we reasoned that cancer-specific gene alterations in glioblastoma could be a potential marker for cancer stem cells and zeroing in on these cells could result in targeted therapies. We discovered a tumor-specific marker of epidermal growth factor receptor (EGFR) called EGFRvIII and found that EGFRvIII often occurred in glioblastoma tumor cells with another marker found on normal stem cells called CD133.

We then developed a "bispecific" antibody (BsAb) that recognizes both of these markers and we showed that BsAb selectively kills cancer stem cells in glioblastoma tumors that express both CD133 and EGFRvIII, but not normal stem cells. When glioblastoma cells treated with BsAb were injected into mice, tumor formation was severely inhibited and significantly more animals survived after treatment with it.

To advance this discovery to the clinic, we have assembled a world-class and highly experienced multi-disciplinary team of experts who have carefully considered the pharmacology, toxicology and manufacturing issues that may occur during the development of BsAb for clinical use. As a result, we are ideally positioned to accomplish our immediate goal, which is to complete the necessary work to file an investigational new drug application with the Food and Drug Administration to study the safety of BsAb in a Phase 1 human clinical trial.

Our ultimate goal is to generate a safer and far more effective treatment for patients with glioblastoma that significantly improves their quality of life and long-term survival. If successful, this will be the first antibody therapeutic that is specifically designed to attack cancer stem cells, and it could be applied to other types of cancers.

Statement of Benefit to California (provided by applicant)
According to the Central Brain Tumor Registry of the United States (CBTRUS), approximately 22,340 new cases of malignant brain tumors were diagnosed the United States in 2011 with associated healthcare costs in the billions of dollars. Glioblastoma is the most common and most aggressive form of malignant brain tumor, and more Californians are diagnosed with glioblastoma each year than any other state in the nation. There is a consequent significant economic toll not only to Californians suffering from glioblastoma but also to taxpayers who bear some of the financial burden due to uninsured healthcare costs and costs related to lost job productivity, not to mention the tremendous emotional toll this disease has on patients, their families and their communities. Therapies to improve both the quality and length of life are desperately needed for glioblastoma patients who live on average a dismal 14 months once diagnosed.

In our research, we have shown that two markers of cancer stem cells, CD133 and EGFRvIII, are tightly associated in glioblastoma tumors. We have created a recombinant bispecific antibody (BsAb) to selectively target CD133 and EGFRvIII. This highly targeted approach kills glioblastoma tumor cells but not normal cells. Our primary objective for this study is to file the investigational new drug (IND) application necessary to advance the BsAb to a Phase 1 clinical trial for use in glioblastoma patients.

Californians will experience tangible benefits from this research project in several significant ways:

1) Most important, this research has the promise to dramatically extend the long-term survival rates for Californians with glioblastoma and to improve their quality of life. This will result in healthier citizens, increased employment, and reduced economic burden to the state. In addition, this therapy is potentially applicable to multiple other human cancers with high rates of occurrence in California, such as colon, lung, breast, prostate, ovary and head and neck cancers.

2) Filing the IND application will result in employment and increased knowledge of California-based companies and consultants in such areas as contract manufacturing, analytical, clinical and preclinical research and development organizations necessary to generate clinical grade antibody, develop and interpret requisite assays, conduct preclinical development programs and prepare for clinical research efforts.

3) If the therapeutic BsAb generated is commercialized, profits derived from the production of the BsAb by CIRM policy will result in improved treatments to insured patients and lower-cost treatments to the uninsured, thus ultimately benefiting all Californians.

4) Funding this research will help raise awareness of California's prominence as a national and international leader in translational stem cell research and could potentially benefit glioblastoma patients world-wide.

Review Summary
The overall goal of this project is to develop a bispecific antibody (bsAb) designed to target cancer stem cells (CSCs) in glioblastoma (GBM) tumors, by simultaneously binding to CD133 and EGFRvIII, co-expressed on the surface of GBM CSCs. The project plan lays out translational research and development activities leading to an Investigational New Drug (IND) filing, including construct optimization and humanization, evaluation of production systems, mechanism-of-action (MOA) studies, manufacturing activities and preclinical safety evaluation.

Significance and Impact
- GBM is a devastating disease with no effective treatment; this project could have high impact if successful.

- If this bsAb is as specific as the applicants claim and without any serious off-target toxicity, the product could be a breakthrough for CD133+/EGFRvIII+ tumors.

- It is difficult to determine, based on available preclinical data, if intravenous delivery of a bispecific antibody will be significantly more potent than previous strategies where monospecific antibodies were delivered directly to GBM/glioma in human clinical trials

- It is unlikely that an antibody will effectively cross the blood brain barrier (BBB) based on previous studies in this area

Project Rationale
- A key question raised by the reviewers concerned whether the antibody will cross the BBB:

-Getting antibodies across the BBB is a non-trivial issue; a serious concern is whether the concentration they will have to deliver to a patient to get enough across the BBB will have toxic effects peripherally. In addition, although the BBB may be open in glioma, GBM cells have migrated long distances and it is difficult to deliver antibody to all those areas to get the distribution needed.

-It would be important to confirm if the bispecific antibody crosses the BBB before starting IND-enabling studies for an intravenous route.

- It is not clear that this product will be sufficiently specific for tumor cells and will not target healthy cells expressing either target antigen, which raises a significant safety concern; it is unclear if there is any advantage to having a single molecule target two distinct epitopes; the applicant may not have thought through all the possible safety concerns.

- The project rationale is based on the targeting of cells that co-express EGFRVIII and CD133, which may represent a subgroup of GBM cells in a patient, but this does not take into account tumor heterogeneity.

- Reviewers were not convinced that the bispecific antibody targeted the CSC population.

- The TPP for this application was relatively weak

Therapeutic Development Readiness
- The applicant has not yet selected the final development candidate.

- Timelines do not appear to be feasible.

- The project is at a stage that is still too early to be trying to formally develop this product for IND-enabling studies.

Feasibility of the Project Plan
- Overall, the product development plan is reasonably complete, but there are specific flaws in the plan indicative of a lack of experience on the part of the PI and team.

- Defining the pharmacokinetics and specificity of a bispecific antibody will be complex.

- The applicant is proposing to conduct a significant amount of mechanistic and cell biology work which may not be necessary from a regulatory perspective. More effort should be focused on defining the product affinity, specificity, selectivity, pharmacokinetics and safety in relevant animal models.

- Knowing the effective route of delivery will have impact on formulation, concentration and dosing. Testing of the effectiveness of the bsAb (delivered in various routes) against implanted established GBMs in animal models would complement and significantly expand the in vivo information the applicants provide.

Principal Investigator (PI) and Development Team
- The PI has good understanding of GBM but limited product development experience

- Although there is less concern with the team itself as a number of highly reputable experts have been brought into the team and a leadership plan is in place, reviewers were not convinced that this group understands what needs to be done or fully appreciates what is required to file a complete well-supported IND on this candidate antibody therapeutic.

Collaborations, Resources and Environment
- It's the wrong environment and capabilities (lack of drug development experience) to do a classic drug development project

- IP will need to be licensed

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 high for just taking a product through to an IND filing.

Conditions Applied by the Planning Award Grants Working Group
- The Planning Award GWG set a condition that "to be eligible for the Disease Team Research Award competition, the applicant must provide at the time of Full Application a revised and appropriate development plan. The GWG recommended that the applicants work closely with their consultants to rationalize and redesign the development plan."

- The GWG felt the condition was met.

The following Scientific Working Group members had a conflict of interest with this application:
Black, Cavagnaro, Weber

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05394: Human Embryonic Stem Cell-Derived Cardiomyocytes for Patients with End Stage Heart Failure

Recommendation: Recommended for Funding **Final Score:** 68
Total Funds Requested: $19,999,899

Public Abstract (provided by applicant)
Patients with end-stage heart failure have a 2-year survival rate of only 50% with conventional medical therapy. This dismal survival rate is actually significantly worse than patients with AIDS, liver cirrhosis, stroke, and other comparable debilitating diseases. Currently available therapies for end stage heart failure include drug and device therapies, as well as heart transplantation. While drug and device therapies have proven effective at reducing symptoms, hospitalizations and deaths due to heart failure, new approaches are clearly required to improve this low survival rate. Organ transplantation is highly effective at increasing patient survival, but is severely limited in its potential for broad-based application by the very low number of hearts that are available for transplantation each year. Stem cell therapy may be a promising strategy for improving heart failure patient outcomes by transplanting cells rather than a whole heart. Several studies have convincingly shown that human embryonic stem cells can be differentiated into heart muscle cells (cardiomyocytes) and that these cells can be used to improve cardiac function following a heart attack. The key objective of this CIRM Disease Team Therapy proposal is to perform the series of activities necessary to obtain FDA approval to initiate clinical testing of human embryonic stem cell-derived cardiomyocytes in end stage heart failure patients.

Statement of Benefit to California (provided by applicant)
Coronary artery disease (CAD) is the number one cause of mortality and morbidity in the US. The American Heart Association has estimated that 5.7 million Americans currently suffer from heart failure, and that another 670,000 patients develop this disease annually. Cardiovascular disease has been estimated to result in an estimated $286 billion in direct and indirect costs in the US annually (NHLBI, 2010). As the most populous state in the nation, California bears a substantial fraction of the social and economic costs of this devastating disease. In recent years, stem cell therapy has emerged as a promising candidate for treating ischemic heart disease. Research by our group and others has demonstrated that human embryonic stem cells (hESCs) can be differentiated to cardiomyocytes using robust, scalable, and cGMP-compliant manufacturing processes, and that hESC-derived cardiomyocytes (hESC-CMs) can improve cardiac function in relevant preclinical animal models. In this proposal, we seek to perform the series of manufacturing, product characterization, nonclinical testing, clinical protocol development, and regulatory activities necessary to enable filing of an IND for hESC-CMs within four years. These IND development activities will be in support of a Phase 1 clinical trial to test hESC-CMs in heart failure patients for the first time. If successful, this program will both pave the way for a promising new therapy to treat Californians with heart failure numbering in the hundreds of thousands, and will further enhance California's continuing prominence as a leader in the promising field of stem cell research and therapeutics.

Review Summary
This proposal is focused on the preclinical development of allogeneic human embryonic stem cell-derived cardiomyocytes (hESC-CMs) for the treatment of end-stage heart failure (ESHF). The key objective of this proposal is to complete the preclinical, manufacturing, regulatory and clinical activities required to submit an Investigational New Drug (IND) application to the FDA within the four-year timeframe. The Phase 1 clinical study, which is beyond the scope of this proposal, will assess the safety of transplantation of hESC-CMs in ESHF patients undergoing left ventricular assist device (LVAD) implantation as a bridge toward heart transplantation.

Significance and Impact
- Regenerative treatment for heart failure is an unmet medical need. Potentially millions of individuals could benefit if this therapeutic approach were found to be safe and efficacious.

- Reviewers noted that this would be one of the few hESC-derived therapeutics in this highly competitive field.

- The Target Product Profile (TPP) adequately describes the product, dosing considerations, endpoints and potential safety concerns. The clinical objective should be clarified to reflect the team's minimal and optimal goals for a meaningful clinical and quality-of-life benefit.

- Head-to-head comparisons in preclinical models would be useful to assess competitiveness of the proposed product versus others in early clinical development.

Project Rationale
- The clinical rationale for the project is based on the unmet need for regenerative therapeutics for patients with ESHF.

- This program lays the scientific and regulatory groundwork for a unique first-in-human study which has the potential to answer key questions about cell fate and safety in diseased human hearts.

- The panel understood that the target population for the Phase 1 study is not an intended patient population for treatment, but is rather an important first step to demonstrate safety of the therapeutic candidate.

- One reviewer stated that it was not clear that the preclinical model is representative of ESHF. Others noted it may be the best available model.

Therapeutic Development Readiness
- The therapeutic approach is based on the applicant's (and other's) supporting data in multiple preclinical models of experimental cardiac infarction. These preliminary data show that cells engraft and positively impact function by multiple endpoints.

- Early data show no evidence of teratoma formation or other critical safety concerns in two studies in one preclinical model.

- The intended therapeutic candidate may not yet be fully characterized. The panel noted the importance of batch-to-batch reproducibility of proportions of both cardiomyocytes and other bystander cell types.

- It was not clear from the application whether the team considered the current achievable purity adequate to begin development. Reviewers recommended setting a concrete goal for the first year's process optimization efforts.

Feasibility of the Project Plan
- The project plan is a strength of this application, judged to be conservative and methodical, it addresses all potential roadblocks.

- Reviewers noted sound characterization methods, tools, assays, expertise and a well-considered plan to address the characterization and manufacturing hurdles.

- Transplant rejection and its potential untoward effects should be further addressed in the relevant preclinical model.

- Some milestones did not have clear success criteria; for example success criteria for biologic activity/efficacy should specify a desired functional outcome.

- One reviewer felt that the preclinical studies should include additional study groups; one group with a similar implanted cardiac device, and a second treated with immunosuppression only.

Principal Investigator (PI) and Development Team
- This international collection of experts in cardiac stem cell biology, clinical innovation, imaging, and hESC manufacturing was noted as a major strength of the application.

- Many of the California leaders in cardiac stem cell biology and cardiac therapeutic development are participating in this proposed project.

- The team has a strong track record in cardiac therapeutic innovation.

- The degree of regulatory experience among the scientific team for this type of therapeutic approach was unclear in the application.

- The leadership plan did not address a process for making Go / No Go decisions.

Collaborations, Resources and Environment
- The team will need to negotiate key licenses in order to commercialize the potential therapeutic. This was not judged to be a barrier to completing the project, but should be addressed immediately.

- An extensive network of collaborators, both existing and new, was judged to be a strength of the application.

- The resources available to the team across non-clinical, clinical, and early stage manufacturing are considered among the best-in-class.

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.)
- One reviewer judged the budget to be high overall to take the cell-based therapy to IND filing (with no clinical costs included).

- One reviewer noted the large number of post docs on the award, suggestive of a large amount of research activities.

Programmatic Review (if applicable)
A motion was made to move this application into Tier 1, Recommended for Funding. The project seeks to develop an hESC-derived therapeutic. The application represents a unique opportunity to address cell fate and safety in an optimal first clinical setting, and will move the field significantly beyond information that can be gained in a xenotransplantation setting. The motion carried.

The following Scientific Working Group members had a conflict of interest with this application:
None

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05410: A CIRM Disease Team to Develop Allopregnanolone for Prevention and Treatment of Alzheimer's Disease

Recommendation: Not Recommended for Funding **Final Score:** 63
Total Funds Requested: $19,977,584

Public Abstract (provided by applicant)
Alzheimer's disease (AD) is now a nation-wide epidemic and California is at the epicenter of the epidemic. One-tenth of all people in the United States diagnosed with AD live in California. In the US, 5.4 million people have AD and another American develops AD every 69 seconds. No therapeutic strategies exist to prevent or treat AD. Further, current therapies neither treat the disease nor sustain therapeutic benefit. Our goal is to develop a small molecule therapeutic, allopregnanolone (AP), that will prevent and treat AD. AP promotes the ability of brain to regenerate itself by increasing the number and survival of newly generated neurons. The AP-induced increase in newly generated neurons was associated with a reversal of cognitive deficits and restored learning and memory function to normal in a mouse model of AD. Remarkably, AP also reduced the amount of AD pathology in the brain. The unique mechanism of AP action reduces the risk that AP would cause proliferation of other cells in the body. Preclinical findings indicate that AP has the potential to be effective for both the prevention of and early stage treatment of Alzheimer's disease. Further, AP was effective in aged normal mice and induced neurogenesis and restored cognitive function suggesting that AP could be beneficial for sustaining cognitive function and prevent development of AD in a normal aged population. AP has been proven safe in male and female animals and humans. Together, these findings provide a strong foundation on which to conduct a clinical trial of AP in persons with mild cognitive impairment, persons at risk for AD and in those diagnosed AD. We propose a regenerative therapeutic development project that includes late-stage FDA mandated IND-enabling chronic AP exposure, manufacturing and CMC of AP, IND FDA submissions followed by two clinical trials. The first clinical trial is to assess the safety and tolerance of once per week exposure to multiple doses of AP for 12 weeks and to evaluate whether AP is cleared from the blood. We will also evaluate the effect of AP on cognition and effects in brain that could be indicative of regeneration by measuring, by MRI, hippocampal volume, white matter integrity and a marker of functional connectivity. MRI will also be included for safety purposes, as required by FDA, to rule out occurrence of amyloid related imaging abnormalities (ARIA). In the second, proof of concept trial, 144 participants will be randomized to a single AP dose (selected based on the prior dosing and safety study) or placebo, given weekly over 48 weeks. The primary objectives of this clinical trial are to further assess safety and tolerability and to determine the impact of AP on cognition and MRI biomarker outcomes to support subsequent phase 3 development. Joining us in this endeavor are internationally recognized experts who share our commitment to developing a therapeutic to halt the epidemic of AD.

Statement of Benefit to California (provided by applicant)
California is at the epicenter of the epidemic of Alzheimer's disease (AD). Nationwide there are 5.4 million persons living with AD. Ten percent or over half a million Californians have AD. Among California's baby boomers aged 55 and over, one in eight will develop AD. It is estimated that one in six Californians will develop a form of dementia. By 2030 the number of Californians living with AD will double to over 1.1 million. While all races and ethnic groups and regions of the state will be affected, not all regions within California will be equally affected. Los Angeles County has the greatest population in the state and thus will be the true epicenter of the Alzheimer's epidemic in California. Alzheimer's is a disease that affects an entire family, community and health care system. Nation-wide there are nearly 15 million Alzheimer and dementia caregivers providing 17 billion hours of unpaid care per year. Total costs for caring for people with AD, totals $183 billion per year. California shouldered $18.3 billion of those costs and most of those costs were born by persons and health care services in Los Angeles County. Because of the psychological and physical toll of caring for people with Alzheimer's, caregivers had $7.9 billion in additional health care costs. Proportionally that translates into $790 million of health care costs for Californians. In total, California spent over $19 billion per year for costs associated with Alzheimer's disease. Multiple analyses indicate that a delay of just 5 years can reduce the number of persons diagnosed with Alzheimer's by 50% and dramatically reduce the associated costs. We seek to develop a regenerative therapeutic, allopregnanolone (AP) to prevent and treat AD. AP promotes the innate regenerative capacity of the brain to increase the pool of neural progenitor cells. The AP-induced

increase in neurogenesis was associated with a reversal of cognitive deficits and restored learning and memory function to normal in a mouse model of AD. Further, AP reduced the development of AD pathology. AP crosses the blood brain barrier and acts through a mechanism unique to neural progenitor cells and thus is unlikely to exert proliferative effects in other organs. Because AP was efficacious in both pre pathology and post-pathology stages of AD progression, AP has the potential to be effective for both prevention of and early stage treatment of AD. A regenerative therapeutic for Alzheimer's that both halts the disease while regenerating the brain will restore both the person afflicted with the disease and those that give care.

Review Summary
This proposal focuses on the clinical development of a small molecule therapeutic, allopregnanolone, for Alzheimer's disease (AD). Preclinical data indicate that allopregnanolone increases the number and survival of newly born neurons, reduces AD-related pathology and improves cognitive deficits in a rodent model of AD. The applicant proposes to conduct two clinical trials of allopregnanolone, which has already undergone initial safety testing in humans. The first trial would further test its safety, establish dosing and look for preliminary efficacy in AD patients. The second, larger and longer clinical trial would aim to establish proof-of-concept for the therapy by testing allopregnanolone versus a placebo control.

Significance and Impact
- The responsiveness of this proposal to the RFA is marginal. While the applicant presents preclinical data demonstrating that allopregnanolone has effects on neural progenitor cells (NPCs), it is not clear that these effects are responsible for the cognitive improvement observed in rodent models of AD. The pharmacological target of allopregnanolone is widely expressed in the nervous system and thus the drug may produce its effects through mechanisms unrelated to NPC proliferation and differentiation.

- AD represents an enormous unmet medical need as there are currently no effective treatments for this devastating and prevalent disease.

- The Target Product Profile (TPP) does not define the degree of benefit that would be clinically meaningful in mild to moderate AD patients. This would be an important criterion in setting a go/no-go decision point for the program.

- The applicant does not discuss several clinical trials evaluating molecules that share targets with allopregnanolone, including a completed trial of lorazepam in AD and several ongoing trials of pregnanolone. While these trials may not be directly competitive, their study designs or results could inform this development program.

Project Rationale
- The side effects of sedation and memory impairment observed in a previous clinical trial of allopregnanolone add significant risk to the project. These side effects may make it difficult to observe cognitive improvement in AD patients. It is not clear from the clinical protocol that the investigators have carefully considered this possibility and additional preclinical studies may be required to support a trial design where benefit can be observed even if sedation occurs.

- The preclinical data are robust and demonstrate efficacy of allopregnanolone in a rodent model of AD.

Therapeutic Development Readiness
- The applicant has already conducted a pre-IND meeting with FDA and has received positive and constructive feedback. The applicant has designed further preclinical safety studies to address specific FDA concerns.

- Allopregnanolone has been tested in healthy human subjects and initial data supporting its safety have been obtained.

Feasibility of the Project Plan
- The project plan is feasible although the timeline is tight. Inadequate time is built in between database lock for the first trial and protocol submission for the second.

Principal Investigator (PI) and Development Team
- The PI is well qualified to lead this development program. S/he has published extensively on neurosteroids and has an excellent track record to support the proposed studies.

- The Co-PI is highly experienced in the design and execution of clinical studies for AD.

- The applicant has assembled a skilled team that encompasses the many disciplines required for a program of this scope.

Collaborations, Resources and Environment
- The impact of this therapeutic approach could be severely affected by the limited intellectual property (IP) protection for allopregnanolone, which is in the public domain. Reviewers noted that two large and expensive Phase III trials would ultimately be required for FDA approval and funding for these trials would be unlikely without adequate IP protection. They recommended that the applicant develop another compound that could be protected by a composition of matter patent or alternatively, pursue an oral formulation of allopregnanolone which could be protected by a formulation patent.

- The applicant has assembled a strong scientific advisory board with excellent experience in AD drug development.

- The contract research organization that will run the clinical studies is qualified and has extensive experience in neurological indications.

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 noted that clinical trial and manufacturing costs are high and don't track enrollment.

- The budget for preclinical studies is appropriate.

Conditions Applied by the Planning Award Grants Working Group (GWG)
- The Planning Award GWG set a condition that "to be eligible for the Disease Team Therapy Development Research Award competition, the applicant must at the time of Full Application address how a non-toxic and efficacious dose has been or will be distinguished from a dose that acutely impairs memory."

- The applicant addressed this condition in several ways: by changing their proposed route of administration, choosing doses for their first clinical trial lower than that which has been shown to impair memory, and conducting a pharmacokinetic/pharmacodynamic simulation study.

- Reviewers cautioned that the sedative effect of allopregnanolone may not be solely responsible for the memory impairment observed in a previous human trial. They also noted that the applicant does not discuss published studies linking allopregnanolone levels to memory impairment in animal models. However, reviewers ultimately agreed that the condition had been met.

Programmatic Review (if applicable)
A motion was made to move this application into Tier 3, Not Recommended for Funding. Reviewers summarized the scientific review. They argued that given the known side effects of allopregnanolone the risk/benefit ratio for this program might justify a small trial, but not a larger efficacy trial. Reviewers reiterated that even if successful in Phase II studies, it is not clear that this candidate could go further, given the limited IP protection. The motion carried.

The following Scientific Working Group members had a conflict of interest with this application:
None

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05415: MSC engineered to produce BDNF for the treatment of Huntington's disease

Recommendation: Recommended for Funding **Final Score:** 87
Total Funds Requested: $18,950,061

Public Abstract (provided by applicant)
One in every ten thousand people in the USA has Huntington's disease, and it impacts many more. Multiple generations within a family can inherit the disease, resulting in escalating health care costs and draining family resources. This highly devastating and fatal disease touches all races and socioeconomic levels, and there are currently no cures. Screening for the mutant HD gene is available, but the at-risk children of an affected parent often do not wish to be tested since there are currently no early prevention strategies or effective treatments.

We propose a novel therapy to treat HD; implantation of cells engineered to secrete Brain-Derived Neurotrophic factor (BDNF), a factor needed by neurons to remain alive and healthy, but which plummets to very low levels in HD patients due to interference by the mutant Huntingtin (htt) protein that is the hallmark of the disease. Intrastriatal implantation of mesenchymal stem cells (MSC) has significant neurorestorative effects and is safe in animal models. We have discovered that MSC are remarkably effective delivery vehicles, moving robustly through the tissue and infusing therapeutic molecules into each damaged cell that they contact. Thus we are utilizing nature's own paramedic system, but we are arming them with enhanced neurotrophic factor secretion to enhance the health of at-risk neurons. Our novel animal models will allow the therapy to be carefully tested in preparation for a phase I clinical trial of MSC/BDNF infusion into the brain tissue of HD patients, with the goal of restoring the health of neurons that have been damaged by the mutant htt protein.

Delivery of BDNF by MSC into the brains of HD mice is safe and has resulted in a significant reduction in their behavioral deficits, nearly back to normal levels. We are doing further work to ensure that the proposed therapy will be safe and effective, in preparation for the phase I clinical trial. The significance of our studies is very high because there are currently no treatments to diminish the unrelenting decline in the numbers of medium spiny neurons in the striata of patients affected by HD. Our biological delivery system for BDNF could also be modified for other neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia (SCA1), Alzheimer's Disease, and some forms of Parkinson's Disease, where neuroregeneration is needed. Development of novel stem cell therapies is extremely important for the community of HD and neurodegenerative disease researchers, patients, and families. Since HD patients unfortunately have few other options, the potential benefit to risk ratio for the planned trial is very high.

Statement of Benefit to California (provided by applicant)
It is estimated that one in 10,000 CA residents have Huntington's disease (HD). While the financial burden of HD is estimated to be in the billions, the emotional cost to friends, families, and those with or at risk for HD is immeasurable. Health care costs are extremely high for HD patients due to the long progression of the disease, often for two decades. The lost ability of HD patients to remain in the CA workforce, to support their families, and to pay taxes causes additional financial strain on the state's economy. HD is inherited as an autosomal dominant trait, which means that 50% of the children of an HD patient will inherit the disease and will in turn pass it on to 50% of their children. Individuals diagnosed through genetic testing are at risk of losing insurance coverage in spite of reforms, and can be discriminated against for jobs, school, loans, or other applications. Since there are currently no cures or successful clinical trials to treat HD, many who are at risk are very reluctant to be tested. We are designing trials to treat HD through rescuing neurons in the earlier phases of the disease, before lives are devastated.

Mesenchymal stem cells (MSC) have been shown to have significant effects on restoring synaptic connections between damaged neurons, promoting neurite outgrowth, secreting anti-apoptotic factors in the brain, and regulating inflammation. In addition to many trials that have assessed the safety and efficacy of human MSC delivery to tissues via systemic IV infusion, MSC are also under consideration for treatment of disorders in the CNS, although few MSC clinical trials have started so far with direct delivery

to brain or spinal cord tissue. Therefore we are conducting detailed studies in support of clinical trials that will feature MSC implantation into the brain, to deliver the neurotrophic factor BDNF that is lacking in HD. MSC can be transferred from one donor to the next without tissue matching because they shelter themselves from the immune system. We have demonstrated the safe and effective production of engineered molecules from human MSC for at least 18 months, in pre-clinical animal studies, and have shown with our collaborators that delivery of BDNF can have significant effects on reducing disease progression in HD rodent models.

We are developing a therapeutic strategy to treat HD, since the need is so acute. HD patient advocates are admirably among the most vocal in California about their desire for CIRM-funded cures, attending almost every public meeting of the governing board of the California Institute for Regenerative Medicine (CIRM). We are working carefully and intensely toward the planned FDA-approved approved cellular therapy for HD patients, which could have a major impact on those affected in California. In addition, the methods, preclinical testing models, and clinical trial design that we are developing could have far-reaching impact on the treatment of other neurodegenerative disorders.

Review Summary
This proposal is focused on a genetically modified cell therapy for Huntington's disease (HD), an inherited neurodegenerative disorder. The applicant has developed mesenchymal stem cells (MSCs) that are modified to secrete brain-derived neurotrophic factor (BDNF) as a potential treatment for HD. BDNF is a protein that promotes the growth and survival of neurons and is expressed at low levels in the HD brain. The applicant proposes to complete the preclinical safety, efficacy and manufacturing work required to submit an Investigational New Drug (IND) application to the FDA. The applicant also proposes the completion of two clinical trials. The first would be an observational trial to establish a clinical baseline for each HD patient enrolled, which would be completed in Years 1 and 2 of the award. The second trial would be a Phase I study to determine the safety of transplantation of BNDF-secreting MSCs in HD patients, which would be completed in Years 3 and 4.

Significance and Impact
- HD is a devastating disease with a significant unmet medical need. Although BDNF therapy would not be expected to cure HD, it has the potential to slow disease progression. There are currently no treatments available that slow the progression of HD, so the proposed therapeutic could have a major impact on the disease.

- BDNF has been implicated in a number of other neurological diseases and so a successful trial of BDNF-secreting MSCs in HD could also have a broader impact.

- The Target Product Profile (TPP) is focused on the Phase I trial when it should instead reflect the aspirational attributes of an FDA approved product. Clinically meaningful efficacy endpoints should be described in the TPP and the potential for cell overgrowth or tumor formation should be listed under safety, even though the risk is slight.

Project Rationale
- The scientific rationale is compelling. It is based on multiple studies that have shown that BDNF levels are reduced in HD and that restoring BDNF can reduce cell death and improve function in animal models of the disease.

- The applicant has demonstrated preclinical proof-of-concept for the therapeutic approach in a rodent model of HD.

Therapeutic Development Readiness
- The project appears ready for clinical translation. It is likely to result in an IND application at the beginning of Year 3 and completion of the Phase I trial by the end of Year 4.

- The team has already interacted with the FDA and received feedback, manufactured GMP grade BDNF-secreting MSCs and performed initial safety studies.

- The manufacturing strategy and timeline are reasonable and feasible.

Feasibility of the Project Plan
- The project plan is well thought out and feasible.

- The proposed observational trial is a strength of the project plan. The course of HD can be highly variable among patients and the observational trial will provide an important clinical baseline.

- Reviewers recommended that the applicant increase the size of the observational patient cohort significantly. They noted that the anticipated percentage of patients carrying over from the observational trial to the interventional trial is overly optimistic given the many reasons patients may drop out or become ineligible.

Principal Investigator (PI) and Development Team
- The PI has a great deal of experience managing HD patients and has been involved in a number of HD clinical trials.

- The Co-PI has demonstrated success in translating discovery research into first-in-human clinical trials.

- The clinical team is strong and has worked together on previous clinical projects.

- There is some overlap and redundancy in some of the staff roles proposed, for example among the clinical fellow, nurse practitioner and research associate for clinical operations. In addition, there is overlap in the expertise of some of the consultants, both between the consultants and with other members of the team.

Collaborations, Resources and Environment
- The resources and environment are excellent. In particular, the team has access to a GMP facility that has demonstrated the ability to produce GMP grade lentiviral vectors.

- The international collaboration with neural transplantation experts is a strength.

- Consultants with cell and gene therapy experience have been identified.

- The team's intellectual property strategy is not well described and freedom to operate is not presented.

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.)
- CIRM staff recommended that the team parallel track activities to reduce the proposed 12-month gap between IND filing and initial patient dosing.

- Justification should be provided for the GLP validation study.

The following Scientific Working Group members had a conflict of interest with this application:
Cox, Dipersio, Dropulic, Lonser, Pepperl, Weber

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05416: Restoration of memory in Alzheimer's disease: a new paradigm using neural stem cell therapy

Recommendation: Not Recommended for Funding **Final Score:** 61
Total Funds Requested: $20,000,000

Public Abstract (provided by applicant)
Alzheimer's disease (AD), the leading cause of dementia, results in profound loss of memory and cognitive function, and ultimately death. In the US, someone develops AD every 69 seconds and there are over 5 million individuals suffering from AD, including approximately 600,000 Californians. Current treatments do not alter the disease course. The absence of effective therapies coupled with the sheer number of affected patients renders AD a medical disorder of unprecedented need and a public health concern of significant magnitude. In 2010, the global economic impact of dementias was estimated at $604 billion, a figure far beyond the costs of cancer or heart disease. These numbers do not reflect the devastating social and emotional tolls that AD inflicts upon patients and their families. Efforts to discover novel and effective treatments for AD are ongoing, but unfortunately, the number of active clinical studies is low and many traditional approaches have failed in clinical testing. An urgent need to develop novel and innovative approaches to treat AD is clear.

We propose to evaluate the use of human neural stem cells as a potential innovative therapy for AD. AD results in neuronal death and loss of connections between surviving neurons. The hippocampus, the part of the brain responsible for learning and memory, is particularly affected in AD, and is thought to underlie the memory problems AD patients encounter. Evidence from animal studies shows that transplanting human neural stem cells into the hippocampus improves memory, possibly by providing growth factors that protect neurons from degeneration. Translating this approach to humans could markedly restore memory and thus, quality of life for patients.

The Disease Team has successfully initiated three clinical trials involving transplantation of human neural stem cells for neurological disorders. These trials have established that the cells proposed for this therapeutic approach are safe for transplantation into humans. The researchers in this Disease Team have shown that AD mice show a dramatic improvement in memory skills following both murine and human stem cell transplantation. With proof-of-concept established in these studies, the Disease Team intends to conduct the animal studies necessary to seek authorization by the FDA to start testing this therapeutic approach in human patients.

This project will be conducted as a partnership between a biotechnology company with unique experience in clinical trials involving neural stem cell transplantation and a leading California-based academic laboratory specializing in AD research. The Disease Team also includes expert clinicians and scientists throughout California that will help guide the research project to clinical trials. The combination of all these resources will accelerate the research, and lead to a successful FDA submission to permit human testing of a novel approach for the treatment of AD; one that could enhance memory and save lives.

Statement of Benefit to California (provided by applicant)
The number of AD patients in the US has surpassed 5.4 million, and the incidence may triple by 2050. Roughly 1 out of every 10 patients with AD, over 550,000, is a California resident, and alarmingly, because of the large number of baby-boomers that reside in this state, the incidence is expected to more than double by 2025. Besides the personal impact of the diagnosis on the patient, the rising incidence of disease, both in the US and California, imperils the federal and state economy.

The dementia induced by AD disconnects patients from their loved ones and communities by eroding memory and cognitive function. Patients gradually lose their ability to drive, work, cook, and carry out simple, everyday tasks, ultimately losing all independence. The quality of life for AD patients is hugely diminished and the burden on their families and caregivers is extremely costly to the state of California. Annual health care costs are estimated to exceed $172 billion, not including the additional costs resulting from the loss of income and physical and emotional stress experienced by caregivers of Alzheimer's patients. Given that California is the most populous state and the state with the highest number of baby-

boomers, AD's impact on California families and state finances is proportionally high and will only increase as the AD prevalence rises.

Currently, there is no cure for AD and no means of prevention. Most approved therapies address only symptomatic aspects of AD and no disease-modifying approaches are currently available. By enacting Proposition 71, California voters acknowledged and supported the need to investigate the potential of novel stem cell-based therapies to treat diseases with a significant unmet medical need such as AD.

In a disease like AD, any therapy that exerts even a modest impact on the patient's ability to carry out daily activities will have an exponential positive effect not only for the patients but also for their families, caregivers, and the entire health care system. We propose to evaluate the hypothesis that neural stem cell transplantation will delay the progression of AD by slowing or stabilizing loss of memory and related cognitive skills. A single, one-time intervention may be sufficient to delay progression of neuronal degeneration and preserve functional levels of memory and cognition; an approach that offers considerable cost-efficiency.

The potential economic impact of this type of therapeutic research in California could be significant, and well worth the investment of this disease team proposal. Such an approach would not only reduce the high cost of care and improve the quality of life for patients, it would also make California an international leader in a pioneering approach to AD, yielding significant downstream economic benefits for the state.

Review Summary
The goal of this proposal is to develop human neural stem cells (hNSCs) as a potential therapy for Alzheimer's disease (AD). Although Alzheimer's disease affects over 5 million individuals in the US and is the sixth leading cause of death, the few therapies available are only palliative and do not alter the disease course. The rationale behind the proposed therapy is that hNSCs transplanted into the hippocampus will express proteins that promote survival of host neurons, thereby slowing or preventing loss of memory and cognitive functions. The applicant proposes to conduct clinical grade manufacturing of hNSC and to complete preclinical safety and efficacy studies, culminating in the filing of an Investigational New Drug (IND) application for initiation of a Phase I human clinical trial in AD patients.

Significance and Impact
- The reviewers agreed there is a significant unmet medical need for more efficacious and safe therapeutics for AD.

- The Target Product Profile (TPP) was vague, lacking demonstration of how the proposed product would be evaluated and ultimately distinguished from marketed competitor products and other cellular therapies currently in clinical trials.

Project Rationale
- A major weakness of this proposal was the lack of a rationale for how a localized injection of hNSCs could treat a diffuse neurological disease.

- The optimal location for transplantation of the hNSCs is not established. In the preclinical models the hippocampus area was investigated but no alternatives were discussed. While the applicant presents a good rationale for focusing on the hippocampus, at least one reviewer cautioned that this may be too restrictive of an approach.

- Some reviewers commented that the use of only small animal models may not be predictive for humans considering the much smaller ratio of treatment area to brain in the human.

- Reviewers were not convinced that in the engrafted animals the level of formation of functional circuits and repair would be predictive of a therapeutic effect in humans.

- The applicant presents data to support the role of a specific growth factor in achieving preclinical benefit. Alternative methods to deliver the growth factor are not addressed.

Therapeutic Development Readiness
- This application is supported by some very good nonclinical toxicology work in relevant animal models, including a tumorigenicity study.

- One efficacy experiment using human hNSC transplanted in a preclinical model resulted in improvements in context recognition and place recognition when tested at one month, as well as evidence of engraftment of the human stem cell progeny (glia and neurons).

Feasibility of the Project Plan
- Efficacy endpoints described for the clinical trial may be difficult to quantify which may make it difficult to assess preliminary efficacy readout.

- Reviewers were concerned about the commercial feasibility of the cell supply since each working cell bank will be sufficient for a very limited number of patients. It was not clear if this calculation took into consideration higher doses that might be required based on clinical trial dose-finding studies.

- In general reviewers agreed the preclinical model was appropriate, however questioned how adequate this model would be to perform dose-ranging studies, due to potential anatomical limitations, thus potentially advancing suboptimal doses to the clinic.

Principal Investigator (PI) and Development Team
- The PI is an experienced investigator in the neurological field and has previous successful experience with filing IND applications.

- The team has a strong expertise with the preclinical models as well as prior experience testing neural stem cells in clinical trials.

- The leadership plan is well articulated and appropriate.

Collaborations, Resources and Environment
- The resource subcontractors are all excellent and of high quality, including preeminent contract research organizations very experienced in IND-enabling studies, manufacturing and quality control.

- There is a significant amount of Intellectual Property filed around the composition of matter and methods to manufacture, however no Freedom to Operate (FTO) was provided or described.

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 proposed for the preclinical safety studies was excessive. Reviewers suggested perhaps the team could leverage prior safety data from previous IND studies with this proposed cell line.

- Reviewers had mixed opinions about the appropriateness of the manufacturing costs. Some felt the manufacturing costs were excessive while others felt the cost was attributable to the need to remanufacture.

Programmatic Review (if applicable)
A motion was made to move this application into Tier 3, Not Recommended for Funding. The panel recognized that the cell source was potentially ready for clinical development, but expressed strong concerns that aspects of the preclinical and clinical rationale need to be further developed to warrant moving this candidate toward an IND in the Alzheimer's disease indication. The motion carried.

The following Scientific Working Group members had a conflict of interest with this application:
Black, Noble, Pepperl

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05423: Phase I study of IM Injection of VEGF-Producing MSC for the Treatment of Critical Limb Ischemia

Recommendation: Recommended for Funding **Final Score:** 79
Total Funds Requested: $14,184,595

Public Abstract (provided by applicant)
Critical limb ischemia (CLI) represents a significant unmet medical need without any approved medical therapies for patients who fail surgical or angioplasty procedures to restore blood flow to the lower leg. CLI affects 2 million people in the U.S. and is associated with an increased risk of leg amputation and death. Amputation rates in patients not suitable for surgery or angioplasty are reported to be up to 30-50% after 1 year. Patients who are not eligible for revascularization procedures are managed with palliative care, but would be candidates for the proposed phase I clinical trial.

In an effort to combat CLI, prior and ongoing clinical trials that our group and others have conducted have evaluated direct injection of purified growth factors into the limb that has low blood flow. Some trials have tested plasmids that would produce the blood vessel growth factors for a short period of time. These therapies did show benefit in early stage clinical trials but were not significantly better than controls in Phase III (late stage) trials, probably due to the short duration of presence of the growth factors and their inability to spread to the areas most needed. Other clinical trials ongoing in our vascular center and others are testing the patient's own stem cells, moved from the bone marrow to the damaged limb, and those studies are showing some benefit, although the final assessments are not yet completed. Stem cells can have benefit in limb ischemia because they can actively seek out areas of low oxygen and will produce some growth factors to try to encourage blood vessel growth. But in cases where the circulation needs very high levels of rescue, this strategy might not be enough.

As an improved strategy we are combining the stem cell and growth factor approaches to make a more potent therapy. We have engineered human Mesenchymal Stem Cells (MSCs) from normal donor bone marrow to produce high levels of the strong angiogenic agent VEGF for this novel approach (MSC/VEGF). We and others have documented over the past 20+ years that MSC are capable of sustained expression of growth factors, migrate into the areas of lowest oxygen in the tissues after injection, and wrap around the damaged or tiny blood vessels to secrete their factors where they are needed most, to restore blood flow.

These MSC/VEGF cells are highly potent, safe and effective in our preclinical studies. The human stem cells are designed to produce VEGF as "paramedic delivery vehicles armed with growth factor" have rapidly restored blood flow to the limbs of rodents who had zero circulation in one leg. With funding that could be potentially obtained through the proposed application we will follow the detailed steps to move this candidate therapy into clinical trials, and will initiate and complete an early phase clinical trial to test safety and potential efficacy of this product that is designed to save limbs from amputation.

Statement of Benefit to California (provided by applicant)
Critical Limb Ischemia (CLI) represents a significant unmet medical need without any curative therapies in its end stages, after even the best revascularization attempts using sophisticated catheters, stents, and bypass surgeries have failed. CLI affects over 2 million people in the US and the prevalence is increasing due to the aging of our population and the diabetes epidemic. In 2007, the treatment of diabetes and its complications in the USA generated $116 billion in direct costs; at least 33% of these costs were linked to the treatment of ischemic foot ulcers, associated with CLI. Once a patient develops CLI in a limb, the risk of needing amputation of the other limb is 50% after 6 years, with devastating consequences. Treatment costs are immense and lives are significantly shortened by this morbid disease.

The symptoms associated with this very severe form of lower extremity peripheral artery disease (PAD) are pain in the foot at rest, non- healing ulcers, limb/digital gangrene and delayed wound healing. The quality of life for those with CLI is extremely poor and reported to be similar to that of patients with end stage malignancy. Most patients with CLI will undergo repeat hospitalizations and surgical/endovascular procedures in an effort to preserve the limb, progress to immobility and need constant care.

Unfortunately, the limb salvage efforts are often not effective enough, and despite multiple attempts at revascularization, the wounds still fail to heal. The final stage in 25% of cases is limb amputation, which is associated with a high mortality rate within 6 months. Amputation rates in patients not suitable for revascularization are reported to be up to 30-50% after 1 year. Fewer than half of all CLI patients achieve full mobility after an amputation and only one in four above-the-knee amputees will ever wear a prosthesis.

Between 1990-1999, over 28,000 first time lower extremity bypass procedures were performed in California for CLI, and 29% of patients were admitted to the hospital for at least one subsequent bypass operation or revision procedure. The 5-year amputation free survival rate for this group of CLI patients from California was only 51.1%. The direct costs to California for the treatment of CLI and diabetic ischemic ulcers are substantial.

The lost ability of no-option CLI patients to remain in the CA workforce, to support their families, and to pay taxes causes additional financial strain on the state's economy. The goal of the proposed study is to develop and apply a safe and effective stem cell therapy to save limbs from amputation due to disorders of the vasculature that currently cannot be cured. The successful implementation of our planned therapies will significantly reduce the cost of healthcare in California and could bring people currently unable to work due to immobility back to the workforce and active lifestyles, with a significantly improved quality of life.

Review Summary
This goal of this proposal is to develop mesenchymal stem cells (MSCs) genetically modified to produce vascular endothelial growth factor (VEGF) for treatment of critical limb ischemia (CLI). VEGF is well known to promote the growth of new blood vessels and has been previously investigated for treatment of CLI. The investigators propose that the limited success of VEGF in previous clinical trials was due to the short duration of the presence of VEGF as a result of the method used to deliver the growth factor. To address that limitation, the investigators propose using MSCs expressing VEGF to provide a longer exposure to VEGF at the site of treatment. The project proposes to complete preclinical studies and conduct a Phase 1 clinical safety study in patients who have no other clinical treatment options.

Significance and Impact
- Reviewers agreed that CLI is a serious unmet medical need. The proposal was viewed as a high risk project but worth pursuing due to the high prevalence of this disease and the resulting increased risk of leg amputation and death.

- The Target Product Profile (TPP) was viewed as sensible and well written.

- The proposal is highly responsive to the RFA.

- Reviewers were mixed on their views of whether genetically modified MSCs would be substantially more effective than unmodified MSCs and of how significantly the modified cells would increase safety risk.

Project Rationale
- The rationale for the project is appropriate and well presented. VEGF can cause local neovascularization and the MSCs should survive long enough to allow production of VEGF. Secretion of VEGF in a sustained manner by MSCs may improve efficacy over other delivery routes that have been explored.

-Reviewers appreciated that the genetic modification strategy for the MSCs included elements to improve safety.

- The rationale for including a cohort treated with unmodified MSCs was not clear, since MSCs have been shown to be safe in other clinical trials. It was suggested to eliminate that arm of the safety study.

- It was noted that limited duration of survival of the MSCs in vivo might require multiple administrations, rather than a single dose, to see a benefit; however starting with a single dose in the Phase 1 trial seemed sensible.

- Reviewers did not feel that the trial necessarily needed to be limited to no-option patients and suggested reconsidering the proposed patient population, possibly with input from the FDA.

Therapeutic Development Readiness
- The target has been validated, GMP material has been produced, and the team has begun the regulatory process.

-Data on safety and efficacy have been shown in preclinical studies. Given the preclinical progress, it is likely that the clinical trial indeed could be initiated in Year 3.

Feasibility of the Project Plan
- Reviewers recommended that the applicants consider whether a subset of CLI patients with a specific underlying pathology would be better responders and should be considered as an alternative to the proposed patient population.

- Concern was expressed that the preclinical GLP study was to be done using intravenous administration of cells, in contrast to the intramuscular route intended for the clinical trial. Furthermore the duration of the GLP study was viewed as likely insufficient for regulatory approval.

Principal Investigator (PI) and Development Team
- Reviewers agreed that the team is strong and has experience in CLI and successfully translating research to the clinic.

- A strength of the proposal is inclusion of consultants who are familiar with clinical gene and cell-based therapies.

Collaborations, Resources and Environment
- Excellent resources are available, including access to a GMP facility for manufacturing.

- Intellectual property resources are not well described. It was recommended that the team further explore freedom-to-operate.

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 for toxicology studies does not match the work proposed.

- It was noted that some studies were to be performed using smaller GMP batches and then repeated with the clinical material. It was unclear why repeating studies were being proposed and suggested these would not be an appropriate use of CIRM funds.

- Reviewers were unclear about the activities and associated costs that would be performed in the year in between the IND filing and the beginning of patient enrollment and recommended that these activities be clarified.

The following Scientific Working Group members had a conflict of interest with this application:
DiPersio, Dropulic, Pepperl, Weber

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05426: Combination Therapy to Enhance Antisense Mediated Exon Skipping for Duchenne Muscular Dystrophy

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $19,995,609

Public Abstract (provided by applicant)
Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy and one of the most common fatal genetic disorders. Approximately one in every 3,500 boys worldwide is affected with DMD. Extrapolating from population based studies, there are over 15,000 people currently living with DMD in the US. DMD is a devastating and incurable muscle-wasting disease caused by genetic mutations in the gene that codes for dystrophin, a protein that plays a key role in muscle cell health. Children are typically weaker than normal by age three, and progressive muscle weakness of the legs, pelvis, arms, neck and other areas result in most patients requiring full-time use of a wheelchair by age 11. Eventually, the disease progresses to complete paralysis and increasing difficulty in breathing due to respiratory muscle dysfunction and heart failure. The condition is terminal, and death usually occurs before the age of 25. While corticosteroids can slow disease progression and supportive care can extend lifespan and improve quality of life, no therapies exist that address the primary defect or dramatically alter the debilitating disease course.

Exon-skipping is a promising therapy that aims to repair the expression of the dystrophin protein by altering the RNA, but it is unclear whether it will be effective enough to lead to clinical improvements. We have identified a combination therapy that improves the effectiveness of exon-skipping therapy in mouse muscle and in human DMD patient stem cell derived muscle cells in culture. Because the genetic defect is being directly repaired inside of each muscle cell, this therapy is predicted to lessen the disease severity. The early research and further development of the proposed combination therapy require screening for drug efficacy and toxicity using human DMD patient stem cells including: reprogrammed patient fibroblasts converted into muscle-like cells in culture or when transplanted in mice. These cells are necessary because each patient's mutation in the dystrophin gene is different. In order to know who will or will not benefit from the exon-skipping therapy, individualized cell culture and mouse transplant models from a number of DMD patients must be created to effectively characterize the combination therapy. The proposed research program will complete necessary efficacy and toxicity studies to allow submission of appropriate material to the FDA to allow testing of this novel combined therapeutic in children with DMD. It will also involve a team of clinical trialists who will incorporate findings in planning optimal trial design and ensure clinical trial readiness by the grants end. Since exon-skipping therapy relies on knowing individual patients exact DNA mutation, this is a form of personalized genetic medicine. While the specific combination therapy being developed here will treat up to 13% of DMD patients, the strategy is likely to be generalized to be able to treat up to 70% of DMD patients.

Statement of Benefit to California (provided by applicant)
Duchenne muscular dystrophy (DMD) is an incurable and inevitably fatal genetic disorder. It is caused by a defect in the gene that produces dystrophin, a protein critical to the function of normal skeletal muscle. DMD affects more than 1,000 patients in California, 15,000 nationwide, and 300,000 worldwide. Because the genetic mutation responsible for the disease occurs on the X chromosome, the overwhelming majority of patients are male. Children are typically diagnosed when they are toddlers. Muscle weakness first appears in the hips and legs and progressively extends to every muscle in the body, including the arms, neck, diaphragm and heart. By age 11, most patients require full-time use of a wheelchair . By their late teens, they have trouble feeding themselves. Inevitably, patients are completely paralyzed and cannot breathe without a ventilator. As their cardiac muscles fails, they develop heart failure. Patients usually die by age 25. Aside from the human suffering caused by DMD, the disease places a large economic burden on patients, their families and society as a whole. Patients require intensive medical care because they cannot perform the simplest activities of daily living. Eventually, each individual requires ventilation and 24/7 care due to progressive loss of all muscle function. The proposed combination therapy is intended to spare skeletal muscle by producing dystrophin. Specifically, the combination therapy will induce skipping of DMD exon 51 in skeletal muscle; a defect in exon 51 is responsbile for 13% of DMD cases. The therapy causes the dystrophin gene inside each muscle cell to

express an internally deleted but partially functional dystrophin protein, lessening the severity of DMD. The approach has been well-validated in animal DMD models. A therapy that effectively slows or reverses disease will allow patients to lead longer, more productive lives and reduce the need for costly supportive services-progress that will benefit patients, their families and society.

Review Summary
This proposal is focused on the clinical development of a combination product, an antisense oligonucleotide (AO) together with an FDA-approved small molecule drug, for Duchenne Muscular Dystrophy (DMD). DMD is an X-linked genetic disorder in which mutations occur in the gene encoding dystrophin, a protein that plays a role in muscle health. The applicant claims that the AO promotes exon skipping, and the resulting protein can replace full length dystrophin. The concept is based on the applicant's preclinical observation that an FDA-approved drug can enhance exon-skipping activity in a preclinical model of DMD, and in an assay of human skeletal muscle myotubes. Important activities will include confirmation of activity against multiple alleles of the dystrophin gene from human DMD patients using in vitro cell models. The goal of this project is to complete the preclinical dosing and efficacy studies, toxicity studies, and complete the regulatory and clinical activities to file an Investigational New Drug application (IND) within the four-year timeframe.

Significance and Impact
- DMD is one of most common lethal monogenic diseases, and no existing treatments significantly reduce the burden of disease.

- The initial proposed therapeutic could possibly address an estimated 13% of the DMD population (approximately 10,000-15,000 cases); the applicant believes that the platform could eventually address 70% of DMD cases.

- Exon skipping is an active area of therapeutics under investigation for this disease. This project focuses on one AO; another directly competitive AO is in clinical development by a second corporate entity.

- At a minimum, a benefit would be a decrease in cost to treat with the single agent AO.

- The Target Product Profile (TPP) was well laid out, although the optimal safety targets were not clear.

- The project is responsive to the RFA as the team intends to use two forms of reprogramming to assess potential efficacy in samples from patients with various human dystrophin mutations.

Project Rationale
- A major flaw in the application was the absence of any data or discussion addressing whether this potential therapy would impact cardiac muscle, since most patients ultimately succumb to heart failure.

- Recent Phase 2b data has been reported that showed increases in dystrophin levels with single agent AO treatment. No functional difference was observed between treated patients and those who received placebo.

- One reviewer cited the Phase 2b results and recommended against funding this program until the absence of functional effect with the single AO agent is delineated.

- The panel questioned the strength of the data supporting the argument that the candidate drug actually increases exon skipping. One reviewer noted the premise is based on unpublished data.

- Data are included in the application showing a 2-3 fold increase in exon skipping at a low dose of AO, with the candidate drug. For one reviewer, methods and controls to quantify exon skipping in the human in vitro model system were not adequately described.

- The application did not show data addressing the maximum level of muscle fibers the team can affect by increasing exon skipping; nor was a threshold demonstrated that might alter clinical outcomes.

Therapeutic Development Readiness
- Both components of the proposed combination therapy have been demonstrated to meet GMP manufacturing requirements; and therefore the panel anticipates no new manufacturing needs.

- It was not clear to several reviewers whether the in vivo xenograft model is either ready or appropriate for efficacy and dose-finding studies.

- Key proof-of-concept studies relied on a surrogate target gene in the preclinical model, and in vitro studies with human cells.

- The applicant notes poor solubility of the small molecule, which may be suboptimal for oral administration. Replacement with more soluble compounds in the candidate combination product would be a major drawback and necessitate additional toxicology testing.

- The observed variability in the Phase 2b clinical studies should be further evaluated in a preclinical setting.

Feasibility of the Project Plan
- Several reviewers commented that progression to IND submission is slow, and were unclear on the rationale for the full four years required to file an IND.

- Several reviewers identified an excellent preclinical model that is often used for DMD, and noted that it is not introduced into this program. This is important because structural and physiologic endpoints should be assessed in a relevant weight-bearing model.

- The safety data for the single AO was judged incomplete for the proposed combination. Several examples were discussed: off-target effects of the AO should be evaluated in combination with the proposed drug; immunogenicity should be evaluated with repeat administration of the AO.

- The team should re-evaluate the rationale and design of the toxicology studies in the clinically relevant model, and integrate the discussion of design into the pre-IND meeting. Such studies are often costly and generally underpowered.

- A robust pK/pD study should be included in this program, to address the very short half life of the AO in the context of the chronically administered small molecule.

- The team should consider evaluation of a clinical biomarker which might reflect durability of response.

Principal Investigator (PI) and Development Team
- The PI has a strong background in genomics and gene expression, and has a track record that demonstrates a commitment to translational research.

- The Co-PI's primary expertise is immunology, with ample experience in translational research and clinical care for this condition.

- The scientific leadership is augmented by individuals with experience with the preclinical model and human induced pluripotent stem cell development. In years three and four, a clinical expert who has conducted trials in DMD will join the team.

- Product development and regulatory expertise is provided by two qualified industry partners.

Collaborations, Resources and Environment
- The applicant institution is well-suited to support the research components of the proposal, and appropriate industry partners have been enlisted to perform key IND-enabling and CMC activities.

- The applicant should secure cooperation from the source(s) of the drug soon. It may be necessary to extend the labeling indication for drug in concert with approval for the single AO.

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.)
- A significant amount of funds will be going to the industry partner in year 1. This partner should consider supplying the AO at either little or no cost, since this may be essential to success of their therapeutic.

- Several reviewers identified financial redundancy with the partner's corporate program.

- Carcinogenicity for the single agent AO should not be funded by this project.

Conditions Applied by the Planning Award Grants Working Group (GWG)
- The Planning Award GWG set a condition that "to be eligible for the Disease Team Research Award competition, the applicant must provide at the time of Full Application written assurance from the companies that own the intellectual property surrounding the two antisense oligonucleotides that the applicant has access to the drugs and permission to file an IND for clinical testing."

- A letter included in the application from one of the AO providers agrees in principle, but raised concerns for reviewers.

Programmatic Review (if applicable)
A motion was made to move this application into Tier 1, Recommended for Funding. Programmatic reasons cited were the devastating effects of the disease and the relatively fewer pediatric indications in the portfolio. The panel expressed general consensus about the desire to fund work in pediatric diseases. However, this application could not overcome the absence of clinical benefit for the single agent, and also the unknowns of the proposed combination product regarding immunogenicity, relevance of the proposed model, and whether the proposed therapeutic would target critical cardiac pathology. The motion was withdrawn.

The following Scientific Working Group members had a conflict of interest with this application:
Chopra, Montgomery

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05735: Allogeneic Cardiac-Derived Stem Cells for Patients Following a Myocardial Infarction

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $19,782,136

Public Abstract (provided by applicant)
The proposed research will demonstrate both safety and efficacy of a heart-derived stem cell product in patients who have experienced a heart attack either recently or in the past by conducting a mid-stage clinical trial. A prior early-stage trial showed that the product can repair damaged portions of the heart after a heart attack in ways that no commercial therapy currently can. Damaged areas turn irreversibly into scar tissue after the initial event, which can predispose a person to future events and lead to an ongoing worsening of general and heart health. Data from the early-stage trial suggest that treatment with the heart-derived cell product under development can turn scar tissue back into healthy heart muscle. The planned mid-stage trial will hopefully confirm that finding in a larger patient group and provide additional data to support the safety profile of the product. The product is manufactured using heart tissue obtained from a healthy donor and can be used in most other individuals. Its effect is thought to be long-lasting (months-years) although it is expected to be cleared from the body relatively quickly (weeks-months). Treatment is administered during a single brief procedure, requiring a local anesthetic and insertion of a tube (or catheter) into the heart. The overriding goal for the product is to prevent patients who have had a heart attack from deteriorating over time and developing heart failure, a condition which is defined by the heart's inability to pump blood efficiently and one which affects millions of Americans. Successful completion of the proposed mid-stage trial would lead next to a final, confirmatory trial and then to the application process by which permission to market the product is obtained from the Food and Drug Administration. The end result could be an affordable stem cell therapy effective as part of a treatment regimen after a heart attack.

Statement of Benefit to California (provided by applicant)
The manufacturer of the heart-derived stem cell product under development is a California-based small company who currently employs 7 California residents. Five new local jobs will be created to support the proposed project. Three medical centers located in California will participate in the proposed mid-stage clinical trial. The trial will hopefully bring notoriety to both the company and the medical centers involved while at the same time provide a novel therapeutic option for the many citizens of California afflicted with heart disease. Recent statistics place California among the 50% of states with the highest death rates for heart disease. Therefore, a successfully developed cell product could have a meaningful impact on the home population. Furthermore, as manufacturing needs grow to accommodate the demands of early commercialization, the company anticipates generating 100+ new biotech jobs.

Review Summary
The proposed project is focused on the clinical development of an allogeneic cardiac-derived stem cell product intended for use in patients with residual left ventricular dysfunction following a myocardial infarction (MI). The applicant proposes to conduct a mid-stage clinical trial to demonstrate both safety and efficacy of the product candidate.

Significance and Impact
- Should the product candidate work as intended, it could have a significant impact on treatment of MI and heart disease.

- Because of the lack of improvements in heart function observed in the pre-clinical efficacy data, some reviewers found it hard to be enthusiastic about the clinical competitiveness of this product candidate.

- The TPP is focused on the results of a phase 2 trial rather than on the attributes of a final product.

Project Rationale
- In general, reviewers agreed that this program is well supported by data from a previous clinical trial as well as supporting data from three animal models, each with different iterations of the product candidate.

- Reviewers agreed that the data warrant further testing.

-The preliminary data trends in animal models are interesting

Therapeutic Development Readiness
- The proposed clinical plan is a major potential risk given the lack of significant cardiac function improvement noted in the Phase 1 study with an earlier candidate and the fact that the applicant proposes starting with a Phase 2 trial with the current candidate, but is still awaiting the pivotal pre-clinical study data.

- The cGMP cell production methods and scale-up manufacturing are well thought out, and physically in place. The procedures are quite developed and are ready for clinical development.

Feasibility of the Project Plan
- Although the therapeutic approach is promising, the proposed trial attempts to accomplish too many steps at once; a new phase I study is warranted first; the proposed clinical plan needs to be re-thought and re-designed.

- The study is being designed around a surrogate marker that has not been shown to correlate with functional outcome measures in the preclinical models or in a Phase 1 trial. This seems to be a fundamentally serious design flaw in the study and will not help the project in terms of achieving regulatory approval or reimbursement.

- Reviewers agreed that based on the data provided in the application, the large trial proposed is not justified. They would have supported the idea of a smaller, better-designed study that could answer a specific question.

- The budget is unrealistic. It is inadequate to perform a multicenter international trial of such scope and complexity.

Principal Investigator (PI) and Development Team
- A major concern is that neither of the two primary leaders has run a trial of this size, making the investment risky in terms of experience.

- Reviewers strongly recommend that an experienced CRO be hired to conduct the trial

Collaborations, Resources and Environment
- The resources and environment are good.

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.)
- See comment under 'Feasibility of the Project Plan'.

- Budget for manufacturing expenses to prepare for Phase 3 is outside scope.

The following Scientific Working Group members had a conflict of interest with this application:
Frey-Vasconcells, Mills, Weber

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05736: Neural stem cell transplantation for chronic cervical spinal cord injury

Recommendation: Recommended for Funding **Final Score:** 79
Total Funds Requested: $20,000,000

Public Abstract (provided by applicant)
1.3 million Americans suffer chronically from spinal cord injuries (SCI); each year ~15,000 individuals sustain a new injury. For California, this means nearly 147,000 individuals are living with a SCI which can leave otherwise healthy individuals with severe deficits in movement, sensation, and autonomic function. Recovery after SCI is often limited, even after aggressive emergency treatment with steroids and surgery, followed by rehabilitation. The need to develop new treatments for SCI is pressing. We believe that stem cell therapies could provide significant functional recovery, improve quality of life, and reduce the cost of care for SCI patients. The goal of this Disease Team is to evaluate a novel cell therapy approach to SCI involving transplantation of human neural stem cells.

In 2005, the FDA authorized the world's first clinical testing of human neural stem cell transplantation into the CNS. Since then, our research team has successfully generated clinical grade human neural stem cells for use in three clinical trials, established a favorable safety profile that now approaches five years in some subjects and includes evidence of long-term donor-cell survival. Relevant to this Disease Team, the most recent study, began testing human neural stem cells in thoracic spinal cord injury. The initial group of three patients with complete injury has been successfully transplanted. The Disease Team seeks to extend the research into cervical SCI.

Neural cell transplantation holds tremendous promise for achieving spinal cord repair. In preliminary experiments, the investigators on this Disease Team showed that transplantation of both murine and human neural stem cells into animal models of SCI restore motor function. The human neural stem cells migrate extensively within the spinal cord from the injection site, promoting new myelin and synapse formation that lead to axonal repair and synaptic integrity. Given these promising proof-of-concept studies, we propose to manufacture clinical-grade human neural stem cells and execute the preclinical studies required to submit an IND application to the FDA that will support the first-in-human neural stem cell transplantation trial for cervical SCI.

Our unmatched history of three successful regulatory submissions, extensive experience in manufacturing, preclinical and clinical studies of human neural stem cells for neurologic disorders, combined with an outstanding team of basic and clinical investigators with expertise in SCI, stem cell biology, and familiarity with all the steps of clinical translation, make us an extremely competitive applicant for CIRM's Disease Team awards. This award could ultimately lead to a successful FDA submission that will permit human testing of a new treatment approach for SCI; one that could potentially reverse paralysis and improve the patient's quality of life.

Statement of Benefit to California (provided by applicant)
Spinal cord injuries affect more than 147,000 Californians; the majority are injuries to the cervical level (neck region) of the spinal cord. SCI exacts a devastating toll not only on patients and families, but also results in a heavy economic impact on the state: the lifetime medical costs for an individual with a SCI can exceed $3.3 million, not including the loss of wages and productivity. In California this translates to roughly $86 billion in healthcare costs. Currently there are no approved therapies for chronic thoracic or cervical SCI.

We hope to advance our innovative cell therapy approach to treat patients who suffer cervical SCI. For the past 9 years, the assembled team (encompassing academic experts in pre-clinical SCI models, complications due to SCI, rehabilitation and industry experts in manufacturing and delivery of purified neural stem cells), has developed the appropriate SCI models and assays to elucidate the therapeutic potential of human neural stem cells for SCI repair.

Human neural stem cell transplantation holds the promise of creating a new treatment paradigm. These cells restored motor function in spinal cord injured animal models. Our therapeutic approach is based on

the hypothesis that transplanted human neural stem cells mature into oligodendrocytes to remyelinate demyelinated axons, and/or form neurons to repair local spinal circuitry. Any therapy that can partially reverse some of the sequelae of SCI could substantially change the quality-of-life for patients by altering their dependence on assisted living, medical care and possibly restoring productive employment.

Through CIRM, California has emerged as a worldwide leader in stem cell research and development. If successful, this project would further CIRM's mission and increase California's prominence while providing SCI therapy to injured Californians. This Team already has an established track record in stem cell clinical translation. The success of this Disease Team application would also facilitate new job creation in highly specialized areas including cell manufacturing making California a unique training ground.

In summary, the potential benefit to the state of California brought by a cervical spinal cord Disease Team project would be myriad. First, a novel therapy could improve the quality of life for SCI patients, restore some function, or reverse paralysis, providing an unmet medical need to SCI patients and reducing the high cost of health care. Moreover, this Disease Team would maintain California's prominence in the stem cell field and in clinical translation of stem cell therapies, and finally, would create new jobs in stem cell technology and manufacturing areas to complement the state's prominence in the biotech field.

Review Summary
This proposal is to develop human neural stem cells (NSCs) to treat chronic cervical spinal cord injury (SCI). The applicant proposes to complete IND-enabling preclinical studies and file an IND within the four-year award period. This project would represent the first-in-human neural stem cell transplantation trial for cervical SCI.

Significance and Impact
- Most SCI patients have cervical injuries, so there is a substantial unmet clinical need. Even small gains in function can yield significant quality of life improvements.

- This is a clinically competitive product, and there is a clear need for new and more effective therapies to minimize or improve neurologic dysfunction following SCI.

- This proposal is for IND-enabling studies for the use of cell-based therapy following SCI and is responsive to the scope of this RFA.

Project Rationale
- The rationale is well thought out. Careful consideration has been made in the selection of regional injury and clinical endpoints with higher likelihood for detection and proof of mechanism.

- The therapeutic cells have been shown to differentiate to multiple cell types in the spinal cord.

- Although reviewers did not find the preliminary data compelling, they agreed that even small incremental steps can have a significant improvement in patients' quality of life.

- Some reviewers felt that the progression to human safety trials should have also included the use of large animal studies to enable assessment of factors that include cell migration and biodistribution.

- Some reviewers expressed concerns that there are no large animal model studies proposed to test certain aspects of the cell delivery technique.

- One reviewer questioned the preclinical design, noting that the project relies on translation of findings in rodents with incomplete injuries to those in humans with cervical injury, and raised concerns as to whether the human cervical injuries are severe enough to warrant the risks of invasive cell transplantation.

Therapeutic Development Readiness
-Reviewers were enthusiastic that the same cells have already been used in clinical trials, thus the ability to manage a Master Cell Bank (MCB) and Working Cell Bank (WCB) has been demonstrated. However, the rationale behind the need for a new cell bank was unclear.

- Reviewers agreed that prior clinical experience and preliminary discussions with regulatory authorities

reflects a mature and experienced launching point for the proposed clinical study, and represent a major strength of this application.

- The role of the previously completed GLP studies in developing the IND is unclear.

Feasibility of the Project Plan
-Well thought out and feasible research plan. Reviewers agreed that the feasibility is high since the same cells are already in the clinic for other indications, including thoracic SCI.

- Reviewers noted that there is work proposed in both sub-acute and chronic models, which the FDA will view as separate indications. Reviewers recommended focusing on the chronic indication and eliminate the proposed studies in acute injury.

Principal Investigator (PI) and Development Team
- This is an experienced team that has demonstrated the ability to move a therapeutic into clinical trials.

- The organization of the team is well thought out and divided into the Stem Cell Biology component and the SCI pre-clinical studies component.

- There was some concern that the team did not appear to include anyone with experience injecting into the cervical spinal cord, which is very technically challenging.

Collaborations, Resources and Environment
- Collaboration with a leading academic spinal cord injury lab was viewed as a strength of the application.

- A strong IP portfolio has been established around the cell line being used in these studies; however, there was no discussion regarding possible concerns over freedom to operate.

- The institutions involved are well equipped to perform these studies.

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.)
- Matching funds have been committed to the project.

- The budgets proposed for IND preparation and for report writing were viewed as excessive.

- Reviewers noted that CIRM should not support work proposed on acute injury.

- Reviewers noted that manufacturing costs and some preclinical study costs seemed excessive in light of the ongoing trial. Some costs may be duplicative with ongoing efforts so redundant costs without justification should be eliminated. It was unclear why equipment for toxicology studies was necessary.

The following Scientific Working Group members had a conflict of interest with this application:
Black, Chopra, Noble, Pepperl

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05737: Phase 3 enabling program for a small molecule in treatment resistant depression and major depressive disorder

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $14,995,455

Public Abstract (provided by applicant)
Clinical depression is a chronic, recurring psychiatric illness that, according to Datamonitor, afflicts more than 12.5 million adults in the U.S. It is a disabling condition that adversely affects the patient's quality of life, eating and sleeping habits, and overall health. Currently, clinical depression is treated with various antidepressants but their use is associated with a number of significant limitations. First and foremost, antidepressants have many undesirable side effects, including sexual dysfunction, fatigue, and weight gain. Moreover, many patients only partially respond to antidepressant therapy while some do not respond at all. In this sub-set of patients who do not respond to antidepressants (treatment resistant depression or TRD), the treatment alternatives are limited. It is this group of TRD patients which our research primarily aims to benefit.

The prevailing therapy for TRD is electroconvulsive therapy, or ECT, which involves a patient first being anesthetized and then having electric currents passed through the brain. Although deemed effective, ECT is known to cause memory loss and confusion in some patients. Through our research program with [Redacted] we seek orally available therapeutic alternative to ECT that is efficacious but without significant side effects. In addition, we believe that [Redacted] could be a novel treatment for patients with MDD devoid of the undesired side-effects of existing treatments.

The potential effectiveness of our drug is premised on two recent discoveries in the field of neuroscience: that it is possible to create new neurons in the adult human brain, and that these new neurons are necessary for antidepressants to work. Our earlier research has shown, in a laboratory setting, that [Redacted} causes human stem cells to grow into new neurons. Additionally, [Redacted] yields positive results in animal depression models. Further, our [Redacted] Phase I trials to date reflect a promising safety profile in humans. Therefore, we believe that [Redacted] has the potential to be a new standard of care for the treatment of TRD and second-line therapy for MDD patients who do not respond adequately to current treatments or cannot tolerate their side effects.

Statement of Benefit to California (provided by applicant)
Depression or major depressive disorder (MDD) is a major public health concern in terms of its prevalence and cost to society. It is associated with significant impairment and decreased productivity. It can lead to changes in immune and endocrine function, increasing susceptibility to physical disease. The proposed research will evaluate the efficacy of an oral medication, [Redacted], for the treatment of MDD with a primary emphasis on patients who are unresponsive to current therapies (treatment resistant or TRD). Current treatments for TRD are invasive, require inpatient care and are accompanied by undesirable side effects such as psychosis and short-term memory loss.

The primary goal of the proposed research program with [Redacted] is to develop an efficacious and less costly therapy for TRD patients without the significant side effects. A secondary goal is to provide a therapeutic alternative for MDD patients who do not adequately respond to current therapies or who cannot tolerate their side effects. The realization of these goals will lead to significant health, social and economic benefits in California. The World Health Organization estimates that depression is the leading cause of disability worldwide. The symptoms of depression impair work, social interaction and personal functioning. Depression can lead to changes in health behaviors such as increased smoking, high-risk sexual activities and increased risk of sexually transmitted diseases, particularly among the young, with major economic consequences. In the most serious cases, it can lead to long-term, costly inpatient care. An NIMH-sponsored analysis (2009), found that patients diagnosed with depression incurred ~ $22,960 in annual health care costs, while those without depression incurred ~ $11,956 in costs.

If the [Redacted] program achieves it goals, it has the potential to radically improve patient care and reduce the negative impact of depression on quality of life factors such as family life, interpersonal

relationships, job retention and performance. It also has the potential to reduce the significant economic burden to the State resulting from the deleterious, long-term health consequences of depression. The Substance Abuse and Mental Health Services Administration estimates that in 2003 approximately 58% of all mental health care, which includes depression, were paid by publicly funded programs. An effective therapy may also reduce the indirect costs associated with depression such as disability benefit payments and loss of earnings and tax revenue associated with those earnings. Finally, this grant helps to foster the further development of a robust and sustainable life science community in [Redacted] by providing jobs and funding to support the research outlined. Over time, [Redacted] has the potential to generate significant revenue which will not only increase the tax base for California but will also allow for further investment in new technology.

Review Summary
This proposal is focused on the clinical development of a small molecule compound for treatment resistant depression (TRD). The compound was identified in a screen for drugs that promote the differentiation of human neural progenitor cells (NPCs) into new neurons. This compound is currently being tested for safety in a Phase I study in healthy volunteers and the applicant proposes to continue development in two Phase II, placebo-controlled clinical studies. The first would be a smaller, shorter, proof-of-concept study, which if successful, would lead to a larger, longer confirmatory trial.

Significance and Impact
- Clinical competitiveness is not adequately addressed. The applicant compares the candidate to electroconvulsive therapy and ketamine but there are multiple atypical antipsychotics labeled for TRD, additional therapies under development and numerous other psychotropics that have shown some degree of efficacy.

- The application is technically responsive to the RFA because the therapeutic candidate was discovered in a screen of compounds that could enhance neurogenesis from human NPCs. However, reviewers noted that no evidence is provided that the compound's effects are mediated by a neurogenic mechanism and that the proposed time course of action effectively rules out this possibility.

- The Target Product Profile (TPP) is not clearly defined and does not include contraindications. In addition, reviewers noted that the clinical endpoint of a rating change on the HAM-D17 scale might not be the most appropriate and suggested using the MADRS or HAM-D24 scale.

- A novel, well-tolerated oral treatment for TRD would have a substantial clinical impact, given the prevalence of this disease and its high cost.

Project Rationale
- The majority of the preclinical animal studies have been performed using the active metabolite of the proposed compound rather than the compound itself. The application would have been stronger if it contained more preclinical efficacy data with the proposed compound including a comparison against a panel of approved anti-depressants.

- Inadequate data are provided to demonstrate safety of the therapeutic candidate relative to ketamine. These compounds share a similar mechanism of action, which raises concerns that the therapeutic candidate could share ketamine's dissociative and psychotic effects. The applicant addresses this possibility but does not present data.

Therapeutic Development Readiness
- The therapeutic candidate is being tested for safety in healthy volunteers overseas. The applicant appears ready to hold a pre-IND meeting with FDA and to file an IND in late summer 2012.

Feasibility of the Project Plan
- The project timeline is very optimistic if not unrealistic. Patient recruitment is extremely difficult in this indication and the applicant does not provide justification for patient accrual expectations.

- The proposed clinical studies do not include a maximum severity cutoff or exclusion for patients with psychotic symptoms, which would be expected for trials of this type.

- The rationale was unclear for testing a single dose in the first proposed Phase II clinical trial followed by

two doses in the second trial. Reviewers recommended that the applicant focus on a well-powered, multiple dose Phase IIa study and consider secondary biomarker endpoints that may indicate durability and mode of action. They also recommended that the applicant engage in end of study dialogue with the FDA prior to initiation of a Phase IIb trial.

- No formal power calculation is provided or rationale stated to support the estimated number of patients proposed for the second Phase II trial.

- There is no discussion of centralized patient ratings for the first Phase II trial. Reviewers noted that subjective scoring is an important issue in these types of trials and one of the reasons there is such a high failure rate.

Principal Investigator (PI) and Development Team
- There is insufficient clinical development and trial experience on the team. The chief medical officer is a consultant and the medical team is diffuse, with clinical responsibility spread across multiple individuals.

Collaborations, Resources and Environment
- The clinical development of this compound could be limited by intellectual property considerations. Reviewers noted that given the patent filing date and an estimated clinical development timeline, the compound could have a very short window of patent protection following FDA approval.

- The outsourcing of preclinical studies and clinical trial monitoring is 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.)

- The proposed budget for the preclinical studies appears high. The budget for phase 3 enabling studies was not discussed but would be out of scope.

The following Scientific Working Group members had a conflict of interest with this application:
None

REVIEW REPORT FOR CIRM RFA 10-05
DISEASE TEAM THERAPY DEVELOPMENT RESEARCH AWARDS

DR2A-05739: Retinal progenitor cells for treatment of retinitis pigmentosa

Recommendation: Not Recommended for Funding **Final Score: --**
Total Funds Requested: $17,306,668

Public Abstract (provided by applicant)
The targeted disease is retinitis pigmentosa (RP), a severe form of blindness that often runs in families, but other times arises spontaneously from genetic errors. This disease is not overly common, yet represents an attainable near term target for stem cell therapy for a number of reasons: 1) RP destroys the light detecting cells of the retina in the back of the eye, yet generally leaves the rest of the visual system and body unharmed, so the clinical goal is circumscribed; 2) RP is prototypical of degenerations of the nervous system, so a cure for this less common disease would accelerate progress towards new therapies for a range of more familiar conditions; 3) scientific research has shown that degenerating rods and cones can be saved in animals by transplanting particular types of stem cells, thus the scientific feasibility of treating RP in this way has already been established in principle.

The therapeutic approach to be championed here is to save the light sensing cells of the eye (rod and cone photoreceptors) in people going blind using a type of stem cell obtained from the immature retina, but not from early embryos. These particular stem cells from the retina, known as progenitor cells, are capable of saving photoreceptors from degeneration following transplantation to the eye. These same cells are also highly efficient at producing new rod photoreceptors and this provides another more sustained pathway by which they preserve the crucial cone photoreceptors. In addition, there is evidence that the stem cells themselves might become functional photoreceptors and thereby stabilize the retina by directly replacing the dying cells in the patient's eye. Thus, transplanted stem cells could treat the targeted disease of RP in multiple ways simultaneously. Importantly, there are a host of reasons why clinical trials in the eye are easier and safer than most locations in the body. The eye is an important proving ground for stem cell-based therapies and provides a stepping stone to many otherwise incurable diseases of the brain and spinal cord.

As part of the current project, our cell type of interest will be grow under conditions ensuring pharmaceutical standards are met. The resulting cells will be tested in animals for safety and to make certain that they are therapeutically potent. An application will be made to the FDA seeking approval for the use of these cells in early clinical trials. Following approval, a small number of patients with severe RP will be injected with cells in their worse-seeing eye and followed clinically for a specified period of time to determine the safety and effectiveness of the treatment.

Statement of Benefit to California (provided by applicant)
Benefits to the state of California and its citizens are both direct and indirect. The direct benefit is medical in that there is currently no cure or established treatment for the individuals and families that suffer from the dreadful hereditary blindness known as retinitis pigmentosa. In addition, there are many people in California and throughout the world that suffer from degenerative diseases of the retina, such as age-related macular degeneration (AMD), and the central nervous system that could benefit from further development and alternate applications of the type of stem cell therapy proposed in the current application. The rapid progress into the clinic that could be achieved via this proposal would help legitimize the use of stem cells for previously incurable diseases and should thereby accelerate the development of stem cell-based therapeutics for a wide range of other conditions. In so doing there would be an indirect benefit to California by making our state a focal point for stem cell breakthroughs. This would increase medical capabilities, strengthen the state's educational system, and energize local biotechnology companies with outside investment and a payoff in jobs and tax revenues. In the current economic situation, the citizens of the state are looking for a return on their investment in stem cell research. The leadership for the state is looking for a novel technology to reinvigorate the economy, provide desirable jobs, and reaffirm the flagship image of California. The project presented in this application has a real chance of provide that sort of spark.

Review Summary
The goal of this proposal is to advance allogeneic human retinal progenitor cells (RPCs) as a therapy for

retinitis pigmentosa (RP), a rare but severe form of hereditary blindness that progressively destroys the photoreceptor cells in the retina which are necessary for receiving and transmitting visual information. The applicant hypothesizes that transplanted RPE could, by differentiating, regenerate lost photoreceptors. The applicant proposes to manufacture RPCs and conduct preclinical safety studies to enable the filing of an IND, and will also conduct clinical trials in patients with RP. A two-tiered clinical trial strategy is proposed comprising an initial clinical trial using cells made according to Food and Drug Administration (FDA) good tissue practice (GTP) regulations, followed by a second study conducted using cells manufactured according to good manufacturing practice (GMP) regulations. Patients with RP will receive RPCs in the most-affected eye and will be followed clinically for a specified period of time to determine the safety and effectiveness of the treatment.

Significance and Impact
- There is an unmet need for the treatment of RP and this work, if successful, is likely to be of high impact.

- The preliminary data presented indicate that this approach has promise and

suggest that RPCs may present an important therapeutic intervention in RP.

- Based on the data provided it is difficult to draw a clear conclusion as to how this is superior to other approaches using cell transplants.

- The proposed method and site of delivery of RPCs is surgically simple and relatively safe from the standpoint of risks such as anesthesia and infection, although there are other serious risks with this approach such as a greater likelihood of an immune response.

Project Rationale
- The applicant has presented compelling non-clinical data in multiple species. Three human clinical case reports performed outside the USA are consistent with the non-clinical data.

- It was clear that RPC-mediated photoreceptor rescue (rather than regeneration) was the predominant effect; no guidelines are provided as to how long they expect this (the effect) to last.

- The scientific rationale is clear and strong.

- The 2-tier clinical strategy proposed is not rational.

Therapeutic Development Readiness
- The applicant proposes to use "GTP" RPCs initially and then switch to "GMP" RPCs; the FDA may consider them to be two different products. A single therapeutic candidate should therefore be chosen (GTP vs GMP).

- It seems they have not selected their lead candidate yet as required by the RFA, so there is a question of readiness.

- The cells aren't optimized, which calls into question the feasibility of the timeline.

-They need to first understand the cells and finish the optimization before doing any other safety studies.

Feasibility of the Project Plan
-The proposed 2-tier clinical plan to use GTP RPCs initially and then transition to GMP cells was a major issue in the review:

> - There is concern about the identity of the GTP versus GMP cells; the products may not be the same; the GTP to GMP transition is a concern; results may be difficult to translate from one study to the other.
>
> - More clarity is needed to understand what is different between GTP and GMP RPCs and whether or not clinical data from GTP RPCs is predictive of GMP RPCs. A major risk of this project is that the cells from the GTP process will have different biological properties from the GMP cell product.

- No data are available to support the comparability of the GTP and GMP cells; the FDA may very well consider them two different products.

-Reviewers expressed concern about the lack of immunosuppression in the proposed clinical trial. The applicant has not provided enough evidence that there is lack of graft rejection; graft rejection can occur in the eye without evidence of inflammation, so the claim of no rejection is unsubstantiated. Immune rejection may be an issue, especially in the event of re-treating.

- Focusing only on the GMP RPC, the development plan outlined by the applicant appears comprehensive and entails a number of manufacturing activities and a series of non-clinical studies that are typically necessary for a long term persisting cellular therapy product.

- It does not seem the applicant intends to perform safety studies with the GTP RPC, but only for GMP RPC. It is unclear why the applicant believes the safety studies required for GMP RPCs will not be needed for GTP RPCs.

-Adventitious virus testing will be performed on the master cell bank only if requested by FDA. The responsible action would be to perform this testing regardless of FDA input.

- The applicant will need to do tumorigenicity studies, but the proposed timeline does not reflect this.

- Clinical trial monitoring procedures are not described.

- The applicant proposes to identify candidate potency markers using a proteomics approach. Reviewers were concerned that this sounds like a very large project in itself and may not be completed during the grant funding period.

Principal Investigator (PI) and Development Team
- The PI and development team are excellent and a strength of the proposal

-The GMP manufacturing facility appears to be qualified.

- The clinical investigators are excellent as are the clinical sites.

-The entity responsible for clinical trial monitoring is not described.

Collaborations, Resources and Environment
- Resources and environment: Outstanding

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.)
- There is significant budgetary discrepancy between the two clinical sites that is not justified adequately.

- The budget for the toxicology subcontract is not justified adequately;

- The project seems over-resourced.

The following Scientific Working Group members had a conflict of interest with this application:
None