CIRM PRECLINICAL DEVELOPMENT AWARDS – RFA 014-02

Tier 1 = ; Tier 2 =
Tier 3 =

Application #	Title	Score	Median	SD	Low	HIgh	Budget	Tier	Number of Scores in Tier T1	T2	T3
PC1-08103	Placental Stem Cells for the In Utero Treatment of Spina Bifida	89	90	2	85	92	$2,184,032	1	13	0	0
PC1-08142	Development of a Chondrogenic Drug Candidate Targeting Cartilage-residing Mesenchymal Stem Cells for the Treatment of Osteoarthritis	83	85	7	70	98	$2,633,592	1	14	1	0
PC1-08118	Scaffold for dermal regeneration containing pre-conditioned mesenchymal stem cells to heal chronic diabetic wounds	77	80	6	64	85	$5,039,008	1	11	1	2
PC1-08117	A hNSC Development Candidate for Huntington's Disease	77	75	5	70	90	$4,951,623	1	11	2	0
PC1-08111	Pre-clinical development of gene correction therapy of hematopoietic stem cells for SCID-X1	76	75	6	64	84	$1,000,000	1	10	2	1
PC1-08100	Genetically Corrected, Induced Pluripotent Cell-Derived Epithelial Sheets for Definitive Treatment of Dystrophic Epidermolysis Bullosa	73	75	9	50	81	$4,483,375	2	8	3	2
PC1-08105	Preclinical development of a WNT activated autograft (autograft^WNT) containing endogenous stem cells to enhance skeletal healing.	72	75	10	45	85	$7,026,969	2	8	3	4
PC1-08086	Human Stem-Cell Based Development of a Potent Alzheimer's Drug Candidate	71	75	10	50	96	$1,737,271	2	8	3	4
PC1-08128	Embryonic Stem Cell-Derived Chondroprogenitor Cells to Repair Osteochondral Defects	71	75	9	50	80	$7,660,211	2	10	1	4
PC1-08126	A Translational Program of Neural Stem Cell Relay Formation for SCI	69	69	7	55	78	$6,408,504	2	5	4	5
PC1-08122	Exosomes from cardiac stem cells as platform therapeutic candidates: application to Duchenne muscular dystrophy	--					$7,430,686	3	0	1	14
PC1-08098	Development of a Pan BCL2 Inhibitor to Target Dormant Cancer Stem Cells in Refractory Hematologic Malignancies	--					$3,929,922	3	0	0	14
PC1-08132	IND-enabling studies for the clinical use of human embryonic stem cell (hESC)-derived dopaminergic (DA) neuronal precursors shown to be efficacious & safe in the MPTP-lesioned animal model of Parkinson's Disease (PD)	--					$8,777,951	3	1	2	11
PC1-08096	Development of Gene Therapy for HIV Using Potent, Multiplexed anti-HIV RNAs and In Vivo Gene Delivery.	--					$2,517,691	3	0	0	14
PC1-08092	Human Embryonic Stem Cell-Derived Neural Stem Cell Transplants in Amyotrophic Lateral Sclerosis	--					$9,714,835	3	1	1	13
PC1-08115	A Genetically Programmed hESC-derived Neural Stem/Progenitor Cell Line for Transplantation in Parkinson's Disease	--					$7,348,391	3	0	2	13
PC1-08087	Preclinical development of an acellular small intestinal submucosa extracellular matrix device augmented with allogeneic human mesenchymal stem cells for surgical implantation in patients with chronic myocardial infarction	--					$5,857,967	3	1	1	12
PC1-08108	Regeneration of a Normal Corneal Surface by Limbal Stem Cell Therapy	--					$5,793,107	3	1	0	14
PC1-08129	Induced Stem Cell Implants for Spinal Fusion Intervention	--					$4,537,573	3	0	0	14
PC1-08147	Injectable stem cell recruiting biomaterial for treating critical limb ischemia	--					$1,072,500	3	0	0	15
PC1-08104	Harnessing Native Fat-Residing Stem Cells For Spine Fusion: From Early Translation To Preclinical Development	--					$7,996,493	3	0	0	15

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

M E M O R A N D U M

Date: March 10, 2015

To: Application Review Subcommittee, Independent Citizens Oversight Committee (ICOC)

From: C. Randal Mills, Ph.D. - President and CEO

Subject: CIRM Team Recommendations re: Applications submitted under RFA 14-02, Preclinical Development Awards

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In accordance with Section 7, Article V of the Bylaws of the Scientific and Medical Research Working Group and Section 6, Article VI of the Board's bylaws, both as amended on 3/19/13; the President and scientific team members, following internal review and consideration would like the Application Review Subcommittee to consider the following in making its funding decisions:

Authorized by the ICOC:	$40.0 MM	~ 5-8 awards
Tier 1 applications recommended for funding:	$15.8 MM	5 awards

CIRM Recommendations

Tier 1 Applications: The CIRM team supports the Grants Working Group's recommendations to fund the five Tier 1 applications.

Tier 2 & 3 Applications: The CIRM team does not recommend funding any application below tier 1.

Rationale

CIRM is committed to supporting those superior projects that have the greatest chance to deliver a stem cell related therapy to patients in need. To this end, the Institute held a competitive application process, which was followed by a rigorous review by the Grants Working Group. Five applications were adjudicated to be the most scientifically meritorious and were therefore recommended for funding. There were no anomalies that would suggest the results of the review are not valid.

While CIRM recognizes that some applications not in Tier 1 do have the potential to positively impact the field, none was without flaw and all could be improved with further refinement. Unfortunately, the application and review system for this RFA does not accommodate iterative refinement and resubmission, a key feature of CIRM 2.0. As a result, CIRM recommends that interested applicants consider improving their submission and reapplying under the CIRM 2.0 Translational program that will be brought to the ICOC in July. Additionally, applicants have been notified to review the eligibility criteria for PA 15-01: Partnering Opportunity for Late Stage Preclinical Projects - which if met would provide an immediate opportunity for resubmission of an improved application.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08086: Human Stem-Cell Based Development of a Potent Alzheimer's Drug Candidate

GWG Recommendation: Tier 2
CIRM Recommendation: Not Recommended for Funding
Final Score: 71

Public Abstract (provided by applicant)

Over 6 million people in the US suffer from Alzheimer's disease (AD). There are no drugs that prevent the death of nerve cells in AD, nor has any drug been identified that can stimulate nerve cell replacement in aged human brain. Importantly, even if nerve cells could be replaced, the toxic environment of the AD brain which caused the disease in the first place will likely kill any cells that are born into that environment unless they are resistant to those conditions or can be protected by a drug. Therefore, drugs that stimulate the generation of new neurons (neurogenesis) alone will not be effective. A drug with both neurogenic and neuroprotective properties is required. With the ability to use cells derived from human neural precursor cells (hNPCs) derived from human embryonic stem cells (hESCs) as a screen for neurogenic compounds, we have shown that it is possible to identify and tailor drugs for therapeutic use in AD. With the support of CIRM, we have recently made a very potent AD drug candidate that is exceptionally effective in promoting the making of new nerve cells from human embryonic stem cells. It is both neurogenic and has therapeutic efficacy in a rodent model of AD. However, this molecule needs more preclinical development work before it can start the formal FDA pre clinical toxicity screening protocols. This work will optimize the chances for its true therapeutic potential in AD, and presents a unique opportunity to expand the use of hESCs for the development of a therapeutic for a disease for which there is no cure.

Statement of Benefit to California (provided by applicant)

Over 6 million people in the US suffer from AD, and unless a viable therapeutic is identified it is estimated that this number will increase to at least 16 million by 2050, with a cost of well over $1 trillion per year, likely overwhelming both the California and national health care systems. There is no treatment to prevent, cure or slow down this condition. In this application we have used the new human stem cell technologies to develop an AD drug candidate that stimulates the multiplication of nerve precursor cells derived from human embryonic stem cells. This approach presents a unique opportunity to expand the use of human

embryonic stems cells for the development of a therapeutic for a disease for which there is no cure, and could lead to a paradigm shift in the treatment of neurodegenerative disease. Since our AD drug discovery approach is fundamentally different from the unsuccessful approaches used by the pharmaceutical industry. It could also stimulate new biotech. The work in this proposal addresses one of the most important medical problems of California as well as the rest of the world, and if successful would benefit all.

Review Summary

This proposal is focused on the development of a small molecule drug for Alzheimer's disease (AD). The candidate small molecule was identified through screening of human embryonic stem cell (hESC)-derived neural precursor cells (NPCs) for compounds that are both neurogenic (induce new neuron formation) and neuroprotective (reduce neuron death). AD is a progressive, neurodegenerative disease and the most common cause of dementia. AD is associated with widespread cell death in the brain and there are limited treatment options, none of which stop or reverse disease progression. The applicant proposes that the candidate small molecule could potentially protect existing neurons in the AD patient brain and stimulate the production of new neurons, thereby improving memory and cognition. Activities proposed in the application include: identification of metabolites of the candidate small molecule; pharmacokinetic (PK) studies; identification of the drug target or pathway; drug synthesis; off-target and safety screens; an efficacy study in an animal model; and preparation for a pre-IND meeting with the FDA.

Significance and Impact

- Reviewers agreed that this proposal addresses a serious unmet medical need and, if successful, could have an enormous impact on the treatment of AD.

- Reviewers described the Target Product Profile (TPP) as highly appropriate and consistent with the objectives of other AD drug development efforts.

Scientific Rationale and Preclinical Development Readiness

- Based on the presented *in vitro* and *in vivo* studies, reviewers agreed that the proposed therapeutic candidate has desirable drug features. For example, they appreciated its pharmacological properties and that it can penetrate the blood-brain barrier.

- Reviewers thought the scientific rationale to be generally sound. However, they noted that identification of drug candidates through phenotypic screening rather

than mechanistic understanding of disease can be considered not typical of current drug development efforts and may result in a lack of information on mechanism of action (MOA).

- Reviewers thought the current absence of information regarding drug target and MOA to be problematic but acknowledged that drugs can be successfully developed without knowing MOA. It is, however, highly desirable and felt it might make several activities easier, such as biomarker studies, design of backup compounds, and partnering with pharmaceutical companies.

Design and Feasibility

- Reviewers suggested that because unacceptable toxicity is the major reason that many small molecule therapeutics fail, it would make sense to prioritize evaluating toxicity in animal models (which is not proposed) instead of focusing on the proposed mechanistic studies, which some reviewers thought were unlikely to be successful. This focus on studies not critical for the preIND meeting was concerning to some reviewers.

- Reviewers commented that the planned critical path activities could lead to a robust package for a pre-IND meeting.

- Reviewers found the preclinical development plan to be feasible. They suggested that it might be useful to conduct pharmacokinetic studies in species other than rodents and that formulation studies may become extensive if observed half-lives require several doses per day in humans.

Principal Investigator (PI), Development Team, and Leadership Plan

- Reviewers expressed concern that the team may lack drug development experience, in particular regulatory and CMC expertise, and saw this as a significant weakness. This was reflected in several elements of the application. For example, the applicant stated that it is unlikely that the FDA would allow a preIND meeting until the toxicity studies are complete, which reviewers believed to be incorrect.

- Reviewers noted that the PI is a well-established and highly accomplished investigator and has assembled a strong team of scientists.

Collaborations, Assets, Resources, and Environment

- It was unclear how several of the proposed collaborations would be executed. For example, reviewers did not think the relationship between the applicant and

the company providing matching funds was adequately described.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08087: Preclinical development of an acellular small intestinal submucosa extracellular matrix device augmented with allogeneic human mesenchymal stem cells for surgical implantation in patients with chronic myocardial infarction

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

Cardiovascular diseases remain the leading cause of death and disability in the United States. On average, an American suffers a heart attack every 34 seconds with one American dying of such an event every 1 minute and 23 seconds. While the chances of surviving the initial heart attack have improved greatly in recent years, once the infarction has occurred, and even with optimal treatment, patients often develop ischemic heart disease (IHD). Current treatments for IHD, however, cannot rescue diseased heart tissue or return heart function to normal. The only current cure is heart transplantation; however donor organ supply is severely limited and the vast majority of patients die from heart failure while on the transplant waiting list.

Stem cell therapies are being explored as novel potential cures for IHD. Numerous cell therapies are currently under investigation for heart diseases, but success rates have been modest. It is thought that this limited success is related in part to the fact that the donor cells are not very well retained in the heart tissue after transplantation and that they also fail to survive after being transplanted. We believe that these are key limitations that we are able to address with our novel regenerative therapy, thereby improving the overall effectiveness of stem cell therapies for heart disease.

Our therapy combines a type of bone marrow stem cells called mesenchymal stem cells (MSCs) and a biologically active scaffold derived from animal small intestinal submucosa called (SIS-ECM). We have found that this bioscaffold has the potential to improve cell retention and survival after transplantation to animal models of heart disease, so by combining the MSCs and the SIS-ECM, we can greatly amplifying the beneficial properties of both the stem cells and the biological scaffold. During the course of this project, we will implant our device onto the hearts of animal models that have been treated so as to mirror the chronic heart disease seen in humans. We will then verify that our device has a positive effect on the heart function of the animal, while at the same time making

sure that the therapy is both safe and feasible. The ultimate goal of our project then is to develop our novel regenerative therapy for heart disease to such a stage that we may, at the end of the project period, engage the FDA for guidance on how to enter the final stages of clinical development of our therapy. This project therefore puts us on the track for ultimately bringing our therapy into the clinic and to the benefit of our patients.

So in summary, we wish with this project to prove that our novel regenerative therapy for IHD is safe and efficacious so that we may start the final stages of clinical development. This in turn will then pave the way for a superior treatment option for the thousands of Americans for whom the unlikely prospect of a heart transplant is currently the only hope.

Statement of Benefit to California (provided by applicant)
An estimated 16.3 million Americans over the age of 20 suffer from coronary heart disease (CHD) with an estimated associated cost of $177.5 billion. Every 34 seconds, someone will have a coronary event and every 1 minute and 23 seconds, someone will die from one. Improvements in treatment and risk factors have resulted in a decrease in mortality associated with CHD. However, 5 year mortality rate remains high and CHD accounted for 1 in 6 deaths in the US in 2007. Current surgical and medical intervention following an acute coronary event seeks to reestablish blood flow to the affected tissue and reduce downstream adverse events. It has been reported that approximately 10% of patients suffering from acute coronary syndrome undergo coronary artery bypass grafting (CABG) surgery within 12 months of the initial cardiac event. Approximately 5000 revascularization procedures are performed per 1 million adults annually in the US (2008 data), with CABG surgeries amounting to about 23% of these procedures. Although timely intervention can greatly reduce negative remodeling and disease progression, current treatment modalities fail to prevent deterioration or promote significant improvement of heart function over time.

While these data represent that scope of the burden of CHD on a national level, the same challenges are also true for the state of California, where heart disease is the leading cause of death. Any treatment that will improve on current therapeutic outcomes would therefore have a tremendous impact on not only on reducing the cost of health care related to heart disease in California, but also dramatically improve the quality of life for millions of patients both in this state and world wide.

We believe that our proposed therapy for heart disease will not only accomplish this goal of improving the lives of millions of Californians and Americans in general. We also firmly believe that we can, with this project, reach that goal on a timeline that would potentially place this therapy in the realm of clinical trial within the next 5-10 year. Moreover, the therapy that we are proposing with the present project is based on a combination of two well researched components, mesenchymal stromal cells and small intestinal submucosa extracellular matrix, that already have a long track record of being safe in human, thus further improving the likelihood of quickly bringing this therapy to the benefit of Californian heart patients. Finally, our proposed therapy can be implemented using procedures that are currently routinely practiced at multiple health care centers through the state, thus ensuring that this cure potentially may be available throughout the state.

Review Summary

The applicants propose preclinical development of a cardiac patch consisting of allogeneic mesenchymal stem cells (MSC) seeded on a clinically utilized resorbable, biologic scaffold for chronic ischemic heart disease (IHD). The team hypothesizes that delivery of MSC on the scaffold will improve cell retention, and thereby the ability to recruit endogenous repair mechanisms. The scaffold can also provide structural support to failing hearts. The team plans to optimize the manufacturing process and to perform route of administration, pharmacology and toxicology studies in small and large animal preclinical models of acute and chronic myocardial infarction (AMI and CMI). They will also work to develop an in vitro potency assay. The applicants plan to engage the Food and Drug Administration (FDA) in a pre-pre-investigational new drug (IND) application meeting early in the award and to culminate the award with a well-prepared pre-IND meeting.

Significance and Impact

- Heart failure represents a major unmet medical need with the only curative option being heart transplantation, and the supply of donor hearts does not meet the need. A product that could delay disease progression could impact the standard of care in heart failure.

- Although reviewers were skeptical that the proposed approach will result in regeneration of heart tissue, if successfully developed, it could slow disease progression.

Scientific Rationale and Preclinical Development Readiness

- Concern was expressed that the bulk of the efficacy data in support of the program were in an AMI model, while the proposed clinical application of the patch is for a different disease state. This data may not predict what would happen in chronic IHD.

- To date, modest benefits have been reported in clinical trials using MSC in heart diseases. The applicants hypothesize that MSC would show greater benefit if they persisted at the transplant site for longer periods, and that seeding the cells on their patch will accomplish this goal. However, reviewers did not find compelling preliminary data supporting this hypothesis in the application.

- Because of the points above, reviewers found the application did not meet the readiness criteria set forth in the RFA. They suggested the applicants first assess performance of the patch in relevant preclinical models of chronic IHC, and then, based upon the results, consider applying for funding under a similar RFA.

Design and Feasibility

- It was noted that development of the proposed product (MSC on a scaffold) to the pre-IND stage should be feasible as both elements are separately utilized in the clinic already.

- The complex end stage manufacturing proposed at the clinical site was noted as a potential challenge.

- Reviewers were not convinced that all the required preclinical studies could be completed in 30 months.

- The standard of care for heart failure is evolving to include left ventricular assist devices and resynchronization therapies. It was suggested that the applicants consider how the proposed approach will complement these treatments.

Principal Investigator (PI), Development Team, and Leadership Plan

- The team is very strong, has a history of working together, and has the ability to carry out the proposed studies.

Collaborations, Assets, Resources, and Environment

- The host institution is an excellent environment for translational stem cell research.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08092: Human Embryonic Stem Cell-Derived Neural Stem Cell Transplants in Amyotrophic Lateral Sclerosis

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

Amyotrophic Lateral Sclerosis (ALS) is the most common adult motor neuron disease, affecting 30,000 people in the US and the typical age of onset is in the mid-50s or slightly younger. ALS is a degenerative neural disease in which the damage and death of neurons results in progressive loss of the body's functions until death, which is usually in 3-5 years of diagnosis. Current ALS treatments are primarily supportive, and providing excellent clinical care is essential for patients with ALS; however, there is an urgent need for treatments that significantly change the disease course. The only Food and Drug Administration approved, disease-specific medication for treatment of ALS is Rilutek (riluzole); which demonstrated only a modest effect on survival (up to 3 months) in clinical trials. This Preclinical Development Award is focused on developing an ALS therapy based on human embryonic stem cell (hESC) derived neural stem cells (heNSC) and/or astrocyte precursor cells transplanted into the ventral horn of the spinal cord. Several lines of evidence strongly support the approach of transplanting cells that exhibit the capacity to migrate, proliferate and mature into normal healthy astrocytes which can provide a neuroprotective effect for motor neurons and reduce or prevent neural damage and disease progression in ALS. In this project, we will complete the steps necessary to hold a successful pre-IND call with the FDA including demonstration of manufacturing consistency and safety of heNSC.

Statement of Benefit to California (provided by applicant)

ALS is a disease for which there is literally no currently effective therapy. While there are some mild palliative approaches to treatment, in virtually all cases the diagnosis of ALS is effectively equivalent to a death sentence. Clearly, in view of the dire prospects facing these patients, aggressive action on multiple, parallel therapeutic fronts is critical. It is particularly important in our view to develop an aggressive set of cell therapy programs so that we have multiple "shots on goal" in parallel.

Review Summary

This proposal is focused on the development of a human embryonic stem cell derived neural stem cell (heNSC) therapy for amyotrophic lateral sclerosis (ALS). ALS is a rapidly progressive neurodegenerative disease that results in the death of motor neurons in the spinal cord, progressive loss of movement and, ultimately, patient death. There are currently no effective treatments for ALS. The applicant proposes that heNSCs transplanted into the spinal cord will mature into astrocytes, a cell type that could protect patient motor neurons and potentially slow or halt disease progression. Activities proposed in the application include: manufacturing of Good Manufacturing Practice (GMP) compliant cell banks; cell bank characterization and stability studies; assay development; pilot safety studies in small and large animal models; and preparation for a pre-IND meeting with the FDA.

Significance and Impact

- Reviewers agreed that this proposal addresses a tremendous unmet medical need and that the development of any successful therapy would impact standard-of-care.

Scientific Rationale and Preclinical Development Readiness

- Reviewers thought the preclinical efficacy data inadequate to justify moving forward with clinical development. They understood and accepted the difficulty of showing benefit in an animal model of ALS but thought a combination of other proof-of-concept data could be collected to support a therapeutic role for heNSC-derived astrocytes, such as: in vitro and in vivo glutamate clearance; in vivo migration and integration; and in vitro or in vivo neuroprotection.

- Reviewers raised questions regarding the scientific rationale for developing a cell therapy that may require a long time to differentiate and mature in vivo to treat a disease that can progress so rapidly.

- Reviewers found the characterization of the astrocyte population generated from heNSCs to be generally inadequate, especially in regards to its capacity to clear glutamate.

- Reviewers thought the rationale for use of this therapeutic in the disease to be well supported by the scientific literature but felt there was inadequate data in the application supporting rationale.

Design and Feasibility

- Reviewers were concerned that some of the preclinical animal studies likely proposed too few animals per treatment group to produce interpretable data and others (such as the pilot tumorigenicity study) proposed too many to be feasible or appropriate for a pilot study.

- Reviewers raised concerns regarding the design of the tumorigenicity study. They noted that multiple routes of administration may not be necessary and recommended using the intended clinical route of administration.

- While reviewers agreed that FDA did not specifically require disease specific animal model studies demonstrating preclinical efficacy, they had concerns regarding the applicant's interpretation of FDA comments and thought additional proof of concept data might be required. They also recommended the applicant seek concurrence on preclinical design as soon as possible.

-Reviewers questioned whether any of the proposed study would allow for a reasonable determination of an appropriate and potentially active dose for the proposed clinical trial.

- Reviewers had difficulty interpreting the complex, tiered cell banking system proposed and the rationale behind it.

- Regarding the draft clinical trial synopsis and a later phase trial envisioned by the applicant, reviewers suggested that unilateral injection may not be the best approach for efficacy assessments. They noted that ALS does not progress uniformly on both sides of the body, so the contralateral side may not serve as a reliable control.

- Reviewers were unclear if the proposed drug delivery study was using the clinical device.

Principal Investigator (PI), Development Team, and Leadership Plan

- The PI is well-respected ALS researcher and the team is highly experienced.

Collaborations, Assets, Resources, and Environment

- No relevant concerns were highlighted under this review criterion.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08096: Development of Gene Therapy for HIV Using Potent, Multiplexed anti-HIV RNAs and In Vivo Gene Delivery.

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

Over 1,000,000 people are infected with HIV in the US alone and the numbers continue to grow. The current therapy for HIV, a combination of anti-viral drugs, is effective at suppressing the HIV virus but is not curative. Drugs must be taken daily or the virus will destroy the immune system and thus lead to progression to AIDS. Treatment fatigue leading to non-compliance or treatment interruption due to medical, social or financial reasons is a major problem with effective treatment for HIV. Thus there is still a significant need for an alternative therapy for this disease. One proposed alternative is the creation of an HIV-resistant immune system through transplantation of blood stem cells that carry an anti-HIV gene. Blood cells that are produced from these stem cells are resistant to HIV and may protect the patient from progression to AIDS in the absence of anti-retroviral drugs. Additionally, a protected immune system may retain the ability to fight off the HIV infection through natural immunity, leading to an eventual cure. These concepts are currently undergoing testing in clinical trials using standard stem cell transplantation methods which are similar to those used to treat cancer patients. However, these methods are risky, complicated and expensive and would be difficult to provide to a large number of patients outside of a large metropolitan hospital setting. As an alternative, we propose developing a therapy that will allow for the creation of a genetically resistant immune system without the need for stem cell transplantation. Our approach is to deliver the anti-HIV genes directly into the bone marrow of HIV+ patients using a genetically altered virus similar to HIV but without the immune destroying properties of HIV. We have tested the HIV-inhibiting properties of these viruses in our laboratory and are now testing them in clinical trials using the stem cell transplant procedures but propose to use them to develop the non-transplant procedure. If successful, direct delivery of the genes to the bone marrow would result in the production of an HIV-resistant immune system with a one-time treatment and eliminate (or reduce) the need for a lifelong commitment to taking antiviral drugs daily. We will perform pre-clinical product development and safety studies and initiate a discussion with the Food and Drug Administration to begin the process of testing this approach in human clinical trials. This approach has the potential to

revolutionize HIV therapy and eliminate the need for lifelong drug dosing. This should have a significant impact on the lives of those living with HIV infection, those who care for those patients and those who are at risk of transmissible HIV infection.

Statement of Benefit to California (provided by applicant)

According to the Henry J. Kaiser Family Foundation, in 2010 there were 24,129 Medicare enrollees with HIV/AIDS in California and Medicare spending for HIV/AIDS totaled $524,024,808 (average of $21,717 per enrollee). According to the most recent Semi-Annual report of HIV/AIDS cases in California as of June 30, 2014, there are >122,000 people diagnosed with HIV/AIDS in the state and the number is increasing at an average of 9.5% per year. This represents a major health and economic issue for the citizens of the state. Many patients have undetectable virus in their blood while on the currently recommended anti-retroviral therapy but treatment interruption and non-compliance with strict drug dosing regimens is frequent and leads to viral rebound and disease progression. Thus, anti retroviral drug therapy is not curative and an alternative form of treatment is warranted. One potential alternative approach to HIV/AIDS care is the development of methods to create an HIV-resistant immune system though transplantation of genetically modified (HIV-resistant) blood stem cells. We have spent the last 15 years developing and testing the genes and transplant procedures. Our research is now being tested in clinical trials across the state (and nation) to determine how, when and for whom this treatment might work. The ultimate goal for the project is to provide a one-time therapeutic intervention that would result in lifelong protection from AIDS and perhaps even elimination of the HIV virus altogether. Since 80% of HIV/AIDS care is related to prescription drug purchases, this procedure, if successful, has the potential to reduce healthcare spending proportionally. Reduction of the costs of HIV/AIDS treatment will leave more money for HIV prevention and education to further reduce the burden on the state healthcare system. A collateral benefit is that the reduction in the number of patients with active infection will decrease the transmission of virus through sexual activity, blood donation and other accidental exposures. This means that California's healthcare workers, first responders and others who may come in contact with blood and blood products will also will be at reduced risk of infection. During this process, our research has also provided jobs for hundreds of researchers, doctors, nurses and other healthcare professionals. Additionally, funds provided by CIRM have been used to purchase goods and services from California corporations and pumped countless dollars back into the economy as the result of this activity. The visibility and potential of stem cell medicines has also attracted top scientific talent to California, thus increasing our profile as

world leaders in the area of regenerative medicine. Together, the projects funded by this and other CIRM grant mechanisms benefit the people of the state of California in a multitude of ways that will only grow as therapies are developed and become available first in the state of California.

Review Summary

The applicant is proposing to develop a gene therapy approach for in vivo modification of human hematopoietic stem cells (HSCs). This approach is intended to modulate the immune system of an individual infected with the human immunodeficiency virus (HIV) to provide protection from the virus and prevent progression to acquired immunodeficiency syndrome (AIDS). The applicant proposes preclinical product development; preclinical safety and efficacy studies; and clinical protocol development to support a preIND meeting with the Food and Drug Administration (FDA) on the initial trial with the proposed therapeutic.

Significance and Impact

- A gene therapy approach that replaces antiretroviral therapy (ART) and restores health following a single administration would completely revolutionize the standard for care for HIV infection.

- If successful, the proposed approach has the potential to address an important unmet medical need by obviating the need for life-long drug therapy and overcoming poor compliance, toxicities, and drug resistance.

- The proposed optimal, as well as minimally acceptable, efficacy endpoints in the target product profile (TPP) would significantly impact standard of care, though reviewers expressed concern that the proposed minimally acceptable biologic endpoint might not be useful or impactful.

- The use of gene therapy to treat HIV is being studied elsewhere in the context of bone marrow transplant, which may not be feasible for a large part of the HIV positive population. The concept of using gene therapy to directly modify the immune system is, therefore, potentially transformative.

Scientific Rationale and Preclinical Development Readiness

- In the opinion of the reviewers, additional data is needed to support preclinical development. While the preliminary data convincingly demonstrated an impressive protective effect of the candidate in vitro, reviewers did not think adequate in vivo preclinical data with the final product was presented in the application.

- The final product does not appear to be sufficiently specified for proceeding with preclinical development as defined in the RFA.

- Though one potential development candidate appears superior to others, it is not absolutely clear that the best possible protective construct has been achieved, as the reviewers thought the data established only marginal activity in the preclinical model.

- RECOMMENDATIONS TO THE TEAM: Though this was not a consideration in the score, some reviewers believed the applicant could benefit from the conduct of a pre-preIND meeting as soon as possible. This would allow the applicant to understand FDA concerns and design a development program that incorporates FDA comments regarding the approach and proposed first trial.

Design and Feasibility

- Reviewers thought the proposed preclinical large animal model study was not described in sufficient detail and expressed concerns that the study might not be sufficiently powered to determine success.

- Some reviewers noted that while the large animal study is somewhat limited, it could be informative for the preIND meeting and future study design. Others believed this study to be high risk given the opinion that compelling and supporting data in small animal models has not yet been satisfactorily achieved.

- Given the number of cells to be transfected, there were some scaling concerns revolving around potential low multiplicities of infection (MOI) and potential low transduction efficiencies. In the absence of targeting, reviewers were concerned that the number of vector particles proposed might be insufficient, making it difficult to understand how the optimal, or even minimal, biologic activity will be achieved. Reviewers thought the scale calculations need better clarification.

- Reviewers noted that product development efforts for optimizing transduction methods, defining current good manufacturing practices (cGMP) compliant production procedures; and conducting preliminary proof of concept (POC) and biodistribution should position the applicant well for preIND meeting.

- Some reviewers expressed concern regarding a trial design proposing interrupting treatment and recommended a more conservative approach. Others thought this approach appropriate if the preclinical data were compelling.

- RECOMMENDATIONS TO THE TEAM: Though this did not highly impact the score, reviewers commented that the selectable marker system requires an alkylating agent, which could impact the existing immune system of the HIV positive patient. Reviewers acknowledged that this is a general concern in the field but suggested the applicant consider alternative systems to alleviate this potential issue.

Principal Investigator (PI), Development Team, and Leadership Plan

- This is an expert team with extremely high subject matter competency, and reviewers did not express any concerns with the ability of the team to execute the proposed project activities.

- Though the PI and team are excellent, reviewers did not think their competence in development came through in the application, as highlighted by what some reviewers perceived as an absence of sufficient clarity around the product.

Collaborations, Assets, Resources, and Environment

- The collaboration with the large animal center is appropriate, and all investigators appear highly qualified. However, in the opinion of the reviewers, the crucial in vivo preclinical large animal study is described in much less detail than other studies, which suggests that the team is not sufficiently integrated.

- Resources are adequate to complete the proposed work.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08098: Development of a Pan BCL2 Inhibitor to Target Dormant Cancer Stem Cells in Refractory Hematologic Malignancies

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

Cancer relapse is the leading cause of death for individuals younger than 85. Relapse rates in leukemia, a frequently fatal cancer of blood forming cells that afflicts both adults and children, are exceedingly high. Although many drugs have been developed to treat leukemia, leukemia frequently returns in a form that is not curable, causing disability and eventual death. During the last few years, scientists have discovered that some leukemia cells possess stem cell properties that make them more potent in promoting leukemia growth and resistance to common types of treatment. Specifically, these leukemia stem cells have the capacity to clone themselves, survive and go to sleep, or in other words become dormant, in the bone marrow. Leukemia stem cells, thus, evade therapies that target dividing cells. More than in other cancers, scientists understand the exact molecular changes in the blood forming cells that cause leukemia. However, existing drugs do not generally eliminate dormant leukemia stem cells that persist in patients and continue to grow, spread, invade and kill normal cells. In fact, the models used for drug development in the pharmaceutical industry have not generally been designed to detect drugs or drug combinations capable of destroying leukemia stem cells. While drugs capable of targeting leukemia stem cells may already exist, or could be simple to make, but there has not been an easy way to identify these drugs. Recently, physicians and scientists at Universities and research institutes have developed tools to isolate and to analyze LSC donated by patients. By studying the LSC, the physicians and scientists have identified the molecules that these cells need to survive. The experimental results strongly suggest that it will eventually be possible to destroy leukemia stem cells with drugs or drug combinations, with minimal damage to most normal cells. Now we need to translate the new knowledge into practical treatments. The team is composed of highly experienced scientists and physicians who first discovered leukemia stem cells in many types of human leukemia and who have developed the leukemia stem cell model systems to test drugs. The investigators in the team have identified a key drug candidate and have already performed pharmacology and toxicology studies. This team includes experts in drug development, who have been successful in quickly bringing new leukemia targeting drugs to clinical

trials. The supported interactive group of physicians and scientists in California has the resources to introduce into the clinic a new drug for leukemia that may also represent a more effective therapy for other therapy resistant cancers for the benefit of our citizens.

Statement of Benefit to California (provided by applicant)

Cancer is the leading cause of death for individuals under 85 and usually results from relapse in the setting of therapeutic resistance. Our team and others have demonstrated that anti-apoptotic BCL2 family member overexpression promotes disease progression in tyrosine kinase inhibitor (TKI) resistant chronic myeloid leukemia (CML) and many refractory hematologic malignancies. The emergence of dormant cancer stem cells promotes apoptosis resistance in the bone marrow niche. While targeted BCR-ABL TKIs have resulted in improved survival of patients with chronic phase CML, the prevalence of CML has increased to 70,000 individuals and is expected to reach 112,000 by 2020. Unfortunately, a growing proportion of patients with CML become intolerant or simply cannot afford full dose BCR-ABL inhibitor therapy as a result of spiraling annual costs and thus, progress to advanced phase disease with a 5-year survival rate of less than 30%. With a combined US prevalence of 236,000, myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs) also become therapy resistant following BCL2 family member upregulation and progress to rapidly fatal secondary AML (sAML). Because sAML also arises following chemotherapy to treat solid tumors, it has increased in frequency resulting in a MDS/AML market that is expected to increase to $617 million in 2017. Finally, therapy resistant T cell acute lymphoblastic leukemia (T-ALL) is also characterized by BCL2 family member upregulation. Thus, a novel pan BCL2 inhibitor capable of targeting dormant CSCs would form an essential component of a combination CSC eradication strategy that may prevent relapse in refractory hematologic malignancies as well as other advanced cancers that upregulate BCL2 family members. Thus, anti-apoptotic BCL2 family member inhibition with Sabutoclax could represent a vital component of a potentially curative strategy for advanced malignancies that may obviate the need for costly continuous TKI and other therapies. Elimination of dormant CSCs that contribute to therapy-resistance related relapse, which is the primary cause of cancer death, is of high clinical importance. Thus, development of a small molecule pan-BCL2 inhibitor would fulfill a vital unmet medical need, fuel California biotechnology stem cell R&D efforts and decrease health care costs for patients with cancer.

Review Summary

The objective of this proposal is to complete studies required to conduct a preIND meeting for a small molecule drug candidate that targets cancer stem cells (CSC) in refractory hematologic malignancies (leukemias). The drug candidate targets all the members of a family of molecules that have been shown to promote survival of dormant CSCs in refractory leukemias. Proposed activities include manufacturing activities and the conduct of preclinical safety, efficacy and dose finding studies.

Significance and Impact

- Reviewers acknowledged that treatment-resistant leukemias remain an important unmet clinical need.

- Reviewers did not find the data presented to be highly promising and they expressed doubt that the proposed candidate would be a competitive product.

- Reviewers were unconvinced that the cells being targeted are indeed CSC.

Scientific Rationale and Preclinical Development Readiness

- Reviewers found the preclinical efficacy data to be a key weakness of the proposal. The data was not compelling and the reviewers considered it insufficient to warrant further development of the proposed candidate.

- Because the benefit seen in preclinical models was viewed as relatively modest, reviewers raised concerns regarding the likelihood of it translating to a patient benefit.

- Reviewers agreed that the mechanism of action of the candidate seems clear and it has the advantage of addressing the entire target gene family.

Design and Feasibility

- Reviewers expressed concern that the safety and efficacy data provided may not support a clear therapeutic window in patients.

- Reviewers noted that the project appears to be a fairly straightforward small molecule development program and that the proposed project plan is reasonable.

Principal Investigator (PI), Development Team, and Leadership Plan

- The PI and collaborators appear strong.

- A concern was raised that the PI may be overcommitted.

- Reviewers suggested that the project would benefit from having an experienced regulatory consultant.

Collaborations, Assets, Resources, and Environment

- Resources and facilities are excellent.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08100: Genetically Corrected, Induced Pluripotent Cell-Derived Epithelial Sheets for Definitive Treatment of Dystrophic Epidermolysis Bullosa

GWG Recommendation: Tier 2
CIRM Recommendation: Not recommended for funding
Final Score: 73

Public Abstract (provided by applicant)

Genetic skin diseases constitute a diverse group of several hundred diseases that affect up to 2% of the population and include common disease such as psoriasis, atopic dermatitis, and wound healing. Patients with one genetic disease, Recessive Dystrophic Epidermolysis bullosa (RDEB), lack a normal collagen VII (COL7A1) gene and suffer from debilitating blistering and scarring that can be lethal by young adulthood. The disease is devastating and despite all efforts, current therapy for RDEB is limited to palliative wound care. None of the current approaches address the observation that RDEB patients suffer from chronic wounding and severe depletion or exhaustion of epidermal stem cells. Such depletion represents a key roadblock in somatic gene therapy efforts due to the paucity of donor cells and potential for transformation due to accumulated mutational load in remaining stem cells. Development of induced pluripotent stem (iPS) cells that are generated from the somatic cells of individual patients provides an ideal source of therapy. In addition, the advent of novel genome editing technologies allows the manipulation and repair of iPS cells prior to differentiating them into patient tissues. iPS Cell Therapy for Dystrophic Epidermolysis Bullosa (DEB), called DEBCT, is a corrected, patient-specific iPS-derived keratinocyte sheet grafts that possesses strong scientific and clinical support for its disease-modifying activity. During product development, the team received written responses from our Pre-pre IND meeting with the FDA that helped focus product development. The goal of this project is to enlist the aid of industry consultants to address manufacturing, safety, and regulatory issues in preparation for a successful FDA pre-IND meeting.

Statement of Benefit to California (provided by applicant)

Genetic skin diseases constitute a diverse group of several hundred diseases that affect up to 2% of the population and include common disease that affect Californians such as psoriasis, atopic dermatitis, and wound healing. Patients with one genetic disease, dystrophic Epidermolysis bullosa (EB), lack collagen VII (COL7A1) and suffer from debilitating blistering and scarring that can be lethal by

young adulthood. The disease is devastating and despite all efforts, current therapy for DEB is limited to palliative wound care.
While many therapeutic attempts have occurred, none of the current approaches address the observation that RDEB patients suffer from chronic wounding and severe depletion or exhaustion of epidermal stem cells. Such depletion represents a key roadblock in somatic gene therapy efforts due to the paucity of donor cells and potential for transformation due to accumulated mutational load in remaining stem cells. Development of induced pluripotent stem (iPS) cells that are generated from the somatic cells of individual patients provides an ideal source of therapy. In addition, the advent of novel genome editing technologies allows the manipulation and repair of iPS cells prior to differentiating them into patient tissues. iPS Cell Therapy for Dystrophic Epidermolysis Bullosa (DEB), called DEBCT, is a genetically-corrected, patient-specific iPS-derived keratinocyte sheet grafts that possesses strong scientific and clinical support for its disease-modifying activity.

If successful, the approach in this project could be used to correct many other genetic defects. The ability to therapeutically reprogram and replace skin would allow this procedure to develop therapeutic reprogramming approaches for a variety of both common and life-threatening skin diseases, bringing an enormous benefit to the people of California. Moreover, because a by-product of this project is corrected iPS cells that are pluripotent, patient-specific corrected iPS cells could form the basis of future systemic therapies to other organs besides the skin to treat common genetic disorders.

Review Summary
The ultimate goal of this proposal is to develop an autologous cell therapy to treat patients with mutations in the gene encoding type VII collagen. This mutation causes the blistering skin disorder dystrophic epidermolysis bullosa (DEB). The therapeutic product would be manufactured from induced pluripotent stem cells (iPSCs) derived from each patient, genetically modified to correct the mutation and then converted into skin sheets to be transplanted onto the patient. This would provide an immune-matched source of new skin that produces normal type VII collagen and is expected to properly anchor to the body. In order to get ready for a well-prepared Pre-Investigational New Drug (IND) meeting, the applicants plan to demonstrate reproducibility of the manufacturing process that they have developed for their iPSC-derived skin product including establishing GMP-compatibility and comparability of a manufacturing improvement made to the process. They also intend to complete development of and qualify the assays that will be used to demonstrate the quality and safety of the cellular therapeutic

produced for each patient, and to produce all necessary documentation for their Pre-IND application package.

Significance and Impact

- Reviewers found this to be a high risk / high impact proposal. A gene-corrected iPSC-derived autologous cell product is a very exciting regenerative medicine goal, and although the regulatory hurdles are formidable, the proposed work represents cutting edge science and an interesting challenge. Reviewers considered it well aligned with CIRM's mission.

- It is unequivocal that DEB, a rare but devastating condition, represents an unmet medical need.

- If successful, the proposed therapeutic approach would represent a true advance over standard of care for DEB.

- To some reviewers, it was clear that the applicants are pursuing the recessive form of DEB, while others were uncertain whether DEB patients with dominant forms of the disorder would also be targeted. This is a concern since the two patient groups have different risks and may require certain aspects of preclinical and clinical studies to be designed differently.

Scientific Rationale and Preclinical Development Readiness

- The proposed therapeutic is based on an interesting, scientifically sound approach that could provide a constant source of cell product for DEB patients. Reviewers believed that the complexity of the cell product raises the question, though, whether the overall approach is practical.

- The applicants are currently performing a clinical trial with a different product that has some important similarities to the one proposed. Positive results from the ongoing trial could serve as proof of concept for the proposed therapeutic, but reviewers believed that little detail was provided to substantiate claims of successful treatments of patients.

- Reviewers supported the rationale for targeting a preferred patient subpopulation to minimize immune recognition of the replaced protein.

- The vector design is novel in this disease indication; it represents an innovative way of more safely performing gene modification.

Design and Feasibility

- The reviewers opined that the manufacturing process for the cell product is very complex. Reviewers acknowledged that the applicants have made remarkable progress toward developing a relatively effective process, but also felt that this remains a major hurdle, especially the establishment of a consistent differentiation process.

- Reviewers in general judged the proposed plan to be well designed, but were unconvinced that the applicants clearly identified mitigation strategies for hurdles they may encounter in the proposed studies.

- Reviewers were skeptical of the claim that the applicants have fully worked out an improvement to a step in cell manufacture, as this was not well substantiated by preliminary data and is a known to be a challenging hurdle.

- The timelines are aggressive; reviewers were unconvinced the team would be able to complete all necessary activities in the proposed timeframe.

- The team has conducted a pre-pre-IND meeting with the Food and Drug Administration (FDA), and reviewers appreciated that they have incorporated some of the FDA suggestions into this proposal.

- DEB patients are highly susceptible to squamous cell carcinoma (SCC), a form of skin cancer. The applicants propose to screen gene-corrected iPSC lines to exclude those that harbor genetic abnormalities linked to developing SCC. While reviewers felt this is a laudable goal, they felt the proposed markers may not be relevant in the DEB population.

- Reviewers believed that applicants did not adequately address a concern that large blisters, typical in DEB patients, are often chronically infected with resistant bacteria, which may present a challenge for effective skin grafting and alternative grafting approaches may need be considered to deal with this likely scenario.

Principal Investigator (PI), Development Team, and Leadership Plan

- The team seems suitable for the proposed studies, as they have demonstrated experience with disease models, and are gaining relevant experience in their ongoing clinical trial. Overall, reviewers felt that this team has the capacity to achieve the goals of the proposal.

- Reviewers were uncertain whether the PI has the requisite experience to move

this cell-based therapy through preclinical development to the clinic.

- Reviewers criticized the fact that the project manager, a critical member of this team, has not yet been hired.

Collaborations, Assets, Resources, and Environment

- Overall, good consultants, including experts on regulatory issues, have been recruited to the project.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08103: Placental Stem Cells for the In Utero Treatment of Spina Bifida

GWG Recommendation: Recommended for funding
Final Score: 89

Public Abstract (provided by applicant)

Myelomeningocele - also known as spina bifida - is a devastating and costly defect that causes lifelong paralysis as well as bowel and bladder incontinence in newborns. It is one of the most common birth defects worldwide, with four children in the United States born with spina bifida every day. Spina bifida affects the physical, educational, social, and psychological development of these children. Most patients require multiple surgeries and hospitalizations throughout their lives. Physicians are now able to diagnose this disease during pregnancy, and new fetal surgical techniques allow surgeons to safely operate on these children in the womb. This unique fetal surgery was studied in the award winning Management of Myelomeningocele Study (MOMS). The MOMS trial showed - for the first time ever - that the paralysis associated with spina bifida could be improved. Children treated in the womb were more likely to walk independently than those who were repaired after birth. However, the improvements seen were not perfect and the majority of children treated with fetal surgery still had some level of paralysis or lower extremity weakness.

Our research has built upon the success of the MOMS trial to address the residual deficits seen in children even after treatment with fetal surgery. We have developed a placental stem cell based therapy that can be applied at the time of fetal repair, in order to reverse spinal cord damage. After six years of laboratory research investigating different stem cell types and the best way to deliver a stem cell based treatment in the womb, we have discovered a placental stem cell therapy that cures spina bifida in the animal model. Animals treated with these cells can make a full recovery and are able to walk normally without any evidence of lower extremity paralysis. These amazing results require additional testing and FDA approval before the therapy can be used in humans. With this proposal, we will optimize this stem cell product, validate its effectiveness, determine the optimal dose, and confirm its preliminary safety in order to translate this new treatment to clinical trials. Stem cell therapy for spina bifida could cure this devastating disease, alleviating a massive burden on children, families, and society.

Statement of Benefit to California (provided by applicant)

Spina bifida is one of the most common, costly, and disabling birth defects. Within the United States, four children per day are born with this devastating disease. In California, the 5-year statewide incidence of spina bifida was 6.8 cases per 10,000 live births between 1999 and 2003, significantly higher than the Healthy People 2010 target of 3 per 10,000 births. Additionally, spina bifida disproportionately affects Americans of Hispanic and Latino descent, who make up 37.6% of California's population. Given the disproportionately high incidence of children born with spina bifida in California, and the lifelong disability these children live with, spina bifida is a substantial economic burden to the state. The estimated average total lifetime cost to California is approximately $532,000 for each child born with spina bifida. However, for many children, the cost may be several million dollars due to repeat surgical procedures, frequent hospitalizations, and the need for ongoing physical and cognitive rehabilitation. In addition to the direct medical costs associated with spina bifida, the indirect costs include: pain and suffering, cost of specialized childcare, and the lost earning potential of unpaid caregivers, which compound the impact the disease has on California's economy.

There is currently no cure for spina bifida, and interventions that mitigate the negative consequences of the disease (lower body paralysis, bowel and bladder incontinence) are urgently needed. For the first time, hope for an improved treatment option was provided by the award winning Management of Myelomeningocele Study (MOMS). The MOMS trial was a multicenter randomized controlled trial demonstrating that the paralysis associated with spina bifida might be improved by surgical repair of the defect before birth. This promise of fetal intervention for spina bifida was based on the hypothesis that early in utero treatment would have the potential to fix the defect before permanent spinal cord damage occurred. While the MOMS trial did demonstrate an improvement in the lower extremity paralysis of those patients undergoing in utero repair compared to postnatal repair, these improvements were not universal for all children. This proposal presents an innovative placental stem cell-based therapy to augment fetal repair and further improve and possibly cure the devastating and costly neurologic deficits of spina bifida. A cure for spina bifida would relieve California families and society of the tremendous emotional and economic cost burden of this debilitating disease, and would be life changing for future children afflicted with spina bifida.

Review Summary

This proposal is focused on the development of a placental stem cell therapy for myelomeningocele, also known as spina bifida (SB). SB is one of the most common birth defects and is characterized by malformation of the spine during development and, in severe cases, protrusion of the spinal cord from the lower back. SB can cause incontinence and paralysis and most patients require multiple surgeries throughout their lives. Recent advances in imaging and fetal surgery have allowed doctors to diagnose SB during pregnancy and operate on the fetus, leading to improved outcomes. The applicant proposes that transplanting a placental stem cell based therapy at the time of in utero fetal surgery will repair spinal cord damage and further improve patient outcomes. Activities proposed in this application include: characterization and assay development for the therapeutic candidate; efficacy and dose optimization studies in preclinical animal models; safety studies in preclinical animal models; and preparation for and conduct of a pre-IND meeting with the FDA.

Significance and Impact

- Reviewers agreed that the proposed therapeutic addresses a serious unmet medical need and, if successfully developed, could significantly impact standard-of-care for SB. They noted that there is an existing fetal surgery treatment approach for this condition but there is still a great need for further improvement.

Scientific Rationale and Preclinical Development Readiness

- Reviewers agreed that the scientific rationale is very sound and supported by impressive preliminary data that in utero repair can be accomplished through this approach.

- Reviewers judged the project ready to move into preclinical development.

Design and Feasibility

- Reviewers generally found the proposal to be feasible but noted that the timelines are tight and some experiments require seasonal, timed pregnancies. They cautioned that time management and efficiency will be critical for the success of the project but felt confident that this team is aware of and can manage these issues.

- Reviewers were impressed at the quality of the proposal and thought the plan was appropriately designed to support the preclinical IND meeting.

- Reviewers found the team to be well positioned to mitigate potential issues and execute the proposed plan.

- Reviewers felt that aspects of the project related to CMC (Chemistry, Manufacturing & Controls) could to be strengthened. They suggested that cGMP master cell banks of the candidate lines be made prior to comparison, so that work doesn't need to be repeated and the animal studies can support IND filing. They also suggested that work begin now to replace fetal bovine serum in the manufacturing process and that the same thaw/wash procedure envisioned for clinical use be employed preclinically.

Principal Investigator (PI), Development Team, and Leadership Plan

- Reviewers agreed that this is the ideal team to carry out the activities described in the proposal and to move the development candidate forward.

- Reviewers described the PI as a world expert in SB and fetal repair of defects.

- Reviewers praised the well-developed leadership plan that includes clear lines of communication.

Collaborations, Assets, Resources, and Environment

- Reviewers felt that the applicant institution is one of the few places in the world with the right personnel and facilities to successfully carry out the proposed research.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08104: Harnessing Native Fat-Residing Stem Cells For Spine Fusion: From Early Translation To Preclinical Development

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

Osteoporosis, which means 'porous bone", is an incredibly common illness that is marked by gradual decrease in bone mass and bone density that results in higher risk for bone fracture. Estimates suggest that the annual osteoporotic fracture cost will rise to $240 billion worldwide by 2040. Patients with osteoporosis also have difficulty forming new bone, which results in increased failures during orthopaedic surgery. We are addressing this urgent need to replenish osteoporotic bone by combining a natural cell source and bone forming stimulus to optimize osteoporotic bone formation.

Current stem cells on the market, such as mesenchymal stem cells (MSC), are of poorly understood origin, are of variable composition, and require weeks of culturing before they can be clinically used. In addition, currently available MSC show marked reductions in their numbers and activity in the osteoporotic patient. All these factors mean that current stem cell products do not adequately address the needs of an osteoporotic patient.

In contrast, perivascular stem cells (PSC) that naturally surround arteries and veins can be easily purified within hours and without need for cell culture. PSC was first discovered by our team in 2008. With the support of a CIRM Early Translational Grant (2011-2014), we have recently investigated PSC obtained from 173 humans and fully validated safety and bone-forming efficacy. Moreover, PSC are resistant to age- and osteoporosis-related changes. In sum, PSC efficiently form new bone in the setting of osteoporosis, demonstrating the capacity to fuse vertebrae in small and large animals. To amplify the ability of PSC to form bone, we are delivering a natural bone stimulant called NELL-1, which has been shown to be safe and effective in large animal models. The combination PSC+NELL-1 product allows for safer and more targeted bone formation than current standards of care. The goal of the present project is to develop the PSC+NELL-1 product for osteoporotic spine fusion.

The development of PSC has broad implications for human disease beyond bone regeneration. PSC are easily isolated and stored: in theory, an individual supply for each patient can be saved for later use. Moreover, as a "platform technology" PSC, when given the proper environment, can regenerate multiple different tissue types, including bone, fat, cartilage, muscle, and even nerve.

NELL-1 protein also has significant use beyond bone repair. It has been proven effective in the regeneration of cartilage, treatment for osteoporosis, and as a non-toxic anti-inflammatory molecule. In sum, we expect the development of the PSC+NELL-1 product to have far reaching medical benefits beyond the simple regeneration of bone.

Statement of Benefit to California (provided by applicant)
This proposal describes preclinical development studies for a combination product with proven superiority to current bone graft substitutes. After initial funding by a CIRM Early Translational Grant, we have successfully attained all milestones and our Developmental Candidate now provides a full package of progenitor cells, bone growth factors, and a scaffold to "jump start" bone formation in the osteoporotic patient. In addition to its scientific and clinical impact, this project has many near- and long-term benefits to the State of California:

1. Musculoskeletal injuries and diseases are the leading cause of work-related and physical disability in the United States. California generates an annual GPD of $1.8 trillion, making it the eighth largest economy in the world. By promoting bone repair, our mature technology will reduce: the loss of work productivity; work disability costs; and the loss of state income tax.

2. The natural decline in the number of osteogenic stem cells (from 1/10,000 in new born bone marrow to 1/2,000,000 by age 80) is associated with osteoporosis and fragility fractures in the aging population. In 2005, the health care burden for osteoporosis exceeded $1.4 billion in California alone. By treating existing fractures and preventing new ones, this platform technology can significantly reduce the long-term health care burden for California's public health insurance program.

3. This project directly adds jobs at California universities and at the California-based companies involved. Of note, an estimated $18 million dollars of out-of-state funding has been generated over the last three years for research on

PSC+NELL-1. This extra funding represents an External:CIRM funding ratio of 3.8:1.

4. This project has produced - and will produce more - intellectual property owned by [Redacted]. Our team has a track record of attracting private investment and procuring supplies and equipment from strategic California-based companies.

5. This project is precisely the type of cutting-edge, multi-disciplinary stem cell therapy that Californians imagined when they approved proposition 71 in 2004. CIRM has transformed the research infrastructure at [Redacted], increased our ability to recruit world-class stem cell scientists, and attracted the attention of superb scientists from other disciplines to this new field. Our team has compiled an impressive list of accomplishments and we are confident in our ability to file an IND submission in a timely fashion. Funding of this project will fulfill the promise of proposition 71.

6. PSC is a "platform technology" that can be optimized for the regeneration of other mesenchymal tissue, including adipose, muscle, cartilage and even nerve. Current development of PSC-based applications includes both heart and cartilage regeneration, representing an additional and outstanding potential benefit to the State.

Review Summary

This proposal is focused on the development of a multi-component combination product, consisting of autologous perivascular stem cells (PSCs) and a bone stimulant protein (NELL-1) in a matrix material (PSCs+NELL-1) for spinal fusion in patients with degenerative disc disease including those with osteoporosis. Spinal fusion is a surgical technique in which two or more damaged vertebrae are joined using hardware (e.g. screws) and additional bone tissue from the patient or a donor. The goal of spinal fusion is to reduce pain caused by movement of damaged vertebrae by fusing and immobilizing them. The applicant proposes that the use of PSCs+NELL-1 instead of autologous bone grafts will improve spinal fusion and outcomes. Activities proposed in the application include: development of processes for and production of Good Manufacturing Practice (GMP) compliant NELL-1, PSCs+NELL-1 and associated ancillary reagents and device; assay development; product stability studies; pilot preclinical studies; and submission of IND-enabling preclinical study protocols to the FDA for comment.

Significance and Impact

- Reviewers described the product concept as overly complicated and likely to provide only incremental benefit if successful. They did not think that the cost-benefit ratio would be favorable enough to impact standard-of-care.

- Reviewers were not convinced that this proposal addresses a significant unmet medical need.

- Reviewers felt that the target indication is too broadly defined in the Target Product Profile (TPP). They noted that for some indications, success of spinal fusion does not correlate with long-term clinical benefit, so the proposed therapeutic could improve fusion but not patient outcomes. They suggested that the TPP focus on a patient population for which spinal fusion is clearly indicated.

Scientific Rationale and Preclinical Development Readiness

- Reviewers were not convinced there is sound scientific rationale for including all of the various components of the proposed therapeutic candidate.

- Reviewers questioned whether an autologous approach would be superior to an allogeneic one, given variability among patients and the added complexities of manufacturing and testing autologous products. Particularly with osteoporotic patients, they questioned the ability to harvest PSC of sufficient number and quality.

Design and Feasibility

- Reviewers noted that the FDA raised a number of serious concerns during two separate meetings that will need to be addressed. They were not convinced there is a plan in place to address all of these concerns.

- Reviewers felt the path for preclinical development of this therapeutic candidate as very complicated and felt that it may be difficult to complete all of the proposed activities in a 30-month timeline.

- Reviewers were concerned that the budget may not be adequate in certain areas, such as cell bank production and stability studies.

Principal Investigator (PI), Development Team, and Leadership Plan

- Reviewers appreciated the team's excellent organizational structure. There is a clear multi-PI/PD plan with segments of discrete responsibility.

Collaborations, Assets, Resources, and Environment

-No relevant concerns were highlighted under this review criterion.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08105: Preclinical development of a WNT activated autograft (autograft^WNT) containing endogenous stem cells to enhance skeletal healing.

GWG Recommendation: Tier 2
CIRM Recommendation: Not recommended for funding
Final Score: 72

Public Abstract (provided by applicant)
Stem cells are key regulators of tissue repair. Aging naturally diminishes the number of stem cells and their capacity to respond to injury, which in turn hinders tissue healing. One of the great unmet challenges for regenerative medicine is to devise ways to increase the number of these endogenous stem cells and revive their ability to replicate and promote healing.

The scientific foundation of our work is that a naturally occurring stem cell factor, WNT3A, is a central regulator of stem cell self-renewal and bone formation. We devised methods to re-activate a patient's own stem cells as part of a standard surgical procedure called “autografting.”

Autografting involves harvesting bone marrow and bone chips from one part of the body and transplanting the tissue to another site that requires bone regeneration. Autografts can generate new bone because they contain stem and bone progenitor cells. Autografts work well in young patients but in middle-aged and older patients they become unreliable and inadequate. In our experiments, autografts treated with L-WNT3A show significant activation of the stem cell population; the autograft then exhibits higher cell proliferation and lower programmed cell death. Autografts^WNT are also significantly more osteogenic. When Autografts^WNT are used for spinal fusion or osteonecrosis they lead to significantly improved bone formation compared to controls. These beneficial effects are especially pronounced in older animals. Thus, our research addresses a present and ongoing challenge to healthcare for older Californians and the world, and we do it by mimicking the young body's natural response to injury and repair.

There are other bone-inducing growth factors on the market but their use is now associated with life-threatening complications, leaving orthopedic surgeons with few alternatives. To avoid these kinds of safety concerns we developed a novel way of delivering the WNT protein, which avoids direct introduction of the potent stem cell factor into the human body. Also, because this approach directly

activates the body's own stem cells, it avoids many of the toxicity concerns associated with delivering foreign stem cells from a donor into the body.

To our knowledge, there is no existing technology that displays the effectiveness or that holds such potential for the stem cell-based treatment of bone conditions as does this WNT-based strategy. We have now partnered with an established, early-stage investor and together, our team of experienced scientists, clinicians, drug developers and entrepreneurs will ensure that investigational new drug (IND) filing is reached in 30 months.

Statement of Benefit to California (provided by applicant)
Without a doubt, the most significant social, political and economic issue we face -in California, in the US, in the world- is our aging population. Within 5 short years, and for the first time in recorded history, the number of people over age 65 will exceed the number of children under age 5. With this dramatic demographic shift comes “quality of life” issues associated with aging. Consequently, outlining a clear pathway to healthy, active, and productive aging is of the utmost importance.

Our proposal addresses the single greatest chronic impairment associated with aging: namely, the loss of bone health. Our skeletons become progressively more fragile as we age, and this fragility translates into poor bone healing potential. Why does this happen? And can the effects be reversed? We know that the response of human stem cells declines with age, and now our own data demonstrate that this age-related deterioration in bone-forming potential can be reversed. We provide evidence that treating a patient’s own stem cells with a potent stem cell activator called “WNT” results in significantly better bone healing when a patient’s own stem cells -in the form of an autograft- are used. In preclinical studies we have demonstrated both the efficacy and safety of WNT treated autografts, and believe that it will serve as a powerful treatment for individuals with diminished healing potential in California, and beyond.

Review Summary
This application seeks to develop an improved therapy for bone regeneration by enhancing or restoring the osteogenic potential of a patient’s own stem cells as part of a surgical bone grafting technique called “autografting”. The proposed development candidate will comprise bone-derived cells that are harvested from a patient and treated ex vivo with a proprietary formulation of Wnt3a, a protein involved in stem cell self-renewal and tissue regeneration. Treated autografts will be then transplanted into sites requiring bone repair. Major project activities

include completion of preclinical studies, determining effective dose range, developing and validating appropriate manufacturing processes and assays, selecting the target indication, and defining the clinical plan. The final objective of this proposal is to conduct a well-prepared Pre- Investigational New Drug (IND) meeting with the Food and Drug Administration (FDA).

Significance and Impact

- Reviewers felt that the Target Product Profile, as constructed, may be too broad to provide appropriate direction for development and should be focused around a single indication that will be the subject of the clinical trial.

- If successfully developed, the proposed approach could improve upon the standard of care, potentially extending the use of autograft procedures in older patients.

- A concern was raised about the level of reliance of the proposed approach on autograft, which can be quite variable in functionality.

- Of the two lead indications described in the draft clinical synopses, reviewers considered osteonecrosis of the hip to represent a more compelling unmet need.

Scientific Rationale and Preclinical Development Readiness

- The rationale for exploiting the Wnt3A pathway in bone repair is well supported by preliminary data.

- Reviewers believed the data presented were sufficient to support the readiness of the proposed candidate for preclinical development.

Design and Feasibility

- Reviewers had mixed impressions of overall feasibility due to questions as to how the FDA would classify and regulate the therapeutic candidate. While some believed this might be straightforward, others believed it could be extremely challenging. There was general agreement that earlier FDA engagement and advice is critical for establishing a clear and achievable path to IND and that a pre-pre IND meeting should be scheduled at the onset.

- Reviewers felt that the proposed studies require some refinement, including a focus on a single indication and alignment to FDA feedback, to achieve a well-prepared Pre-IND meeting.

- The proposal provides clear go/no go decision points and milestones.

- The applicants have extensive experience with the proposed animal models and should have little trouble achieving technical landmarks.

- Reviewers noted that while the proposed surgical approach is achievable, it could be further streamlined to minimize time spent under anesthesia. In this regard, further input from surgeons should prove useful.

- Reviewers commented that an alternative to autograft, such as a synthetic carrier for Wnt3A, might allow for more experimental reproducibility and present an easier regulatory path.

Principal Investigator (PI), Development Team, and Leadership Plan

- The PI has largely pioneered and developed the proposal and is dedicated to its clinical application. He/she plays a predominant role on the investigative team.

- Reviewers suggested that this project would strongly benefit from a qualified regulatory expert who would not only advise, but work as an integral part of the development team.

Collaborations, Assets, Resources, and Environment

- The PI has assembled an outstanding team of collaborators with premier expertise in the areas of Wnt signaling and bone biology.

- No concerns were raised regarding the assets or resources available to the applicant team.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08108: Regeneration of a Normal Corneal Surface by Limbal Stem Cell Therapy

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

More than 3.2 million people worldwide are blind in both eyes from corneal diseases. Limbal stem cell deficiency (LSCD) has been recognized as a major cause, either primary or secondary, of significant visual loss and blindness in many corneal disorders. The corneal epithelium is constantly renewed and maintained by limbal stem cells (LSCs). When there is lack of sufficient amount of LSCs needed to repopulate the corneal surface, the cornea becomes opaque, and this opacity results in significant loss of vision and blindness. Corneal transplantation is ineffective in treating LSCD. Only transplantation of LSCs can regenerate a normal corneal surface. In patients who have LSCD in only one eye, LSCs can be obtained by a small biopsy of the healthy eye and expanded in culture. This therapy has been available in Europe since 1997 and is the most desired therapy because of its clinical success and minimal risk to the donor eye. However, this stem cell therapy is not available in the United States, partially because of safety concerns. In addition, there is lack of standards in the cultivation of LSCs for transplantation and clinical outcome measures. Well-designed clinical trials are needed to evaluate this stem cell therapy.

To address safety concerns, we have developed an autologous LSC cultivation system in a controlled, xenobiotic-free culture condition that efficiently expands the stem cell population in a reproducible and cost-effective manner. The cultivation system produces a cell sheet that contains LSCs and is readily transplantable onto the corneal surface to treat LSCD.

In this proposal, we will extend the development of xenobiotic-free production of autologous LSCs and carry out preclinical development studies that include development of incoming quality control of the biopsy tissue, systematic optimization and characterization of LSC production, qualification of in-process controls, and quality control release testing. The LSC manufacturing process will be transferred to a cGMP-compliant manufacturing facility, and production under cGMP conditions will be prospectively evaluated. A detailed clinical protocol for a Phase I clinical trial will also be developed. The proposed preclinical studies will

enable us to prepare for and conduct a pre-IND meeting with the FDA. In parallel, biomarker assay development will focus on in vitro and in vivo measurable parameters that can be used to standardize the LSC culture process and measure clinical activity of transplanted cultivated LSCs in future clinical trials. Implementation of several parameters in our culture process and clinical protocol will make it possible to establish standardized, patient-specific stem cell therapy to restore sight in a safe manner to patients in California and the rest of the United States. The knowledge learned from our study will pave the way for the next generation of treatments that could bring us to the forefront of LSC therapy.

Statement of Benefit to California (provided by applicant)

Our proposal is to complete preclinical development studies which will enable us to conduct a pre-IND meeting for a stem cell therapy to treat a blinding corneal disorder, limbal stem cell deficiency (LSCD). Corneal diseases are the second leading cause of treatable blindness in the world. LSCD has been recognized as a cause, either primary or secondary, of significant visual loss and blindness in common corneal disorders, such as chemical/thermal burn, keratopathy related to contact lens wear, and chronic conjunctivitis. Because of visual impairment, patients with LSCD lose the ability to drive, read, and watch TV. If their vision is severely impaired, they are often disabled and require a caregiver. Furthermore, patients with LSCD develop recurrent corneal erosion that causes severe pain and sensitivity to light. Frequent breakdown of the corneal surface greatly increases the risk of infection, which requires frequent medical intervention and could lead to perforation of the cornea. All of these effects have a negative psychological impact on patients and their family members. Therefore, LSCD imposes a significant social and economic impact on our society.

California is the most populated state in the USA: more than 36 million people currently reside in the state, and the population is expected to increase to 46 million by 2030. The number of residents with LSCD may disproportionately increase as a result of multiple environmental risk factors. A safe treatment to restore vision would be an important benefit to the people of California.
Our project will further benefit California through the training of new stem-cell researchers who will advance innovative technology in stem cell-based therapy. Standardization of the cultivation protocol provides a foundation for future improvement of this patient-specific stem cell therapy and has application to other stem-cell related diseases. We will utilize the technical services from companies in California to carry out some of our standardized preclinical testing. This approach could create more jobs in our state. When this project enters the clinical phase of development, it will bring together physicians and scientists and

attract funding from the federal government and investment from the private sector. Stem cell transplantation to treat LSCD, a stem cell-related disease, is well aligned with the broad mission of CIRM.

Review Summary

The applicant proposes to develop autologous limbal stem/progenitor cells expanded under xenobiotic-free conditions on denuded human amniotic membrane to treat unilateral limbal stem cell deficiency (LSCD) secondary to corneal injury/disease. The objective of this proposal is the conduct of a well-prepared pre-IND (Investigational New Drug) meeting with the Food and Drug Administration (FDA) within 30 months. To meet this objective, the applicants propose to finalize the production process, transfer the technology to a cGMP (current Good Manufacturing Practices) compliant manufacturing facility, demonstrate cGMP production, develop biomarker assays for process standardization and assessing clinical activity, and develop a detailed clinical protocol.

Significance and Impact

- Reviewers were not convinced that the proposed therapy offers any advantage over the surgical technique currently being used to treat unilateral LSCD and noted that it will likely be more costly.
- Reviewers noted that most patients have bilateral, not unilateral LSCD, and that the proposed treatment likely will not help the former.

Scientific Rationale and Preclinical Development Readiness

- Regulatory acceptance by the FDA was a rationale for the proposed xenobiotic-free expansion of limbal stem/progenitor cells but reviewers questioned whether this approach was needed given recent advances in surgical technique for treatment of unilateral LSCD.

- There is strong preclinical and clinical rationale for limbal stem cell transplantation for the treatment of unilateral LSCD.

- Reviewers regarded the project as ready for preclinical development

Design and Feasibility

- Some reviewers thought that the proposed timeline was too long and the budget was too high. They believed that with the available data and with the right consultants, the project could move very quickly to a pre-IND meeting and to IND filing.

- Some reviewers were of the opinion that the 30 month timeline to complete a well prepared pre-IND meeting with the FDA was feasible if technology transfer for GMP production occurred sooner and if a well considered regulatory strategy was implemented to address informal comments from the agency.

Principal Investigator (PI), Development Team, and Leadership Plan

- Reviewers noted that the PI has appropriate expertise and generally considered the team to be strong, noting that they had done very good work.

- Reviewers considered the lack of a named project manager to be a weakness.

- Some reviewers were unconvinced of the adequacy of CMC (chemistry, manufacturing and controls) expertise on the team.

Collaborations, Assets, Resources, and Environment

- Reviewers noted no relevant concerns under this review criterion.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08111: Pre-clinical development of gene correction therapy of hematopoietic stem cells for SCID-X1

GWG Recommendation: Recommended for funding
Final Score: 76

Public Abstract (provided by applicant)

Severe combined immunodeficiency caused by mutations in the IL2RG gene on the x-chromosome (SCID-X1 or "bubble boy disease") is a devastating genetic disease that results in boys not being able to form an immune system. If they are exposed to the environment for even a short period of time they can get infections that a normal immune system would eliminate without problems but instead can be lethal. While in the past the only treatment for this disease was to keep the boys protected from the environment by being isolated in a bubble, hence its colloquial name, now we treat SCID-X1 with allogeneic bone marrow transplantation (allo-BMT). In allo-BMT the defective immune system of the patient is replaced by the functional immune system of the donor. Allo-BMT now saves the life of 70-95% of patients depending on where the donor immune system comes from and how sick the patient is before receiving the transplant. There remain, however, significant limitations to allo-BMT. These include that in some patients the new immune system is still not as good as a normal immune system, thus keeping the patient at risk for lethal infections, and toxicity from the new immune system causing a reaction in which the donor immune system sees the patient as "foreign" and attacks the tissues causing graft vs host disease. In rare patients, however, a single stem or progenitor cell that gives rise to the immune system will have a spontaneous mutation that reverts the disease causing DNA sequence back into a non-disease causing sequence thereby correcting the gene. The goal of this program is to develop a specific gene correction procedure that could be applied to almost every patient with SCID-X1 rather than to it naturally occur in an extremely rare lucky few.

Towards this end we have developed a system in which we make a specific break in the IL2RG gene. This break activates the cell to repair the break and we can take advantage of the cell fixing the break to insert a good copy of the gene at the site of the break. In this way, we utilize the cell's own repair machinery to fix the gene. We have shown that we can do gene repair in human blood stem and progenitor cells from anyone and create corrected cells thousands of corrected stem and progenitor cells rather than just a single cell rarely occurs naturally. We

have shown that these modified cells can create blood cells, including immune cells. The goal of this specific project is to further improve the gene correction system by optimizing the different components, to assure that the gene correction system is safe and does not cause deleterious effects in the blood stem and progenitor cells, to scale the process up to a size that would be needed to treat a patient and to perform the regulatory tasks that are needed to bring what would be a first-in-human gene correction approach to patients.

Statement of Benefit to California (provided by applicant)
SCID-X1 is a rare disease that only affects a handful of patients in the state of California each year. Finding a genetic cure based on gene correction, therefore, might seem not to be of great benefit to the state of California or its citizens, This would be a mistaken impression for several reasons. For the handful of patient's and families that are affected that are affected every year, dealing with the disease will be among the most challenging life events they will ever face and finding a gene correction cure would be of tremendous, life-changing benefit to them. Moreover, t's significance far outstrips its incidence because of its notoriety as the "bubble boy disease" and the recognition that it is a seminal proof-of-concept genetic disease. That is, if one can figure out how to genetically correct stem cells to cure SCID-X1 then that provides the foundation for a strategy to genetically correct stem cells that cause a multitude of other genetic diseases. That is, a pipeline for gene correction for all children with genetic diseases in California will be started. As succinctly summarized by the head of research and development of a large international pharmaceutical company "One will get you a hundred."

While the medical benefits of first curing SCID-X1 and then curing other genetic diseases is clear, the financial ramifications of turning chronic lifelong genetic diseases that directly cost society sometimes millions of dollars per patient per lifetime and indirectly cost society even more into acute diseases that can be cured with one procedure are enormous.

Finally, California attracts the best and the brightest from all over the world because it is known as a place where transformative, innovative, and impactful discoveries are made and supported. When we are successful with this definitive and innovative approach to curing a genetic disease, it will continue to re-affirm the seminal importance of California and its citizens in making the world a better place.

Review Summary

The applicant proposes to develop a treatment for X-linked severe combined immunodeficiency (X-SCID) in children. This lethal inherited genetic disorder can be treated with allogeneic bone marrow transplantation, but this treatment option is limited to a minority of the eligible patients and has potential risk of debilitating graft versus host disease. The proposed therapy employs a gene editing approach to correct the defective gene in isolated autologous blood stem and progenitor cells, followed by cell transplantation to restore the patient's immune system. Proposed research activities will focus on optimization of the gene editing procedure to ensure robust gene correction without causing deleterious effects. Additionally, aspects of scale-up and regulatory procedures will be addressed.

Significance and Impact

- The proposed therapy could have a major impact on care of children with X-SCID who do not have matched bone marrow donors, in whom GVHD can be major problem.

- Although reviewers thought the immediate patient population to be small, the project could serve as a proof-of-concept for several related indications.

- Reviewers noted that the proposed approach, which applies elegant technology to a crippling disease, offers a potentially safer approach to gene modification.

Scientific Rationale and Preclinical Development Readiness

- The scientific rationale is sound, and the preliminary data looks promising and generally supports use of the proposed therapeutic and the research plan.

- The team has identified the development candidate should be able to conduct a well supported pre-IND meeting at the end of the award period.

Design and Feasibility

-Reviewers thought the proposed program to be feasible but noted that experimental design has some weaknesses. In general, reviewers thought the plan to be more reflective of a research plan than a drug development plan. For example, there was some concern that too much effort would be consumed improving the frequency of corrected cells and not enough effort into defining the acceptable criteria for achieving clinical significance.

- Some experimental timelines were not adequately restricted and clear go/no go criteria and corresponding goals were not adequately articulated or described.

- Reviewers thought that the scale-up process is important and addressed appropriately but is planned late in the project timeline. Reviewers recommended that important questions be prioritized in the overall project timeline.

- Reviewers noted that the applicant outlined a logical stepwise path of optimization and characterization.

- Reviewers thought the complex manufacturing process was not well described in the proposal and would have particularly appreciated more detail on the transition to cGMP manufacturing methods.

- Milestones appear achievable in proposed 30-month timeline.

- Reviewers noted that some assay systems are in place for required tests, but thought they lack detail, and were concerned that requirements are stated without supporting evidence that they are achievable.

-Reviewers recommended the conduct of an early pre-preIND meeting to gauge the accuracy of manufacturing and assay systems assumptions.

Principal Investigator (PI), Development Team, and Leadership Plan
- This is an outstanding scientific team with the required expertise in the patient population and therapeutic approach.

- Additional expertise on regulatory affairs is needed to improve the likelihood of project success.

- Reviewers considered it a weakness that the project manager has not been identified, as this is an important component of project success.

Collaborations, Assets, Resources, and Environment
- No relevant concerns were highlighted by reviewers under this review criterion.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08115: A Genetically Programmed hESC-derived Neural Stem/Progenitor Cell Line for Transplantation in Parkinson's Disease

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

At present there is no cure for Parkinson's disease (PD). Here, we propose to conduct preclinical testing of human mid-brain neural progenitor cells (hNPCs) towards developing a potentially curative cell therapy in PD. These hNPCs are derived from human embryonic stem cells (hESCs) that are programmed with the transcription factor MEF2C, which drives them more specifically towards dopaminergic (DA) neurons, the major brain cell type lost in PD. This therapy may be most effective in patients who were once responsive to L-DOPA, but became non-responsive to such treatment over the years. 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. At the very least, patients may return to a state where L-DOPA therapy is again efficacious.

The impact of development of a successful cell-based therapy for moderate-to-severe PD would be very significant. There are approximately one million people in the United States with PD and about ten million worldwide. Although L-DOPA therapy controls motor symptoms in most patients for a period of time, many reach a point where they no longer 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 experience in stem cell-based approaches, we will be able to successfully complete all the preclinical work proposed within this grant period, and then swiftly move into studies that will allow us to perform FDA-approved clinical trials.

Statement of Benefit to California (provided by applicant)

At present there is no cure for Parkinson's disease (PD). Here, we propose to conduct preclinical testing of human mid-brain neural progenitor cells (hNPCs) towards developing a potentially curative cell therapy in PD. These hNPCs are derived from human embryonic stem cells (hESCs) that are programmed with the transcription factor MEF2C, which drives them more specifically towards

dopaminergic (DA) neurons, the major brain cell type lost in PD. This therapy may be most effective in patients who were once responsive to L-DOPA, but became non-responsive to such treatment over the years. 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. At the very least, patients may return to a state where L-DOPA therapy is again efficacious.

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Review Summary

This application describes development of an allogeneic neural progenitor cell line (NPC) from human embryonic stem cells (hESC) that have been genetically modified to promote differentiation of the NPCs to dopaminergic (DA) neurons. The applicants intend to develop the differentiated DA neurons as a cell replacement therapy to treat patients that have moderate to severe Parkinson's Disease (PD), a neurodegenerative disease that leads to the death of DA neurons in the brain. The proposal includes cell manufacturing activities (banking modified hESC, differentiating the cells to NPC for characterization and in vitro testing, and developing a process for manufacturing clinical grade NPC) and transplantation of the NPC into two animal models of PD (to obtain preliminary dosing, efficacy and safety data). The team expects these activities will provide sufficient information to support their objective of conducting a well-prepared pre-IND meeting with the FDA by the end of the project period.

Significance and Impact

- Reviewers noted that the intended modification of hESC before differentiation to DA neurons would distinguish this therapeutic candidate from similar cell therapies being developed to treat PD. However, they questioned whether the

increased complexity of this product would be matched by sufficiently increased benefit to justify the more challenging regulatory pathway.

- Reviewers agreed that developing improved therapies for PD addresses an unmet medical need. For many PD patients, current drug therapies that restore dopamine become less effective at suppressing symptoms as the disease progresses. Thus, a cell therapy that provides long term replacement of functional DA neurons could have a significant impact on the standard of care for PD patients.

Scientific Rationale and Preclinical Development Readiness

- Development of a cellular therapeutic for the treatment of PD is based on sound scientific rationale. Some reviewers noted that other groups are much further in the clinical development of very similar therapeutic candidates and it is not clear that these cells would have a competitive advantage.

- While the data presented suggest modest improvement in the rodent PD model, reviewers were not convinced that the cell population used for transplant had differentiated in vivo to the target cell type.

- The unusually rapid effects of the treatment in the rodent PD model suggest the cells may be acting through a transient mechanism. Reviewers commented that durable integration of functional DA neurons would likely be required for successful clinical treatment of PD.

Design and Feasibility

- Reviewers raised serious concerns about the project plan and proposed order of activities. They strongly encouraged the team to identify and transition to using clinically-compatible methods and reagents for manufacturing the NPC before performing costly and lengthy preclinical safety/toxicity studies, in particular those proposed in large animals. In addition, it was recommended that the team manufacture a clinical grade source/master cell bank as early as possible to support NPC production for IND-enabling preclinical studies and future clinical trials.

- Reviewers noted that the regulatory path to developing the modified cellular therapeutic may be complex and were unconvinced that the team is sufficiently aware of the regulatory requirements to support its clinical development.

- Reviewers suggested conducting a pre-preIND meeting with the FDA earlier than proposed to help guide development of a more streamlined and efficient set of preclinical studies and potentially accelerating the overall clinical development timeline.

- The schedule of events in the application should be reexamined, as some proposed activities initiate prior to the completion of informative, gating activities.

Principal Investigator (PI), Development Team, and Leadership Plan

- The PI and team are highly experienced researchers in the field of neurodegenerative diseases and are well-connected within the research community. Reviewers felt that the development program would benefit from the addition of people with more translational and clinical expertise.

- Reviewers recommended that the team consult further with regulatory experts regarding cellular manufacturing and preclinical study design.

Collaborations, Assets, Resources, and Environment

- No relevant concerns were highlighted by reviewers under this review criterion.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08117: A hNSC Development Candidate for Huntington's Disease

GWG Recommendation: Recommended for funding
Final Score: 77

Public Abstract (provided by applicant)

Huntington's disease (HD) is a devastating degenerative brain disease with at least a 1 in 10,000 prevalence that inevitably leads to death. These numbers do not fully reflect the large societal and familial cost of HD, which requires extensive care-giving. HD has no effective treatment or cure and symptoms unstoppably progress for 15-20 years, with onset typically striking in midlife. Because HD is genetically dominant, the disease has a 50% chance of being inherited by the children of patients. Symptoms of the disease include uncontrolled movements, difficulties in carrying out daily tasks or continuing employment, and severe psychiatric manifestations including depression. Current treatments only address some symptoms and do not change the course of the disease, therefore a completely unmet medical need exists. Human embryonic stem cells (hESCs) and their derivatives offer a possible long-term treatment approach that could relieve the tremendous suffering experienced by patients and their families. HD is the 3rd most prevalent neurodegenerative disease, but because it is entirely genetic and the mutation known, a diagnosis can be made with certainty and clinical applications of hESCs may provide insights into treating brain diseases that are not caused by a single, known mutation. Trials in mice where protective factors were directly delivered to the brains of HD mice have been effective, suggesting that delivery of these factors by hESCs may help patients. Transplantation of tissue in HD patients suggests that replacing neurons that are lost may also be effective. The ability to differentiate hESCs into neural populations offers a powerful and sustainable alternative to provide neuroprotection to the brain with the possibility of cell replacement. We have assembled a multidisciplinary team of investigators and consultants with expertise in basic, translational and clinical development and have identified a lead developmental candidate, ESI-017 neural stem cells, that have disease modifying activity in HD mice with sufficient promise to perform systematic efficacy and safety studies in HD mice with cells generated for this project. We will utilize the collaborative research team, additional preclinical and clinical investigators, stem cell experts and FDA consultants to finalize work that will lead to a productive pre-IND meeting with the FDA and a path forward for clinical trials with the neural stem cell development candidate.

Statement of Benefit to California (provided by applicant)

The disability and loss of earning power and personal freedom resulting from Huntington's disease (HD) is devastating and creates a financial burden for California. Individuals are struck in the prime of life, at a point when they are their most productive and have their highest earning potential. As the disease progresses, individuals require institutional care at great financial cost. Therapies using human embryonic stem cells (hESCs) have the potential to change the lives of hundreds of individuals and their families, which brings the human cost into the thousands. For the potential of hESCs in HD to be realized, we have brought together a team of investigators highly experienced in HD basic science and preclinical development, stem cell research, HD clinical trials and FDA regulatory activities to evaluate a human stem cell derived neural stem cell line, ESI-107 NSC in HD mouse models. This selection of this development candidate is based on efficacy in behavioral and electrophysiology measurements in a rapidly progressing mouse model of HD. HD is the 3rd most prevalent neurodegenerative disease, but because it is entirely genetic and the mutation known, a diagnosis can be made with certainty and clinical applications of NSCs may provide insights into treating brain diseases that are not caused by a single, known mutation. We have assembled a strong team of California-based investigators to carry out proposed studies to move ESI-017 NSCs to the point of a productive pre-IND meeting with the FDA to ultimately move this clinical product into Investigative New Drug-enabling (IND) activities with the goal of performing clinical trials in HD subjects. Anticipated benefits to the citizens of California include: 1) development of new human stem cell-based treatments for HD with application to other neurodegenerative diseases such as Alzheimer's and Parkinson's diseases that affect thousands of individuals in California; 2) improved methods for following the course of the disease in order to treat HD as early as possible before symptoms are manifest; 3) transfer of new technologies and intellectual property to the public realm with resulting IP revenues coming into the state with possible creation of new biotechnology spin-off companies; and 4) reductions in extensive care-giving and medical costs. It is anticipated that the return to the State in terms of revenue, health benefits for its Citizens and job creation will be substantial.

Review Summary

This proposal is focused on the development of a human embryonic stem cell (hESC)-derived neural stem cell (NSC) therapy for Huntington’s disease (HD). HD is an inherited, progressive, neurodegenerative disease that causes cell death

predominantly in a part of the brain called the striatum. HD patients suffer from uncontrollable movements, cognitive and psychiatric symptoms, and inevitably die from their disease. There are very limited treatment options for HD and none impact disease progression. The applicant proposes that transplantation of NSCs into striatum of HD patients will protect and support remaining brain cells. Activities proposed in the application include: manufacture and characterization of a current Good Manufacturing Practice (cGMP) compliant NSC bank; efficacy studies in two different preclinical models; pilot safety studies; exploratory mechanism of action studies; and preparation for and conduct of pre-pre- and pre-Investigational New Drug (IND) meetings with the Food and Drug Administration (FDA).

Significance and Impact

- Reviewers agreed the proposed therapy would address a tremendous unmet medical need and, if successfully developed, has the potential to have a major impact on the health and well-being of HD patients. This would be the case even if the treatment were to produce a rather marginal benefit.

- Reviewers noted that the proposed therapeutic is unlikely to replace lost neurons but acknowledged this is not the therapeutic intent and agreed that the data supports a positive impact on the disease without neuronal replacement.

Scientific Rationale and Preclinical Development Readiness

- Reviewers were generally impressed by the preclinical efficacy data from multiple models using multiple measures. They noted that the time period assessed might be too short to make definitive conclusions about the persistence of observed benefits but that the right long-term studies are proposed and will be critical.

- The reviewers expressed concern that the mechanism of action of the transplanted NSCs is not definitively known, which is a weakness. However, reviewers agreed that the hypothesized mechanism is quite plausible as it is supported by the preclinical data, and they appreciated that studies are proposed to address the question.

- Reviewers noted that the applicant appears to assume that migration of the cells away from the implantation site would be a positive, or at least neutral, outcome but this is not proven and warrants additional consideration and testing.

- Reviewers thought the selected cell lines to be an appropriate choice of therapeutic candidate and noted the importance of the heterogeneous cell population that includes neural derivatives for a positive outcome.

Design and Feasibility

- Reviewers found the project plan and milestones to be logical and feasible.

- Reviewers suggested that since efficacy studies are going to be carried out in the more slowly progressing HD animal model it would make sense to perform dosing studies in that model as well.

- Reviewers commented that the draft clinical trial synopsis could use refinement and suggested the applicant seek input from groups working to develop and validate clinical outcome measures for HD.

- Reviewers noted that the differentiation protocol appears relatively complex and has not yet been transferred to a closed system. They felt this may be a bottleneck in development of the manufacturing process.

- Reviewers suggested that the team consider moving the planned pre-pre-IND meeting earlier in the timeline to obtain FDA input on preclinical study design.

Principal Investigator (PI), Development Team, and Leadership Plan

- Reviewers noted that the PI is well-known in the HD field, has an excellent track record, and has assembled a very strong team.

Collaborations, Assets, Resources, and Environment

- Reviewers praised the team's collaborators and noted that their letters of support strengthened the application.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08118: Scaffold for dermal regeneration containing pre-conditioned mesenchymal stem cells to heal chronic diabetic wounds

GWG Recommendation: Recommended for funding
Final Score: 77

Public Abstract (provided by applicant)
The goal of our CIRM-funded Early Translational (ETA) grant was to engineer a product to improve healing in diabetic foot ulcers, a devastating consequence of diabetes that occurs in about 25% of all diabetic patients and is responsible for most leg or foot amputations. More than 6 million people in the US and up to 91 million people worldwide have diabetic foot ulcers (DFU). There is a clear medical need. There are products on the market that can improve wound healing for some, but not all patients. This causes a large financial burden for the health care system, and great suffering for the patients who live with open wounds, often infected, that progress to amputations. Therefore there is a clear medical need for advanced therapies to heal diabetic ulcers faster.

We proposed to create a combination product consisting of a scaffold for dermal regeneration (SDR) populated with human allogeneic mesenchymal stem cells (MSC) that have been pre-conditioned for optimized reparative function. We formed a team of established wound and stem cell/matrix experts, and this team has indeed successfully engineered and demonstrated efficacy of the preconditioned MSC-SDR in two animal models, and is now ready to progress to further dose-finding and initial biosafety studies in support of our very promising Development Candidate.

During the Early Translational grant, we developed a product that consists of an FDA-approved scaffold for dermal regeneration (SDR) filled with human bone marrow-derived Mesenchymal Stem Cells (MSC). These are then pre-incubated for 2 days in hypoxia and in the presence of a beta adrenergic antagonist. We have completed studies that demonstrate that this â€œnext generationâ€ stem cell product is highly efficacious in healing diabetic skin wounds, using mouse skin wound models in diabetic mice that have impaired and delayed healing and a porcine model.

In the PreClinical Development award period we propose to bring this product closer to clinical use for human patients. We propose dose finding studies to

achieve the optimal dose with the largest safety margin. We will use a large animal wound model where skin wounds more closely resemble those in humans, to carry out these efficacy and early safety studies. We will use this time to create a Master Cell Bank of pure and effective human MSCs and to generate standard operating procedures to move us into the clinical arena. Finally, we will prepare a package for presentation to the FDA for moving the preclinical product forward toward a Phase 1/II clinical trial that will demonstrate efficacy and safety of the product in affected patients.

Statement of Benefit to California (provided by applicant)
While the number of individuals with all forms of chronic wounds is increasing in the general population, particularly with the rise of diabetes and aging of the population, the number of individuals affected by diabetic foot ulcers (DFU), the target disease for the development candidate in this proposal, is increasing in California at an alarming rate. That is because the prevalence of type 2 diabetes is now increasing within the state of California to epidemic proportions. In 2002, over one million California adults age 45 and older were diagnosed with diabetes, and by 2011 that number had risen to 2.3 million: 8.4% of the California population (1).

For reasons that are not all that clear, there are marked differences in the prevalence of diabetes in different Californian ethnic and racial groups. Among Californians 65 and older, diabetes is significantly more common in African Americans (25.6%) , and Latinos (24.4%) as compared to Caucasians (12.2%). (1) The diabetes brings with it devastating health impacts: it is the sixth most common cause of death in the United States. Among the morbidities associated with diabetes, DFU is one of the most debilitating. Approximately 15-25 percent of patients with diabetes will develop DFU, and of those, six percent will be hospitalized due to infection or other ulcer-related complications. According to a recent census, DFU is the leading cause of lower limb amputation and greater than 85% of amputations are preceded by an active foot ulcer.

Sadly for our state, we lead others in the US in the prevalence of DFU: "Of the 45 areas (44 states and DC) that reported information to the Behavioral Risk Factor Surveillance System, the world's largest, on-going telephone health survey system, the BRFSS diabetes module shows that Indiana (16.3%), California (16.2%), and Nevada (16.2%) had the highest age-adjusted prevalence of a history of foot ulcer among persons with diabetes, and Colorado (7.4%), Wisconsin (8.8%), and Hawaii (8.9%) had the lowest " (2).

Treatments for curing DFU are very far from optimal. Current standard of care can cure only about 30% of DFU and even the most advanced therapies, cell-based devices containing skin derived keratinocytes and fibroblasts, boosts the cure rate only to about 50%, leaving a tremendous unmet need for new effective cures for DFU, particularly in California. We anticipate that the development candidate that we propose, a stem cell-based "biological bandage", will bring a new and effective cure to our citizens who are suffering from diabetic foot ulcers.

Sources: 1) California Health Care Survey, UCLA, http://www.chis.ucla.edu/
2) CDC reports Morbidity and Mortality Weekly Report (MMWR), http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5245a3.htm

Review Summary

This application is focused on the preclinical development of a combination product of human mesenchymal stem cells (MSCs) in a dermal scaffold for regeneration (DSR) for the treatment of diabetic foot ulcers. This MSC-DSR is "pre-conditioned" for two days under low oxygen conditions with a small molecule drug prior to application. Diabetic foot ulcers are a major complication of diabetes that occur in 15-25% of patients and can eventually lead to lower leg amputation. The MSC-DSR would be administered topically to a patient's foot, like a wound dressing. Activities proposed by the applicant include: MSC manufacturing, banking and testing; dosing and preliminary safety studies; an efficacy study in a relevant preclinical model; and preparation for and conduct of a Type C meeting with the FDA.

Significance and Impact

- Reviewers agreed that diabetic foot ulcers are a serious unmet medical need, especially with the increasing prevalence of diabetes.

- Reviewers appreciated the applicant's unique approach and noted that, if successful, it could have significant impact on standard-of-care.

Scientific Rationale and Preclinical Development Readiness

- Reviewers were impressed by the amount of preliminary data presented in the application. They appreciated that the data support the benefit of "pre-conditioning" and the superiority of this combination MSC-DSR over its components alone.

- Reviewers' major concerns centered on the manufacturing process and stability of the final product. They believed that manufacturing is relatively complicated

and were unconvinced that current stability data support a typical “off-the-shelf”use of the product. They recommended process development work to improve stability and support clinical development beyond Phase 1.

- Reviewers noted that variability of MSCs from different donors could be a significant manufacturing concern and would have appreciated greater discussion of this issue.

- Reviewers would have appreciated a comparison of preclinical efficacy of the MSC-DSR to local administration of the beta adrenergic antagonist alone.

- Some reviewers were concerned about the possibility of immune rejection of allogeneic MSCs, but others were not, citing clinical experience and the potential for paracrine benefit without long-term cell persistence.

- Some reviewers expressed concern that the beta adrenergic antagonist could indirectly result in local vasoconstriction, which would be counterproductive, but other reviewers did not consider this to be a problem.

Design and Feasibility
- Reviewers found the proposal to be feasible and milestones achievable over the 30-month timeframe.
- Reviewers described this proposal as ready to enter a preclinical development program.

- Regarding the draft clinical trial synopsis, reviewers suggested that safety should be the primary endpoint and that the Phase 1 study should not be blinded.

Principal Investigator (PI), Development Team, and Leadership Plan
- Reviewers described the team as well-qualified, with extensive experience working with MSCs.

Collaborations, Assets, Resources, and Environment
- Reviewers praised the excellent infrastructure for translational science at the applicant institution.

- Reviewers appreciated the team’s collaboration with a large industry partner, which will aid clinical competitiveness.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08122: Exosomes from cardiac stem cells as platform therapeutic candidates: application to Duchenne muscular dystrophy

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

The proposed research will set out to demonstrate the feasibility, in animal models, of a novel treatment for Duchenne Muscular Dystrophy (DMD)-associated Heart Failure (HF) using CDC-exosomes. CDC-exosomes are natural products secreted by human cardiosphere-derived cells (CDCs), which have shown the ability to achieve myocardial regeneration. CDC-exosomes have the potential to become an off-the-shelf therapy that may be applicable to a wide variety of heart-related inflammatory, fibrotic and degenerative diseases, and possibly also to non-cardiac disorders with similar underlying disease mechanisms. The focus of this preclinical research will be on animal models (in vivo) of DMD-associated HF and in the lab (in vitro). Currently, in humans, DMD-associated HF aggressively progresses from normal function in young boys, to abnormalities in cardiac structure and function by age 15, to overt symptomatic HF, to advanced HF and death often before age 30. This progression of HF is associated with high risk of hospitalization and intense overall health care resource utilization. Causes of death during the course of the natural history of DMD-associated HF include sudden cardiac death (which increases as HF worsens), or progressive HF culminating in circulatory collapse.

DMD afflicts ~25,000 boys and young men in the USA. The central cause is a genetic abnormality in the dystrophin complex, with secondary damage to skeletal muscle and heart tissue. Although virtually all patients are treated empirically with corticosteroids and other medications, no treatment has been proven effective. HF afflicts virtually all DMD patients aged >15 years, and is often the cause of death. Moreover, much of the disability in the later years of DMD is due to HF rather than to skeletal muscle disease. Thus, DMD HF represents an important, neglected target for innovative therapy.

CDC-exosomes may have an advantage over CDCs in the clinical setting based on early preclinical results. CDCs (both autologous and allogeneic) are already in human trials, but cells have limitations as therapeutic agents. Exosomes have the following potential advantages over living cells: 1) prolonged shelf life; 2)

reductionist identity and release criteria; 3) the potential for lack of immunogenicity, with a high likelihood of being able to administer repeat doses safely. Thus, CDC-exosomes (as cell-free derivatives of CDCs) are of potentially significant translational value. Clinical development of the product should be expedited given its first-in-class status: no other treatment has the potential to regrow living heart muscle tissue in a clinical situation such as DMD, where the loss of tissue is assumed to be irreversible.

By the end of the project, we expect to have completed extensive preclinical research on human CDC-exosomes. The data collected will allow us to be poised to manufacture this Development Candidate and submit to FDA the necessary documentation to initiate clinical testing.

Statement of Benefit to California (provided by applicant)
Duchenne muscular dystrophy (DMD) afflicts ~25,000 boys and young men in the USA. The central cause is a genetic abnormality in the dystrophin complex, with secondary damage to skeletal muscle and heart tissue. Although virtually all patients are treated empirically with corticosteroids, no treatment has been proven effective. Heart failure (HF) afflicts virtually all DMD patients aged >15 years, and is often the cause of death. Moreover, much of the disability in the later years of DMD is due to HF rather than to skeletal muscle disease. Thus, DMD HF represents an important, neglected target for innovative therapy. Management of the disease focuses on reducing the symptoms and slowing disease progression. There is no known cure for DMD HF nor has there been a proven strategy to stop its progression, or to reverse the established disease. This research is aimed at using CDC-exosomes, which are natural products secreted by human cardiosphere-derived cells (CDCs). CDCs are the only known therapeutic agents that have been proven clinically effective in regenerating the human heart.

If our research is successful, we may offer a cost-effective way to reduce the tremendous damage to Californians inflicted by this type of heart failure associated with DMD. This in turn may also reduce the economic burden presently borne by taxpayers who support the health care systems in California. In addition to the public health benefits, spinoff technology developed by this disease team will benefit existing California-based biotechnology companies, leading to fuller employment and an enhanced tax base.

Review Summary
The applicants propose to initiate preclinical development of exosomes isolated from cardiosphere-derived cells (CDC) for the treatment of heart failure in

pediatric Duchenne Muscular Dystrophy (DMD) patients, with the objective of conducting a well-prepared pre-IND meeting with the FDA by the end of the award. Heart failure afflicts most DMD patients over 15 years old, and is often the cause of death. The applicants suggest that CDC-derived exosomes retain the myocardial regenerative capacities of CDCs, and have potential manufacturing and therapeutic advantages such as prolonged shelf life, simplified product characterization, and lack of immunogenicity. The activities proposed in the application include developing and optimizing a manufacturing process, examining long-term efficacy, dosing, immunogenicity and toxicity in a rodent model, evaluating dose, delivery, safety and efficacy in a large animal model of heart failure, and conducting a pre-IND meeting with the FDA.

Significance and Impact

- The proposal addresses an unmet need, heart failure in Duchenne Muscular Dystrophy.

- DMD patients initially suffer primarily from skeletal muscle failure, with heart failure occurring later in life. This approach does not target the underlying genetic disease, which reviewers felt is an important consideration when targeting this patient population.

Scientific Rationale and Preclinical Development Readiness

- The reviewers expressed concern about the rationale for developing this product specifically for DMD patients rather than any other patient population with heart failure. There was concern about first testing this product in a highly impacted, primarily pediatric target population, as opposed to adult patients with other types of heart failure that could similarly benefit.

- Reviewers felt that additional experiments to demonstrate the efficacy of the exosomal product were necessary. For example, longer-term experiments would provide a better picture of how long the observed efficacy might last. In addition, the application did not provide sufficient data directly comparing exosomes to the CDCs from which they were derived.

- Reviewers were not convinced that the activity of the exosomes is attributable to an effect on stem cells.

Design and Feasibility

- Reviewers expressed concerns about the feasibility of the complex exosomal manufacturing process.

- Appropriate dosing and immunogenicity of the product may present challenges to moving it forward.

- Reviewers felt that the development candidate should also be tested in the canine model of DMD heart failure to better understand its impact on the target indication, rather than relying on the porcine model and the mdx mouse model.

Principal Investigator (PI), Development Team, and Leadership Plan

- The applicants have excellent experience bringing a cell therapy for heart disease to the clinic.

- Reviewers weren't convinced that adequate manufacturing expertise was in place given the anticipated complexities of the manufacturing process.

Collaborations, Assets, Resources, and Environment

- The reviewers felt that the division of labor between the applicant and the co-funding company was not clearly delineated.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08126: A Translational Program of Neural Stem Cell Relay Formation for SCI

GWG Recommendation: Tier 2
CIRM Recommendation: Not recommended for funding
Final Score: 69

Public Abstract (provided by applicant)

There are no approved treatments for severe spinal cord injury (SCI). This is an area of great unmet medical need; SCI currently affects 273,000 patients in the US alone, with 12,000 new injuries incurred each year. Taken with an average yearly cost of ongoing care of ~ $100,000, and ~ $660,000 the first year following injury (NSCISC Spinal Cord Injury Facts and Figures 2013), the annual cost of SCI in the US is greater than $30B. Perhaps more importantly, SCI extracts a great human toll in quality of life, life expectancy, employment and satisfaction. This disease affects a disproportionate number of individuals in early life, leading to a lifetime of disability.

To meet this clinical need, we are attempting to develop a stem cell therapy for severe SCI. Our methods combine neural stem cell (NSC) grafts with a growth factor and FDA-approved scaffolds to provide superior graft survival and filling of the injury site. This approach results in the remarkable outgrowth of thousands of stem cell-derived axons over long distances across lesion sites of the most severe SCI, resulting in the formation of new functional electrical relays, and significant improvements in functional outcomes in turn.
Our approach is distinct from other candidate therapies of stem cells for SCI. Other approaches aim to enhance the function of the small proportion of original axons that are spared by injury; in contrast, our approach of rebuilding connections can theoretically restore the function of greater numbers of lost axonal connections. Our combination of stem cells with biomaterials and a growth factor results in superior NSC survival and growth at the site of SCI, resulting in potentially superior functional outcomes compared to other stem cell approaches. Finally, ours is the only stem cell-based therapy that has significantly improved functional recovery after severe SCI in animal studies: severe SCI is the most common and debilitating form of human injury. Further, in preparation for human translation, we have tested our candidate therapy in a large animal model, and have confirmed the ability of implanted NSCs to extensively regenerate connections in models most relevant to injured humans.

We now propose a comprehensive program of preclinical development of human NSCs for potential translation to a clinical program. We have identified a lead candidate NSC source, and the means to produce these cells in compliance with requirements for clinical cell manufacturing. We propose a set of safety and dosing studies that if successful, will enable the filing of an Investigational New Drug (IND) application with the FDA to bring this candidate therapy to human clinical trials. Our team of investigators is highly experienced in all aspects of stem cell biology, SCI research and human clinical trials in SCI. We have brought several other programs to first-in-human clinical trials, and aim to follow this path now with human NSCs for functional regeneration following SCI.

Statement of Benefit to California (provided by applicant)

The completion of this proposal would benefit California in three ways, by (1) improving the quality of life and decreasing the personal and financial burden of care for Californian patients living with spinal cord injury, (2) maintaining California's status as one of the foremost centers of translational stem cell research in the world, and (3) directly providing jobs to Californians. Scaling the overall prevalence and incidence of spinal cord injury in the US (273,000 and 12,000 per year - NSCISC Spinal Cord Injury Facts and Figures at a Glance 2013) to the population of California, we estimate that 33,000 Californians are currently living with spinal cord injury, and that 1,400 new injuries occur each year. With an average yearly cost of ongoing care of $100,000, and treatment costs of $660,000 per person in the first year following injury (Spinal Cord Injury Facts and Figures 2013), we estimate that the annual cost of spinal cord injuries in California has now surpassed $4 billion. The life expectancy and employment of patients with spinal cord injury are also significantly reduced compared to uninjured persons. We expect that completion of this proposal will lead toward an Investigational New Drug application with the Food and Drug Administration, allowing us to evaluate a promising spinal stem cell engraftment program for functional repair of severe spinal cord injuries. In consideration of the aforementioned costs of spinal cord injury, if the functional motor improvement we have observed in animal models of spinal cord injury can be evaluated and recapitulated even to a modest extent in human patients, we expect to make a greatly positive impact on quality-of-life for Californians living with spinal cord injury. Additionally, the lead candidate stem cells we have selected for the proposed preclinical evaluation were developed in California, and funded by the California Institute for Regenerative Medicine. The clinical development and deployment of these cells could therefore further demonstrate the impact and necessity of California's unique culture of support for translational stem cell research. Finally, the Principal Investigator and collaborators of this proposal

currently employ over 100 California residents; support of this proposal will continue to support these Californians and, in the future, support new jobs for Californians while greatly benefitting humanity.

Review Summary

Spinal cord injury (SCI) is a devastating and unmet medical need that affects over quarter of a million patients in the US alone. To meet this clinical need, the applicant proposes to develop a therapeutic candidate that combines neural stem cell (NSC) grafts with a growth factor and FDA-approved scaffolds to provide graft survival and filling of the injury site. This approach is proposed to result in outgrowth of stem cell-derived axons across lesion sites with formation of new relays leading to improvements in functional outcomes in patients with severe SCI. Activities proposed in the application include generation and testing of master and working cell banks, dose optimization and short and long term safety studies in preclinical models and preparation for and conduct a pre-IND (Investigational New Drug) meeting with the FDA.

Significance and Impact

- The proposed therapeutic, NSCs within a support matrix, addresses restoration of neuronal connectivity after severe spinal cord injury, an unmet medical need.

- If successful, even with incremental improvements that are clinically significant, this could re-define treatment of SCI in the target patient population.

- There are other therapies in development for SCI that are pursuing other approaches

Scientific Rationale and Preclinical Development Readiness

- Reviewers, while acknowledging the importance of and their enthusiasm for the studies done to date, thought the scientific rationale for the proposed neuronal relay approach to be generally sound but not compelling. Specifically, they did not find the electrophysiological data convincing and suggested that the waveforms for all study animals be shown and correlated to observed changes in behavior. Other points they noted included the relatively small number of animals tested, the lack of certain controls and uncertainty as to whether certain studies were blinded given interpretive subjectivity in outcome measures.

- Reviewers were quite concerned about the observation of cells at points remote to the repair site. Reviewers suggested a long-term (3+ year) study to run parallel

to the proposed studies to examine potential safety issues and support an eventual IND filing.

- Reviewers expressed concern about the sufficiency of the data regarding the proposed growth factor in the combination candidate. They weren't clear about how it was chosen and would have appreciated additional information about the dose, half-life, and safety.

Design and Feasibility

- Some reviewers thought that the right studies have been outlined to position the applicant for a successful Pre-IND meeting while others raised concerns. Specifically, these included a potential need for a multi-year preclinical safety study in light of ectopic tissue formation, whether behavioral measures were in place and the size of certain proposed studies if not pivotal studies (not funded under this award). They encouraged a pre-pre IND meeting (planned by applicant) to get FDA feedback before proceeding with preclinical studies.

- Reviewers noted that the surgical methodology proposed is quite invasive and aggressive. It is reasonable to enable the lesion filling that the applicant intends, but also potentially harmful to patients. Therefore, reviewers thought it would be important that the applicant demonstrate that the proposed model had adequate sensitivity to show possible injury due to myelotomy and debris removal before using it to establish the safety of this surgical technique.

- Reviewers considered it possible that the project plan could be executed within 30 months, although they described it as a very ambitious timeline.

- Reviewers had concerns about a source of clinical grade growth factor suitable for the use in treatment of SCI.

- Reviewers commented that success criteria for the proposed milestones were not adequately defined.

Principal Investigator (PI), Development Team, and Leadership Plan

- The PI is recognized as a world leader in spinal cord injury research.

- Reviewers praised the excellent team, which they felt was a key strength of the application.

Collaborations, Assets, Resources, and Environment

- The project leverages many of the California based/CIRM funded resources for stem cell research.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08128: Embryonic Stem Cell-Derived Chondroprogenitor Cells to Repair Osteochondral Defects

GWG Recommendation: Tier 2
CIRM Recommendation: Not recommended for funding
Final Score: 71

Public Abstract (provided by applicant)

Surgical approaches to the treatment of focal cartilage defects can be classified into repair, replacement, and regeneration therapies. Marrow stimulation procedures such as microfracture result in a repair tissue that is predominantly fibrocartilaginous in nature, which is mechanically less durable than articular cartilage and survives on average 7 years before requiring another procedure. Osteochondral grafting (autologous or allogeneic) replaces the defect with fresh mature cartilage and bone. While the tissue replicates natural cartilage, the grafted cartilage does not integrate or bond with the host tissue. Autologous chondrocyte implantation (ACI) attempts to regenerate tissue by injecting chondrocytes into the defect. Results with this technique are mixed with several randomized clinical trials failing to find a clinically and statistically significant benefit over microfracture or other procedures.

Our approach is to advance third-generation cell therapy by constructing scaffolds that are seeded with chondroprogenitor cells programmed to undergo differentiation into bone and cartilage cells. If successful, this will be the first-in-man embryonic stem-cell-based treatment of an orthopaedic disease that has challenged repeated attempts over the last 400 years. The product has the unique advantage that the same material is universally applicable in all patients with a range of different defect shapes and sizes. The preclinical development, characterization, efficacy, and safety will also support and advance stem-cell-based regenerative medicine in general.

Statement of Benefit to California (provided by applicant)

Arthritis is a common disease and increases with age. The annual cost of treating arthritis in the US is estimated to be over $200B in 2013. Over a million joint replacements are performed in the US alone for end-stage arthritis. However, for younger patients with severe arthritis or impending arthritis there is as yet no treatment that can prevent, cure, or even slow the progression of this disease. In this proposal. we target bone and cartilage defects that are a major factor in

contributing to early osteoarthritis in patients less than 55 years of age. Our approach is to advance third-generation cell therapy by constructing scaffolds that are seeded with chondroprogenitor cells programmed to undergo differentiation into bone and cartilage cells. This proposal falls under the mission statement of CIRM for funding innovative research. A stem-cell-based approach for treating articular cartilage defects in not represented in CIRM's current portfolio. If successful, this will be the first-in-man embryonic stem-cell-based treatment of an orthopaedic disease that has challenged repeated attempts over the last 400 years. This will further validate the significance of the CIRM program and help maintain California's leading position at the cutting edge of biomedical research.

Review Summary

This project aims to develop a novel cell-based therapy for the repair of cartilage defects caused by trauma or disease. The proposed approach would combine allogeneic embryonic stem cell-derived cartilage progenitor cells that have the ability to differentiate and develop into mature cartilage with a scaffolding material with which to facilitate tissue repair. The cell-scaffold combination product would be surgically implanted into a cartilage defect. The proposed activities include making and testing Good Manufacturing Practices (GMP)-compliant Master and Working Cell Banks, technology transfer, scale-up, production and characterization of GMP product candidate, dose finding and pilot preclinical studies. The overall objective of the proposal is to conduct a well-supported pre-investigational new drug (pre-IND) meeting with the Food and Drug Administration (FDA).

Significance and Impact

- Some reviewers thought the unmet need to be only moderate. Others considered there to be a clear unmet need and commercial opportunity in the targeted subgroup of "younger" patients, noting that there are variable reports of the effectiveness and durability of currently available therapies.

- Reviewers commented that the cartilage repair field is competitive with some therapeutic options already available or in development, including other cell therapies. Others believed there to be room for a new treatment option and that the proposed progenitor cell scaffold combination has some features that differentiated it including single surgical procedure, potential to be an off-the-shelf product, availability of a consistent progenitor cell population and a novel scaffold that could contribute to product safety and activity.

- Reviewers strongly encouraged the team to consider developing a frozen formulation when further along, since the stability and shelf life of the current formulation will limit widespread clinical use if the product candidate is successfully developed.

Scientific Rationale and Preclinical Development Readiness

- Reviewers considered the preliminary data supportive of preclinical development readiness. Some reviewers believed that product candidate is likely at a sufficient stage of readiness to proceed to hold a pre-IND meeting with the FDA sooner than proposed.

- While the rationale was viewed as sound, reviewers would have found the preliminary data more compelling had it demonstrated a statistically significant difference between this approach and competing technologies.

Design and Feasibility

- Reviewers generally found the proposed studies well designed and feasible with all necessary techniques already in place. Some reviewers believed that there were opportunities to streamline the plan and that some proposed preclinical studies could be combined and more appropriately conducted after the pre-IND meeting. Seeking expert regulatory input to help identify critical path activities required to achieve a successful pre-IND meeting will further strengthen and could accelerate the project.

- Reviewers commented on the importance of an acceptable risk/benefit profile for this ESC-derived product candidate. With regard to one proposed risk assessment, they suggested that using a single marker to test for undifferentiated stem cells may not be sufficient and that additional markers should be examined that may be more sensitive than the one described in the application.

- Reviewers, while supportive of the use of an allogeneic cell source with a custom scaffold for an off-the-shelf product weren't clear as to whether the proposed therapy was going to be compared against the currently available surgical standard of care, called microfracture. Reviewers felt that direct comparison should be made in both the proposed preclinical models.

- The proposed timelines to a pre-IND meeting are appropriate and could potentially be accelerated.

Principal Investigator (PI), Development Team, and Leadership Plan

- The team is excellent and has strong expertise in cartilage development. Reviewers were appreciative of the planned addition of a second project manager currently being sought.

- Reviewers commented that the team could use additional expertise in regulatory affairs to help define critical path activities to ensure an effective meeting with the FDA and to assist in preparing the pre-meeting materials for submission to the FDA.

Collaborations, Assets, Resources, and Environment

- No relevant concerns were highlighted under this review criterion.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08129: Induced Stem Cell Implants for Spinal Fusion Intervention

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

This work is directly relevant to stem-cell derived therapy that will advance the treatment of a serious injury in humans. This product will provide a novel method for bone graft to address the needs of spinal fusion patients. We will do IND-enabling studies to develop an innovative stem cell bone regenerative therapy.

More than 400,000 Americans require surgery every year for debilitating spinal conditions at an annual cost of more than $10 billion in healthcare expenditures. Spinal fusion surgery is often the only effective procedure for treating pathologic spinal conditions such as scoliosis, spinal deformity due to injury, or degenerative disc disease leading to spinal stenosis, spondylolysis or spondylolisthesis. Current therapeutic approaches are problematic.

The traditional method is to remove the pathology compressing the spinal nerves, and then fuse the spine to stabilize the vertebrae. The current "gold standard" is the use of autologous bone (autograft) harvested from the same patients' hip. But the patient must undergo two surgeries, a painful one for the hip and one for the spine. Bone chips are harvested from the patient's hip and used to fuse bone in the spinal column and stabilize the spine. Limitations of this procedure include longer recovery time, increased surgical blood loss, increased surgical complications, pain and co-morbidities associated with bone harvest from the hip. Often, these patients are elderly or have co-morbidities such as diabetes, osteoporosis, or obesity that has a detrimental effect on their own regenerative potential. Patients may be relieved of their spinal conditions, but many end up with chronic hip pain.

With the advancement of minimally invasive surgical techniques the opportunity to identify autograft replacements is imperative. The team includes [Redacted] and [Redacted]. Their human adult stem cell product for therapeutic intervention has been used in over 200,000 patients since 2005 with no reported adverse effects.

The teams' new biomaterial is a synthetic bone graft alternative that stimulates differentiation of stem cells into bone-forming osteoblasts. Higher yields of bone reformation are achieved therapeutically by combining human bone marrow-derived stromal cells (hBMSCs) with the synthetic biomaterial. The product is readily manufactured and all of the components have already been brought to the clinic in other contexts. We have shown that stimulation of hBMSCs and differentiation to osteoblasts followed by attachment to the biomaterial enhances the efficacy of bone generation. We have proved-out that the safe fully-formulated combination product is efficacious in a preclinical model of spinal fusion. This approach will improve the health of millions of individuals with debilitating spinal conditions including those untreated because of co-morbidities that limit outcomes of current approaches.

Statement of Benefit to California (provided by applicant)

An estimated 30 million adults suffer from chronic back, making back pain the # 1 cause of healthcare expenditures in the US with a direct cost of more than $50 billion/year for diagnosis, treatment and rehabilitation. The majority of patients suffer spine problems related to degenerative conditions. These degenerative conditions can result in debilitating spinal instability with intrusion into the spinal cord and surrounding nerves, leading to loss of locomotor function in advanced cases. The State of California has approximately 1.2 million individuals with chronic spine pain at any given time, with a direct cost of more than $6 billion annually. For patients that had successful spinal corrective surgery, other problems are associated with painful bone collection and post-surgical scenarios. Accordingly, an urgent need for a less invasive, safe, spinal fusion interventions are needed to improve patient outcomes.

Regenerative medicine approaches to bone are important for the impact of bone and spine disorders on the economy and patient welfare. With an aging population, the need for improved grafting options that improve patient outcomes and limit surgical complications is imperative. Currently available bone grafts require the patient's own bone cells taken from their hip to form bone in their spine. Often, the back problem is cured but new hip problems emerge. Many patients requiring spinal corrective surgery are elderly or have co-morbidities such as diabetes, osteoporosis, or obesity that has detrimental effects on success rates.

Stem cell implants are a superior alternative for bone repair, particularly for spinal fusion where the endogenous source of progenitor cells is not present in sufficient quantities to generate enough bone to stabilize the spine. This strategy

has been brought to near clinical fruition using stimulated human bone-marrow derived stromal cells (hBMSCs). Cells are expanded in cell culture to adopt an osteogenic lineage and to provide sufficient number of cells. By combining novel safe cell-stimulating technology and FDA-approved hBMSCs and matrix, a robust technology was created.

An estimated 5% of the Californian population is expected to be personally impacted with a serious spinal condition at some point in their lives. 48,000 will be indicated for spinal fusion surgery next year. Spinal conditions are one of the most prevalent conditions faced by Californians and this is only expected to increase as the population continues to age. Thus, successful completion of this work will provide citizens of California needed advances in bone healing technology of relevance to spinal conditions and improvement in healthcare. Our product is safer to use and cheaper to manufacture than current state of the art technologies. This will result in significantly lower costs to the California healthcare system.

Review Summary

The applicants propose to further develop a combination therapy approach for treating degenerative disc disease that requires surgical intervention. Spinal fusion therapy that uses an autologous graft from the patient's own hip bone to stabilize the vertebra is the current standard of care treatment for the intended patient population. The proposed therapy is a combination product made up of allogeneic bone marrow-derived mesenchymal stem cells (BMSC) stimulated towards an osteogenic lineage with a small molecule and seeded on a synthetic scaffold that would replace autologous bone in spinal fusion surgery. The applicants plan to scale-up and manufacture sufficient product to conduct additional safety and efficacy studies in two preclinical models, define an appropriate dose range, manufacture cGMP-grade product, and develop a regulatory plan for a pre-IND meeting with the FDA.

Significance and Impact

- Reviewers felt that the medical need is modest and at best would represent an incremental step as current therapies are fairly effective and spinal instrumentation with adjunctive biologics is a crowded field.

- Reviewers were not convinced that the proposed approach is significantly superior to alternative or existing approaches.

Scientific Rationale and Preclinical Development Readiness

- Reviewers expressed concern that the preliminary data were not compelling and did not convincingly demonstrate superiority of the proposed approach.

- Reviewers felt that there are potential safety issues with the approach that require better efficacy signals to justify the risk versus the benefit in this indication.

- Reviewers expressed concern that FDA correspondence provided is not sufficiently substantive and does not provide evidence of appropriate guidance from a pre-pre-IND meeting.

Design and Feasibility

- The manufacturing plan lacked sufficient detail, and reviewers questioned the suitability of the proposed facility for GMP production of the therapeutic candidate.

- The reviewers felt that the target patient population for the anticipated clinical trial is not adequately defined and represents an array of patients that may be too broad.

- The proposal lacked cohesion and did not present a plan that demonstrated to reviewers that the team would achieve a well-prepared pre-IND meeting within the expected timeline.

Principal Investigator (PI), Development Team, and Leadership Plan

- The specific role of team members and subcontractors on the proposed project was not adequately detailed. For example, it was unclear to reviewers who is responsible for regulatory affairs or CMC on the project and whether they have appropriate expertise.

- Reviewers questioned the strength of the commitment of team members to the project. For example, the proposed commitment for the project manager is only 10% effort rather than the required 50% minimum.

Collaborations, Assets, Resources, and Environment

- Resources appear to be available and the environment is generally appropriate for conducting the proposed work with exception of the production facility.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08132: IND-enabling studies for the clinical use of human embryonic stem cell (hESC)-derived dopaminergic (DA) neuronal precursors shown to be efficacious & safe in the MPTP-lesioned animal model of Parkinson's Disease (PD)

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

Parkinson's Disease (PD) is a devastating progressive neurodegenerative disorder, stealing vitality from vibrant and productive adults. While it is traditionally thought to be a disease of aging, it can also hit young adults that are genetically predisposed to this condition. It may be caused by toxins in the environment, such as insecticides, and, therefore, has been known to afflict certain communities, e.g., farming regions. It may also be caused by head trauma, such as encountered in the military during combat. It results from the progressive loss of a collection of brain cells that produce a substance called dopamine (DA). DA communicates signals among the neurons of the brain & is involved in cognition, thought, mood & muscle function. Unfortunately, how to best replace those cells & also preserve the remaining DA cells is at the forefront of science. Pills that deliver DA do not necessary provide proper amounts to the critical structures of the brain leading to inadequate treatment & severe side effects. Through our previous research efforts funded by CIRM, we compared the therapeutic effect of various cell types derived from a wide variety of stem cells and found a particular type of stem cell derivative that dramatically improved PD systems in the most authentic animal model of the human disease. This cell type can be transplanted into the precise brain location to replace & possibly rescue the dysfunctional cells. Our project will thoroughly evaluate this cell type using rigorously controlled studies for safety & efficacy in order to develop a therapeutic for PD. Importantly, we will continue do so using this most representative model of true human PD, because it not only mimics all of the human symptomatology but also all of the side-effects of treatment; inattention to this latter aspect plagued earlier clinical trials in PD. A successful therapy for PD would not only be of great benefit for the many patients who now suffer from the disease, or who are likely to develop it as they age (& the aged population is growing), but the results of our research efforts here may in fact also help with the therapeutic development for other neurodegenerative diseases due to greater understanding of stem cell biology as well as their potential complications and side effects.

Statement of Benefit to California (provided by applicant)

Parkinson's Disease (PD) is a particularly devastating disease because, while thought of as a disease of aging, typically impairs adults who are vibrant & productive, significantly impacting their quality of life, those around them, & ultimately the economy in terms of lost productivity & excessive medical costs. As the aging population increases in this country & in this State, the problem is going to become worse. It can also effect younger adults if they have a genetic predisposition. PD can be tied to environmental toxins, such as insecticides, hence hits certain farm communities in the State. It also has been tied to head trauma, including in the military. Therefore, California is particularly effected by this disease. There are limited available therapeutic strategies. Therapeutic approaches that would reduce symptoms & slow disease progression would not only improve patient quality of life, but also reduce the financial impact of the disease. We have discovered that stem cells may perform multiple therapeutic processes in models of PD, including replacing dopaminergic (DA) neurons lost to PD progression. As a result of our previous CIRM Award, a multiyear study performed by our team, implanting multiple types of stem cell derivatives into the most authentic, representative, & predictive animal model of actual human PD, we found that the cells could reverse severe symptoms via multiple mechanisms including by becoming neurons that make DA as well as restoring equipoise to the system. The culmination of our research effort has identified a stem cell-based candidate that we would like to development for clinical use by continuing to use this most representative animal model of human PD, a model that not only mimics all of the human symptomatology but also all the side-effects of treatment; inattention to this latter aspect plagued earlier clinical trials in PD. An advantage of the unique team we have enlisted allows these studies to be carried out at a fraction of the normal cost, clearly a financial benefit to California. Not only might California patients benefit in terms of their well-being, quality of life, & economic benefit from productive adults remaining & re-entering the work force, but it is likely that new intellectual property will emerge that will provide additional financial benefit to California stakeholders, both citizens & companies.

Review Summary

This proposal is focused on the preclinical development of a human embryonic stem cell (hESC)-derived dopaminergic (DA) neuron precursor cell therapy for Parkinson’s disease (PD). PD is a progressive neurodegenerative disease that is classified as a movement disorder but is also associated with cognitive and psychiatric symptoms. A hallmark of PD pathology is the death of DA neurons in

the brain. Dopamine replacement by oral L-DOPA is an effective treatment but it does not address the underlying disease and eventually loses effectiveness as the disease progresses. The applicant proposes that transplantation of hESC-derived DA neuron precursors to PD patient brains will serve to replace the lost DA neurons, improve motor function and reduce patient reliance on L-DOPA. Activities proposed in the application include: DA neuron precursor cell manufacture and banking; safety studies, dose finding studies, and long-term followup in a preclinical animal model; and preparation for and conduct of a pre-IND meeting with the FDA.

Significance and Impact

- Reviewers agreed that the proposed therapeutic candidate addresses a clear unmet medical need and, if successful, could have a significant impact on the health and quality of life of PD patients.

- Reviewers noted that very similar approaches are being actively pursued by other groups and were not convinced that the material presented in the application adequately established whether the applicant's preclinical data are comparable.

Scientific Rationale and Preclinical Development Readiness

- Reviewers raised significant concerns regarding the preliminary data supporting the project's readiness. They felt the data were insufficient to assess whether the DA neuron precursors are of the right subtype and function. Without additional data from in vitro electrophysiology and quantitative in vivo histology (e.g. engraftment, survival, synaptic density) reviewers were not confident that the applicant possesses a promising development candidate.

- The scientific rationale for transplantation of the cell type proposed is well supported and sound but reviewers could not discern whether the applicant is truly generating this cell type.

Design and Feasibility

- Reviewers questioned the extensive proposed use of a large animal model that is expensive and variable and suggested a rodent model could complement and substitute for some of these studies.

- Reviewers commented that studies in the proposed large animal model should be performed using clinical-grade, Good Manufacturing Practice- (GMP)

compliant DA neuron precursors, and it was unclear from the application material if this is what the applicant is proposing.

- Reviewers suggested a redesign of the proposed tumorigenicity study, eliminating dose escalation and spiking and replacing them with a single cohort at the maximum feasible dose.

- Reviewers felt that the duration of immunosuppression proposed in the draft clinical protocol synopsis may be insufficient and could compromise the study. They suggested prolonging it to at least 18 months or preferably two years.

Principal Investigator (PI), Development Team, and Leadership Plan

- The applicant has assembled an excellent team that is well-suited to perform the proposed activities.

Collaborations, Assets, Resources, and Environment

- The project is supported by a well-chosen scientific advisory board with leading experts in the field.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08142: Development of a Chondrogenic Drug Candidate Targeting Cartilage-residing Mesenchymal Stem Cells for the Treatment of Osteoarthritis

GWG Recommendation: Recommended for funding
Final Score: 83

Public Abstract (provided by applicant)

Osteoarthritis (OA) is the most prevalent musculoskeletal disease affecting nearly 27 million people in the United States, and is the leading cause of chronic disability in the United States. Current therapeutic options are limited to pain or symptom-modifying drugs and joint replacement surgery; no disease-modifying drugs are approved for clinical use. OA is characterized by progressive degeneration of the articular cartilage, resulting from abnormal activation, differentiation and death of cartilage cells. A unique and unexplored therapeutic opportunity exists to induce somatic stem cells to regenerate the damaged tissue and reverse the chronic destructive process. Cartilage contains resident mesenchymal stem cells (MSCs) that can be differentiated in vitro to form chondrocytes. This observation suggests that intra-articular injection of a small molecule that promotes chondrogenesis in vivo will preserve and regenerate cartilage in OA-affected joints. Targeting resident stem cells pharmacologically also avoids the risks and costs associated with cell-based approaches. In previous preclinical studies we have identified a small molecule drug candidate that specifically induces chondrocyte differentiation in culture and improves cartilage repair in OA animal models. In the proposed study we will optimize the regimen for dose, frequency and duration. We will also profile the preclinical candidate (PCC) for physicochemical, pharmacological and toxicological properties, draft a detailed plan for phase 1 clinical trial, and prepare documents and conduct a pre-IND meeting with the FDA. If successful, we will initiate IND-enabling studies and subsequent phase 1 clinical trial for the PCC.

Statement of Benefit to California (provided by applicant)

Osteoarthritis (OA) is the most prevalent musculoskeletal disease and globally the 4th leading cause of Years Lost to Disease (YLD). OA affects over 40 million Americans and the magnitude of the problem is predicted to increase even further with the obesity epidemic and aging of the baby boomer generation. It is estimated that 80% of the population will have radiographic evidence of OA by age 65 years. The annual economic impact of arthritis in the U.S. is estimated at over $100 billion, representing more than 2% of the gross domestic product. OA

accounts for 25% of visits to primary care physicians. In 2004 OA patients received 650,000 knee and hip replacements at a cost of $26 billion. Without change in treatment options 1.8 million joint replacements will be performed in 2015. OA is a painful, degenerative type of arthritis; physical activity can become difficult or impossible. Some patients with osteoarthritis are forced to stop working because their condition becomes so limiting. OA can interfere with a patient's ability to even perform routine daily activities, resulting in a decrease in quality of life. The goals of osteoarthritis treatment are to relieve pain and other symptoms, preserve or improve joint function, and reduce physical disability. Current therapeutic options are limited to pain medications and joint replacement for patients with advanced disease. No disease-modifying OA drugs are approved for clinical use. OA is thus a major unmet medical need with a huge clinical and socioeconomic impact and a complete absence of effective therapies. Clearly the development of a new therapeutic that is both symptom and disease modifying would have a significant impact on the well-being of Californians and reduce the negative economic impact on the state resulting from this highly prevalent disease.

Review Summary

The application proposes the preclinical development of a small molecule for the treatment of osteoarthritis (OA) and other conditions causing cartilage damage. OA is a degenerative disease of the joint, articular cartilage and subchondral bone, and is the most common form of arthritis. Currently, no disease modifying drugs for OA are approved for clinical use. The proposed therapeutic will promote selective differentiation of resident mesenchymal stem cells (MSCs) into chondrocytes, the cells that make up cartilage. The PI will conduct a pre-IND meeting with the FDA at the conclusion of this project. To achieve this goal, the PI has proposed studies including development of manufacturing processes, assessment of in vitro activity and cytotoxicity, dosing and safety assessments in preclinical models, and preparation of a clinical development plan.

Significance and Impact

- Reviewers agreed that the proposed therapeutic addresses a significant unmet medical need.

- Currently, the standard of care for OA is pain management for many years followed by joint replacement when the disease reaches its end stage. The proposed approach, if successful, could potentially eliminate the need for joint replacement surgery.

- Despite the high-risk nature of the proposed approach, this proposal represents a chance for CIRM to invest in a project that may be groundbreaking.

Scientific Rationale and Preclinical Development Readiness

- A drug targeting resident stem cells for treatment of OA has a very strong rationale.

- Reviewers praised the team for having performed the proper preclinical studies to date and considered the proposed therapeutic ready to enter preclinical development.

- The background data, including extensive structure-activity relationships studies, provide a strong and compelling basis for the proposal.

- Some reviewers questioned whether MSCs in OA patients would be adequate in number or be responsive to the proposed therapeutic. They suggested that further work be done to characterize MSCs from patients at different stages of OA and their response to the candidate molecule.

Design and Feasibility

- Reviewers praised the application for its efficiency. In particular, the plan is well designed with clearly defined goals and milestones.

- Although much work remains to be done, the proposed timeframe is reasonable.

- The proposed surgical model is well accepted; however, the model tends to present OA-like pathology in a greatly accelerated timeframe compared to humans. Reviewers viewed this as a limitation.

- The team may wish to consider the development of analytical methods ahead of or coincident with the development of the manufacturing process. Thus, reliable results will be readily available during process development.

Principal Investigator (PI), Development Team, and Leadership Plan

- The team is extremely well qualified. They have developed the lead candidate over a number of years and have the necessary skills to complete the pre-IND work as proposed.

- The recent addition of a translation expert from a large pharmaceutical company improves an already strong team.

- Reviewers expressed minor concerns that the proposal lacked substantive clinical input; however, they believed that this aspect would improve significantly in the near future.

Collaborations, Assets, Resources, and Environment

- No relevant concerns were highlighted by reviewers under this review criterion.

REVIEW REPORT FOR CIRM RFA 14-02 PRECLINICAL DEVELOPMENT AWARDS

PC1-08147: Injectable stem cell recruiting biomaterial for treating critical limb ischemia

GWG Recommendation: Not recommended for funding
Final Score: --

Public Abstract (provided by applicant)

An estimated 8 million Americans with peripheral artery disease (PAD) are affected by immobility, intractable ischemia, ulceration, impaired wound healing or amputation. PAD is a chronic disease characterized by the buildup of atherosclerotic plaque in the lower extremities. Critical limb ischemia (CLI), an advanced form of the disease and is characterized by pain at rest and decreased tissue integrity, ultimately leading to ulcers or gangrene, and potentially amputation. There are few effective therapies and therefore amputation rates due to PAD and CLI have not changed significantly in 30 years. These staggering statistics necessitate the development of new therapies for PAD and CLI. Due to limitations with current treatments, there are approximately 120,000 leg amputations in the U.S. The topic has been underserved, with interventional cardiologists only beginning to treat the disease in the past 10-15 years. Alternative therapies have therefore largely mirrored the attempts for myocardial infarction (MI) and heart failure, including drug-eluting stents, cell transplantation, gene delivery, and angiogenic growth factor therapy.

A biomaterial-only therapy provides significant advantages as it can be an off-the-shelf therapy and manufactured at significantly reduced costs. However, for PAD and CLI, very few biomaterial scaffolds have been examined, and to date, they have only been explored for use with angiogenic growth factor or cell therapy. None of these materials have been specifically designed for the ischemic skeletal muscle they are treating. The use of biomaterials scaffolds as acellular, biomaterial-only therapies designed to promote endogenous healing for treating PAD and CLI has yet to be explored and therefore, there is a significant opportunity to develop novel therapies for this disease.
This project is to develop a tissue specific biomaterial that would be effective in patients with intermittent claudication as well as CLI. The product could significantly improve patient care by increasing perfusion to the limb as well as treat the associate muscle atrophy. No current therapies successfully treat either of these conditions.

The proposed project will advance the field of regenerative medicine by creating a simple, cost-effective approach for harnessing the power of endogenous stem cells. Rather than having the expense and difficulties associated with a living cell product, the product will be an off-the-shelf available and cost-effective approach for treating CLI.

Statement of Benefit to California (provided by applicant)

An estimated 8 million Americans with peripheral artery disease (PAD) are affected by immobility, intractable ischemia, ulceration, impaired wound healing or amputation. PAD is a chronic disease characterized by the buildup of atherosclerotic plaque in the lower extremities. PAD is present in 1 of every 20 adults who are over 50. Critical limb ischemia (CLI), an advanced form of the disease and is characterized by pain at rest and decreased tissue integrity, ultimately leading to ulcers or gangrene, and potentially amputation. There are few effective therapies and therefore amputation rates due to PAD and CLI have not changed significantly in 30 years.

This project is to develop a tissue specific biomaterial that would be effective in patients with intermittent claudication as well as CLI. The product could significantly improve patient care by increasing perfusion to the limb as well as treat the associate muscle atrophy. No current therapies successfully treat either of these conditions.

The proposed project will advance the field of regenerative medicine by creating a simple, cost-effective approach for harnessing the power of endogenous stem cells. Rather than having the expense and difficulties associated with a living cell product, the product will be an off-the-shelf available and cost-effective approach for treating CLI.

The benefit to the overall health care of citizens of California would be significant. In addition, this product and development will be completed within the state of California, and the initial clinical trials are expected to be completed in California. This project provides opportunities for a number of business and employees to establish a biologic product on the market.

Review Summary

This application is focused on the preclinical development of an injectable, cell-free, biomaterial scaffold for the treatment of peripheral artery disease (PAD) and critical limb ischemia (CLI). PAD is a common circulatory problem in which the narrowing of blood vessels by atherosclerotic plaques reduces blood flow to limbs, causing symptoms such as leg pain while walking. CLI is an advanced, severe form of PAD, associated with intense pain in the feet and toes as well as wounds and ulcers that won't heal. There are few effective therapies for CLI and

amputation is frequently required. The applicant proposes that a skeletal muscle specific biomaterial injected into PAD or CLI patient muscle could promote blood vessel growth and recruit endogenous muscle stem cells to regenerate damaged tissue. Activities proposed in the application include: development of manufacturing processes and characterization assays; dosing and preliminary safety studies in an animal model; development of a clinical plan; and preparation for and conduct of pre-pre-IND and pre-IND meetings with the FDA.

Significance and Impact

- Reviewers agreed that this application addresses an unmet medical need and could have a significant impact if successful. However, they cautioned that PAD and CLI are very difficult clinical indications for which to develop treatments.

Scientific Rationale and Preclinical Development Readiness

- Reviewers raised significant concerns about the preliminary data supporting the efficacy of the proposed therapeutic. The changes in blood flow presented by the applicant were described as minimal and raised questions about whether they would translate into clinical benefit.

- Reviewers were not convinced from the preclinical data that revascularization with new arteries, rather than capillaries, would result from the proposed therapeutic.

- Reviewers expressed concern that the preliminary data do not clearly support the rationale for using skeletal muscle specific biomaterial versus biomaterial from other sources.

Design and Feasibility

- Reviewers raised concerns about whether the manufacturing plans are feasible in a two-year timeframe. They described the manufacturing processes as cumbersome and subject to excessive losses. They would have appreciated more detail regarding the manufacturing facilities and Good Manufacturing Practice (GMP) compatibility.

- Reviewers thought that the applicant's previous success in preclinical development with a similar biomaterial product supports the project's eventual feasibility.

- Reviewers raised a number of concerns about the draft clinical trial synopsis, including whether the number of patients proposed would be sufficient to evaluate the effect of dose.

Principal Investigator (PI), Development Team, and Leadership Plan

- Reviewers raised concerns that the team lacks appropriate depth and experience in the development of biologic products.

- Reviewers questioned whether the application, most importantly the draft clinical trial synopsis and the TPP, included input from clinicians experienced in treating PAD and CLI.

- Reviewers questioned whether the PI would be able to commit 50% effort to this project.

Collaborations, Assets, Resources, and Environment

- No relevant concerns were highlighted by reviewers under this review criterion.