CIRM RESEARCH LEADERSHIP AWARDS – RFA 09-04

Tier1 - Recommended for funding = ☐

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

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

App #	TITLE	Score	Median	SD	Low	High	Budget	Tier
LA1-08015	Engineering microscale tissue constructs from human pluripotent stem cells	**85**	88	8	70	97	$6,368,285	1
LA1-08014	Niche-Focused Research: Discovery & Development of Hematopoietic Regenerative Factors	**79**	81	7	60	88	$5,174,715	1
LA1-08013	Single Molecule Biophysics and Biology of Cellular Identity	**76**	77	9	50	88	$4,631,091	1
LA1-08011	Rejuvenation of human skeletal muscle stem cell function during aging, injury and disease	**68**	65	6	60	80	$4,974,306	2
LA1-08012	Modulation of the regenerative niche: an improved platform toward clinical trials	**66**	68	10	50	80	$4,805,075	2

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

M E M O R A N D U M

May 16, 2014

From: C. Randal Mills, President; Patricia Olson, Executive Director, Scientific Activities; and Michael Yaffe, Associate Director, Research Activities
To: Independent Citizens Oversight Committee (ICOC)
Subject: Staff Recommendations re applications submitted under RFA 09-04, Research Leadership Awards, #14

In accordance with Section 7, Article V of the Bylaws of the Scientific and Medical Research Working Group and Section 6, Article VI of the Board's bylaws, both as amended on 3/19/13;

the President and the scientific staff, following internal review and consideration:

- recommend that the Board approve funding of the applications in Tier 1 (LA1_C14-08015, LA1_C14-08014, and LA1-C14-08013) as recommended by the GWG and

- find no compelling programmatic reason to fund and where the Board doesn't find one, recommend to not fund applications LA1_C14-08011 and LA1_C14-08012.

REVIEW REPORT FOR CIRM RFA 09-04: RESEARCH LEADERSHIP AWARDS

LA1-08011: Rejuvenation of human skeletal muscle stem cell function during aging, injury and disease

Recommendation: Tier 2 **Final Score:** 68
Total Funds Requested: $4,974,306

PUBLIC ABSTRACT (provided by applicant)

One of the hallmarks of organismal aging is a decline in skeletal muscle mass, regenerative capacity and physiological function. Muscle resident stem cells are essential mediators of muscle tissue regeneration, and thus implicate a central role for stem cells in the aging process. The enormous therapeutic potential of stem cells in regenerative medicine has evoked great excitement for the development of strategies aimed at treating the types of degenerative muscle conditions prevalent in the elderly, in patients with injuries, and individuals stricken with disease. Characterization of human muscle stem cell aging will be the critical first step towards achieving these goals, as such research should be able to identify the mechanisms underlying stem cell functional decline, and at the same time illuminate strategies for intervention. In this project, we propose to identify the bone fide stem cell of human skeletal muscle and generate a novel cocktail of factors, identified from human muscle and blood, that will be harnessed to boost stem cell activity, regenerative capacity and rejuvenate aged tissue. To this end, human muscle stem cells from adult and aged muscle will then be treated with combinations of identified human muscle or blood factors to identify “rejuvenation” factors that augment stem cell function and promote muscle repair in cell culture and transplantation models. In addition, we will develop a strategy to identify “helper” cells located in the blood or muscle that stimulate stem cell activity and augment muscle repair. Together, these strategies should allow for optimized conditions for effective patient specific muscle stem cell transplantation and the ability to deliver soluble factors directly to aged, injured, or diseased individuals for rejuvenation of regenerative processes.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

Population demographics indicate that the percentage of elderly adults is at a historical high, and continues to climb. Concomitant increases in the prevalence of age-related degenerative and malignant conditions and associated morbidities will thus place a heavy burden on future health care resources. The need to develop therapeutic strategies aimed at treating pathophysiological conditions in the elderly is therefore both medically and economically relevant. For this CIRM award, I propose to develop novel approaches for the augmentation of stem cell function and tissue repair to prevent and rejuvenate muscular regeneration and aging. The successful development of stem-cell based therapies will place the state of California in a leading position for treatment of age-related degenerative diseases and diseases of the musculoskeletal system in general. These advances could improve the treatment of age-associated diseases that affect the people of California, potentially reducing morbidity, mortality, and health care costs. Advances in our understanding of aging could also lead to the founding of new biotechnology companies that create high-paying jobs and economic development for California. Finally, the point of the CIRM Leadership Award is to recruit highly successful stem cell laboratories to California. Our laboratory would bring millions of dollars in grant funding from the federal government and from private foundations to California. This would directly create jobs and economic development in California, independent of any discoveries that arise from our future research.

REVIEW SUMMARY

The applicant principal investigator (PI) is an early to mid-career scientist with an active research program focused on skeletal muscle regeneration. The PI has contributed previously to an understanding of muscle aging using the mouse system. He/she now plans to expand this

research focus to aging of human muscle stem cells. Proposed studies aim to identify endogenous soluble factors and small molecules with the potential for rejuvenating aged human muscle stem cell function. Additionally, heterologous "helper" cells, which support stem cell rejuvenation, will be identified using both in vitro and in vivo approaches. These studies should provide new insights into cellular mechanisms that control age-related changes in muscle function and may lead to novel therapeutic approaches for muscle degeneration.

Research Vision and Plans
- The research is focused on a significant problem, as age-related muscle weakness and wasting are increasing medical issues for which there are no current therapies.

- The project is likely to generate interesting results and significant publications.

- Reviewers expressed concern that the proposed investigation is peripheral to the PI's area of expertise and does not build logically from the PI's recent body of work on key regulators of muscle stem cells during repair and aging.

- Studies are proposed in a very simplistic manner, with a narrow focus and serious lack of detail. Previous, relevant work in related fields was not adequately cited in the context of these studies.

- Reviewers did not view the plan as particularly innovative, as other researchers are currently pursuing similar approaches.

- Some reviewers were concerned that the plan was not unified by a coherent hypothesis and lacked sufficient attention to underlying mechanisms of cellular aging and degeneration.

PI Accomplishments and Potential
- The PI has established an active research program focused on mouse muscle stem cells, which is supported by two NIH grants.

- The candidate has produced several significant publications as an independent researcher; however reviewers expressed concern about his/her overall research productivity, which was considered average in his/her current institutional environment.

- The PI has yet to demonstrate an active leadership role either in his/her field of research or in scientific organizations or the broader scientific community.

- Letters of recommendation were strongly supportive and highlighted the applicant's important contributions to the field. However, reviewers were concerned that the letters were all from interconnected individuals representing a narrow research field.

Institutional Commitment and Environment
- The research environment at the applicant institution is outstanding.

- Reviewers were uncertain as to how the environment would enhance the applicant's research or provide an advantage over his/her current situation.

- The institution's recruitment package of salary, research space and start-up funds was considered adequate but relatively small for an established investigator.

- The PI's potential leadership role at the applicant institution is unclear; although the application proposes that the PI will provide a cornerstone for bringing research discoveries to the clinic, the candidate has no demonstrated expertise or experience in translational activities

REVIEW REPORT FOR CIRM RFA 09-04: RESEARCH LEADERSHIP AWARDS

LA1-08012: Modulation of the regenerative niche: an improved platform toward clinical trials

Recommendation: Tier 2 **Final Score:** 66
Total Funds Requested: $4,805,075

PUBLIC ABSTRACT (provided by applicant)

This research program aims to understand the mechanisms by which specific stem cell subtypes co-ordinate tissue repair and regeneration. Stem cells act like “conductors of the orchestra” to co-ordinate new blood vessel formation and subsequent tissue regeneration. Essentially, our goal is to deliver the right cells, to the right place, at the right time, to generate a local environment permitting the body to heal itself. This concept referred to as “stem cell-mediated tissue regeneration” has emerged as a central process to enhance the repair of diseased, aged, or damaged tissues.

Through my research training, I have acquired considerable expertise in the purification and expansion of relevant stem cell subtypes for the pre-clinical development of regenerative therapies. I also have developed unique “humanized” mouse models to study the regenerative functions of human stem cells after direct tissue injection. My long-term goal is to make consistent contributions toward the development of new regenerative therapies.

This CIRM leadership application presents a novel platform for the systematic development of regenerative therapies using combinatorial delivery of clinically applicable stem cells. Through purification using a conserved function of stem cells from human bone marrow or umbilical cord blood, we have identified a clinically relevant starting population of hematopoietic (blood), endothelial (blood vessel), and mesenchymal (vessel wrapping) stem cells that orchestrate several distinct regenerative mechanisms. Importantly, these stem cell subtypes grow efficiently in the lab and can be expanded under clinically applicable conditions to provide the large number of cells required for clinical applications.

We have used these stem cells to regenerate insulin-producing beta cells during diabetes, and to promote blood vessel formation in heart and muscles with compromised blood flow. Indeed, transplanted hematopoietic progenitor cells (HPC) enhanced the recovery of perfusion in the ischemic limbs of mice by inducing neovessel formation, and improved the control of blood glucose hyperglycemic mice via induction of beta cell proliferation. Direct delivery of these cells increased tissue-specific engraftment and improved both islet and limb vascularization. In contrast, culture-expanded mesenchymal stem cells (MSC) induced new islet formation. Transplantation of MSC followed by HPC maximized recovery by inducing both new islet formation and subsequent expansion and revascularization.

These data establish our central hypothesis that transplanted progenitor cells form a regenerative niche in multiple tissues by stimulating blood vessel or islet regenerative mechanisms depending on the secretory activities of the stem cells delivered. Thus, our proposed studies will determine how purified stem cell subtypes can be used in the clinic to form a regenerative niche in multiple tissues.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

Over 1.4 million people in California suffer from ischemic heart disease, and over 75% of the 2 million Californians with type II diabetes will eventually suffer severe vascular complications including heart attack, critical limb ischemia, and stroke. These diseases represent an emerging epidemic that place an immense financial burden on the health care system. The ultimate goal of my research is the efficient development of novel regenerative therapies to provide treatment

options and improve the quality of life in patients who have these chronic diseases.

We exploit the purification and subsequent expansion of lineage-restricted stem cell subsets from human bone marrow and umbilical cord blood to produce a renewable platform for regenerative therapies. These cell types are routinely transplanted in the clinic to treat a variety of hematological malignancies, autoimmune and degenerative diseases, and metabolic disorders. As such, our isolation and expansion technologies are designed to support immediate translation to new clinical applications.

We also specialize in the development of novel transplantation models and tissue delivery methods for the translation of novel cell therapies to humans. Our previous collaborative work were used as proof-of-concept to gain FDA approval for a phase I/II clinical trial transplanting autologous ALDH-expressing cells into the ischemic limbs of patients at risk for limb amputation due to severe peripheral artery occlusive disease. This trial has proven safe and effective with significant improvements reported in limb perfusion, resting pain, and wound healing resulting in limb salvage in 100% of these patients at 1 year post-therapy.

Importantly, the intellectual property gained by this type of research moving forward in California can efficiently impact patients through collaboration with a wealth of clinical scientists in transplantation surgery at the candidate institution and with the translational expertise and GMP infrastructure assembled there. Thus, we are uniquely positioned to develop “first-in-human” trials using combinatorial transplantation of expanded stem cell subsets to “tip the balance” in favor of tissue regeneration versus destruction in ischemic vascular diseases.

The industrial leader in the development of cellular therapies for type I diabetes is headquartered in California. ViaCyte Inc combines the directed differentiation of pluripotent stem cells into pancreatic beta cell precursors (PEC-01TM) with subcutaneous implantation in a protective device “the Encaptra” drug delivery system. Thus, combining regenerative and immunomodulatory MSC with proprietary pluripotent sources of beta cell or cardiovascular precursors represents a complementary and potentially synergistic method to improve therapies designed to treat both diabetes and ischemic cardiovascular diseases.

REVIEW SUMMARY
The applicant principal investigator (PI) is an early to mid-career scientist with an active research program focused on identifying stem cell subtypes, isolated from bone marrow and umbilical cord blood, that enhance tissue regeneration by providing supportive signals to resident (endogenous) cells, and thus function as a regenerative niche. The PI plans to build upon this work to better understand and improve the stem cells’ capacity to improve regeneration using animal models of limb ischemia (restriction in blood supply) and loss of insulin-producing beta cells. The PI also plans to employ the supportive function of these stem cell subsets for ex vivo engineering of blood vessels and beta cells for ultimate use in replacement therapy in patients with ischemic diseases and diabetes.

Research Vision and Plans
- The research is focused on varied forms of ischemia and pancreatic beta cell regeneration, which are areas of significant clinical need for improved treatment options.

- Some reviewers viewed the proposal’s use of distinct stem cell types to trigger different endogenous regenerative events as relatively innovative, while others considered the use of the proposed cell population for the treatment of ischemia neither novel nor unique.

- Research is focused on the regenerative niche, a subject poorly understood but critical for use of stem cells in tissue repair.

- Some reviewers found aspects of the proposed research plan unfocused and lacking adequate detail.

- The proposed beta cell work does not adequately address autoimmunity associated with type 1 diabetes, and as such, it could be only applied to type 2 diabetes. Since other treatment options exist for that disease, the rationale for employing cell therapy, especially complex engineered cell products, is not sound.

- Proposed therapeutic strategies combining multiple cell types would face a steep regulatory hurdle; reviewers felt such approaches would have little direct translational potential.

PI Accomplishments and Potential
- The PI has demonstrated expertise in purification and expansion of the various stem and progenitor cell populations and their evaluation in animal models.

- The PI's research has contributed to a better understanding of the regenerative niche.

- The PI has a reasonable publication record, but reviewers were concerned that his/her most significant work and highest productivity was as a postdoc, prior to becoming an independent scientist.

- Reviewers expressed concern that the candidate PI has yet to demonstrate significant leadership in the scientific community and were uncertain about the PI's potential to become a prominent leader.

Institutional Commitment and Environment
- The applicant institution was recognized as an excellent research environment with a particularly strong record in translational biomedical science.

- The candidate will receive substantial support from the institutional stem cell program.

- Reviewers felt that the environment at the applicant institution would significantly benefit the PI's research program.

REVIEW REPORT FOR CIRM RFA 09-04: RESEARCH LEADERSHIP AWARDS

LA1-08013: Single Molecule Biophysics and Biology of Cellular Identity

Recommendation: Recommended for Funding **Final Score:** 76
Total Funds Requested: $4,631,091

PUBLIC ABSTRACT (provided by applicant)

One of your earliest childhood biology lessons probably occurred when your body demonstrated to you that your skin is an organ that is able to self-regenerate. Indeed wound healing is a fascinating process in which cells carry out a precise and complex choreography that includes cellular differentiation and regulation of gene expression.

Our lab studies a particular cell type called dermal fibroblasts. If a wound occurs, they migrate to the site of injury, change into muscle like cells (myofibroblasts) that contract to help with wound closure, and, once the wound has healed, enter programed cell death to clear the work area. Disruption to this process can result in chronic ulcers or keloid scarring. A major goal of our studies is to understand how the fibroblast to myofibroblast transition is regulated, so that therapeutic strategies can be devised to prevent and treat this pervasive problem.

In addition to our motivation to understand wound healing in order to learn how to control it and cure its pathologies, wound healing is an accessible system to study more general differentiation events involved in tissue regeneration. By studying the changes that fibroblasts undergo during wound healing, we revealed an important mechanism of gene regulation that could help to explain more generally how cells maintain a particular identity and how they can be driven to a different state. The molecules we identified are known to control general gene activity as well as the spatial organization of genes within the cell's nucleus. The studies proposed here will further investigate those findings.

One of the ways in which our laboratory studies how cells control gene activity is by directly visualizing gene expression. Using highly specialized microscopy, biochemistry and computer analyses, we are able to observe the behavior of individual gene regulatory molecules within individual living cells. We will continue to use and improve these methods to better understand how genes are controlled. We believe that these studies will open the door to new strategies in cellular reprogramming and potentially to new strategies for modifying cells for therapeutic use.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

Our research program includes clinically relevant and translational studies of wound healing, development and transfer of new imaging technologies to enable investigators to visualize the behavior of individual molecules within living cells, and basic biological studies seeking to understand fundamental mechanisms of gene regulation that control stem cell pluripotency and differentiation. These endeavors will benefit the State of California in various different and overlapping ways.

Successful development of stem cell-based therapies hinges on the ability to control cell identity and cell fate. By contributing to the understanding of fundamental gene regulatory mechanisms controlling pluripotency and tissue-specific differentiation, the research proposed here has the potential to influence and positively impact a wide range of regenerative medicine studies ongoing in the state.

Chronic skin ulcers are a pervasive and dangerous human medical problem. Current treatments can be slow and painful, and are too often ineffective, resulting in the necessity of limb

amputation. The true economic and personal cost of chronic ulcers is difficult to quantify because public health research most frequently includes it as a symptom of systemic disease. However, in 2009 chronic ulcers were estimated to affect 6.5 million patients in the Unites States, with treatment costs in excess of 25 billion dollars. Our identification of specific factors that control the fibroblast to myofibroblast transition suggests new approaches to differential diagnosis and to treatment of chronic wounds using fibroblasts and myofibroblasts as direct targets or therapeutic agents.

The ability to detect, track and manipulate individual gene regulatory molecules in living human cells is a disruptive technology that already is having a major impact in developmental biology and stem cell research. Technologies for imaging individual molecules in live cells are evolving so rapidly that they are difficult to commercialize and are therefore available only to a relatively small number of laboratories that are able to build these systems from component parts. Our lab will serve as a center to help develop these technologies, and to help other laboratories adopt these powerful new research tools. California also has a rich industrial base in microscopy development and engineering. The development and implementation of new super resolution live cell imaging technologies such as we propose here will offer many opportunities for collaboration between industry and academia, opening new markets and enabling the spread of these innovations throughout academic and bio-pharmaceutical laboratories. This synergism, in turn, will accelerate research in regenerative therapeutics.

REVIEW SUMMARY
The applicant is an early career, independent investigator with expertise in both the development of imaging technology and biology. The proposed research for the Leadership Award comprises a combination of technology development, single molecule live cell imaging and biophysical analysis of transcriptional regulation with the goal of providing new insight into the basic mechanisms regulating gene expression during cell differentiation. This approach will be applied to the study of how fibroblast cells in the skin convert to myofibroblasts during wound healing, a critical process for regenerative medicine.

Research Vision and Plans
- The combination of state-of-the-art biochemical assays with cutting-edge microscopy and imaging methods has the potential to provide valuable new insight into the basic mechanisms regulating gene expression during differentiation.

- The technology development component of the proposal is particularly innovative and leverages existing CIRM-funded infrastructure and expertise at the applicant institution.

- Reviewers differed in their opinion about the potential impact of the proposed work on the stem cell field. Some emphasized that the proposed approaches are entirely novel and felt that they will be very valuable in addressing unanswered questions in stem cell biology, especially given the heterogeneities inherent in stem cell cultures. Others questioned whether information obtained from the proposed experiments will significantly advance the field of stem cell biology, since they are focused on a transcription and do not take into account other aspects of cellular regulation.

PI Accomplishments and Potential
- The PI is recognized as a pioneer in the development of microscopy and computational tools for following the movement of molecules in living cells, a powerful and enabling technology.

- The PI has been extremely successful as a junior investigator and has produced an impressive body of innovative work. This is represented by a large number of published papers, many in the best journals in the field, since establishing an independent laboratory.

- One concern is the applicant's lack of experience working with stem cells. However, since the applicant has established a number of successful interdisciplinary collaborations in the past, reviewers had confidence that s/he would be able to take advantage of local expertise at the applicant institution to collaborate and bring the use of new technology into the stem cell field.

- Letters from mentors and colleagues describe the applicant as an unusually creative scientist, on a high upward trajectory and a 'prize recruit' to California and to the stem cell field.

Institutional Commitment and Environment
- The applicant would be an ideal fit and would strengthen an already excellent environment for developing sophisticated imaging technology at the applicant institution.

- Reviewers appreciated that the PI has already established collaborations at the applicant institution.

- The applicant institution is providing an excellent equipment fund and start-up package to enable the PI's success.

- Overall, the research environment at the applicant institution is excellent. Reviewers appreciated that the institution will provide access to the expertise of stem cell biologists and core facilities working with human pluripotent stem cells.

REVIEW REPORT FOR CIRM RFA 09-04: RESEARCH LEADERSHIP AWARDS

LA1-08014: Niche-Focused Research: Discovery & Development of Hematopoietic Regenerative Factors

Recommendation: Recommended for Funding **Final Score:** 79
Total Funds Requested: $5,174,715

PUBLIC ABSTRACT (provided by applicant)

Bone marrow and peripheral blood transplantation utilizing blood stem cells can provide curative treatment for patients with cancers and non-cancerous diseases of the blood and immune systems. Such treatments can be curative because the stem cells contained within the bone marrow or peripheral blood of healthy donors are capable of replacing the entirety of the patient's blood system and providing a new immune system which can eradicate the patient's cancer cells. The application of blood stem cell transplantation could be applied to a much larger population of patients if methods could be developed to expand blood stem cells in vitro or in vivo. This would be particularly beneficial for the broadened application of human cord blood transplantation for the many patients who lack an immune-matched sibling or unrelated donor. Furthermore, a method to expand human blood stem cells in vivo could be highly beneficial for the thousands of patients with cancer who require toxic chemotherapy which frequently results in decreased blood counts, infections and bleeding complications. A systemic treatment (i.e. a shot) which could cause blood stem cells to grow and produce more blood cells in patients could markedly improve patient's outcomes after they receive such chemotherapy in the curative treatment of cancer. However, the development of treatments capable of inducing human blood stem cells to grow in the body has been very slow, in part due to a lack of understanding of the processes which govern blood stem cell growth in general. In my laboratory, we have developed mouse genetic models which allow us to discover new proteins produced in the bone marrow (the "soil" where blood stem cells reside) which make blood stem cells grow. We have recently discovered that 2 proteins are secreted by blood vessels within the bone marrow and cause blood stem cells to grow rapidly following damage with radiation. We are currently in the process of developing one of these into a growth factor that we can deliver to patients via injection as a means to cause their blood stem cells to grow after cord blood transplantation or following chemotherapy treatment for cancer. In this proposal, we will utilize our unique mouse models to discover the additional growth factors that make blood stem cells grow and we will perform pre-clinical studies to test whether these newly discovered growth factors can cause human blood stem cells to grow in vitro and in vivo. This proposal has the potential to generate new understanding of how human stem cells grow in vivo and to facilitate the development of new therapies which can regenerate human blood stem cells and the blood system as a whole in patients.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

My research program has both basic science and pre-clinical components which I believe will benefit California in several important ways: First, my basic research program will contribute new fundamental knowledge in stem cell biology which will benefit students, fellows and faculty. My research will also synergize with other campus laboratories and other centers in California and will lead to collaborations and accelerated translation of these discoveries for regenerative medicine. Second, my research program has the potential to directly benefit patients in California. We have already discovered two niche-derived proteins which promote hematopoietic stem cell regeneration in vivo and are focusing substantial efforts now to develop these proteins as therapeutics for Phase I clinical trials. For example, we are developing one of the HSC regenerative factors which we discovered for a Phase I clinical trial to test its efficacy as a systemic therapy to accelerate cord blood engraftment and hematologic recovery in adult cord blood transplant patients. This has literal potential benefit for patients since approximately

10% of cord blood transplant patients die from complications of graft failure or delayed hematologic recovery. In addition, patients with cancer who receive myelosuppressive chemotherapy can potentially benefit from systemic administration of [REDACTED] or other HSC regenerative factors that we discover to accelerate hematologic recovery after chemotherapy. If we are able to show that administration of such regenerative factors can accelerate hematologic recovery in patients after chemotherapy, then remission rates for cancer patients may increase via more effective delivery of curative chemotherapy on time and to completion. Third, my research will provide new intellectual property. These inventions from my laboratory will be available for licensure to biotech or pharmaceutical companies in California. I have experience with licensing inventions from my laboratory to biotech companies and am eager to see my future inventions licensed to accelerate development for regenerative medicine. Fourth, my research program will provide new jobs and professional opportunities. At present, my research program provides partial or complete funding for more than 30 employees internally and more than 30 employees at our partner institutions in academia and biotechnology. I will also bring substantial federal research funding with me to California and will be hiring new fellows, technicians and faculty promptly upon my arrival. Taken together, I am hopeful that my research program will have a major benefit for the scientific community of California, for patients who may benefit from treatments we are developing, for the biotechnology community via the development of new intellectual property and for the larger economy via the creation of many new jobs. I sincerely look forward to the opportunity to bring my program to California.

REVIEW SUMMARY

The candidate principal investigator (PI) is a tenured physician-scientist and expert in the biology of hematopoietic stem cells (HSC) and their microenvironment. The proposed research falls within two broad areas, encompassing both basic and translational research objectives. In the first, the applicant plans to build on an existing pipeline of discovery to identify soluble factors that regulate self-renewal and survival of hematopoietic stem cells ex vivo, and to explore the molecular basis by which they do so. In the second, the applicant will perform preclinical studies with lead candidates identified through this pipeline, with the goal of developing clinically useful factors for expanding cord blood and improving the efficiency of HSC engraftment after transplantation. The applicant institution will provide support in the form of protected research time, laboratory space, matching funds, and access to intellectual and physical infrastructure in the basic and translational sciences.

Research Vision and Plans

- The key strength of this proposal is the applicant's clear vision for translating his/her cutting edge discoveries to the clinic, which has been fostered by direct experience as both as a scientist and as a clinician.

- The research plan builds logically on the applicant's previous work, including a robust platform of discovery comprising unique tools, model systems, and a novel focus on the role of vascular factors in the regulation of blood stem cells.

- The proposed research addresses current limitations to the application of HSC transplantation including graft failure, susceptibility to infection and low availability of donor cells. If successful, this research could lead to improved HSC transplantation procedures and potentially expand their therapeutic use into new areas.

- The proposal is high risk due to its narrow focus on a lead candidate and the inherent challenges of translational research. Reviewers were confident, however, that some risk would be mitigated by continued generation of new lead candidates through the applicant's robust discovery pipeline.

- The proposal lacked a detailed discussion of potentially adverse effects that might occur with use of the HSC regenerative factors identified through this research, such as altered anti-viral or graft vs. tumor responses, development of autoimmunity, or promoting the growth/survival of malignant cells. It will be important to consider the influence of these factors on other blood cell types when assessing their perceived benefits.

- While the experimental plans lacked detail, reviewers acknowledged the track record and continued productivity of the applicant PI in support of the project's overall feasibility and potential.

PI Accomplishments and Potential

- The PI is a nationally recognized, accomplished physician-scientist who has made significant and impactful discoveries in the fields of hematopoietic stem cell biology and bone marrow transplantation. Reviewers described him/her has having introduced a "whole new dimension of investigation" to HSC biology.

- The PI's standing as a leader is evidenced by service on a number of national committees and editorial boards, including a recent appointment as chair of an important National Institute of Health (NIH) study session.

- The application includes strong and enthusiastic letters of support from notable leaders in the field of hematology and regenerative medicine.

Institutional Commitment and Environment

- Institutional support is strong, comprising a generous start up package that includes matched funds, significant protected time for research, a large laboratory space, and access to world-class resources and infrastructure.

- Reviewers were convinced that recruitment of the applicant would synergistically advance the clinical-translational efforts of his/her own research and that of the stem cell community at the applicant organization.

- The environment at the applicant organization is outstanding for hematopoietic stem cell biology and has appropriate equipment and technical resources to support the initiation of clinical trials that may result from this program.

REVIEW REPORT FOR CIRM RFA 09-04: RESEARCH LEADERSHIP AWARDS

LA1-08015: Engineering microscale tissue constructs from human pluripotent stem cells

Recommendation: Recommended for Funding **Final Score:** 85
Total Funds Requested: $6,368,285

PUBLIC ABSTRACT (provided by applicant)

Tissues derived from stem cells can serve multiple purposes to enhance biomedical therapies. Human tissues engineered from stem cells hold tremendous potential to serve as better substrates for the discovery and development of new drugs, accurately model development or disease progression, and one day ultimately be used directly to repair, restore and replace traumatically injured and chronically degenerative organs. However, realizing the full potential of stem cells for regenerative medicine applications will require the ability to produce constructs that not only resemble the structure of real tissues, but also recapitulate appropriate physiological functions. In addition, engineered tissues should behave similarly regardless of the varying source of cells, thus requiring robust, reproducible and scalable methods of biofabrication that can be achieved using a holistic systems engineering approach. The primary objective of this research proposal is to create models of cardiac and neural human tissues from stem cells that can be used for various purposes to improve the quality of human health.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

California has become internationally renowned as home to the world's most cutting-edge stem cell biology and a global leader of clinical translation and commercialization activities for stem cell technologies and therapies. California has become the focus of worldwide attention due in large part to the significant investment made by the citizens of the state to prioritize innovative stem cell research as a critical step in advancing future biomedical therapies that can significantly improve the quality of life for countless numbers of people suffering from traumatic injuries, congenital disorders and chronic degenerative diseases. At this stage, additional investment in integration of novel tissue engineering principles with fundamental stem cell research will enable the development of novel human tissue constructs that can be used to further the translational use of stem cell-derived tissues for regenerative medicine applications. This proposal would enable the recruitment of a leading biomedical engineer with significant tissue engineering experience to collaborate with leading cardiovascular and neural investigators. The expected result will be development of new approaches to engineer transplantable tissues from pluripotent stem cell sources leading to new regenerative therapies as well as an enhanced understanding of mechanisms regulating human tissue development.

REVIEW SUMMARY

The candidate principal investigator (PI) is an early to mid-career scientist leading an active research program focused on the interface of tissue engineering and stem cell biology. The proposed research emphasizes technologies to engineer three-dimensional (3D) multicellular aggregates that will model stem cell differentiation and morphogenesis processes. The PI has made numerous advances in designing novel culture systems that incorporate various bioengineering techniques. This proposal utilizes these approaches to develop transplantable 3D cardiac and neuronal tissues derived from human pluripotent stem cells (hPSCs). The candidate PI intends to promote the maturation of microscale 3D multicellular aggregates for use in regenerative medicine therapies.

Research Vision and Plans

- Reviewers were extremely enthusiastic about the candidate’s emphasis on a developmental biology-based approach (in lieu of a purely traditional engineering approach) for organ development.

- The proposed research addresses several unmet needs in stem cell biology, including the control of purification and differentiation processes.

- The proposed research represents a substantially vital step between the ability to generate specific cell types and the use of these cells in the repair of tissue damage.

- Results from the proposed studies could help develop stem cell-based drug screening platforms and engineered tissues for heart and brain regeneration.

- Reviewers viewed the integration of embryo extracellular matrix (ECM) components in 3D culture as important and innovative.

- Reviewers suggested that Aim 3, with a focus on oxygen concentration effects on stem cell differentiation, should be developed more fully.

PI Accomplishments and Potential
- Reviewers praised the candidate PI as an excellent scientist who is integrating bioengineering and stem cell approaches.

- Reviewers considered the candidate PI to be in the top tier of his/her field.

- PI is one of the leaders in developing a set of innovative cell culture techniques for pluripotent stem cells.

- The candidate has earned a high level of respect from scientific peers, who consider him/her to be a highly energetic scientist and a leader in the field.

- The candidate PI's training and letters of reference are exemplary.

- The candidate has an excellent record of funding.

- The PI has demonstrated high productivity, publishing a substantial number of articles; some reviewers noted that these primarily appeared in bioengineering journals rather than in high profile biology or biomedical journals.

Institutional Commitment and Environment
- This institutional commitment is very strong and includes adequate laboratory space, substantial start-up and equipment funds, and access to state-of-the-art core resources.

-The institution investigators and resources are outstanding, and these provide an excellent environment for the proposed research.

-Reviewers were excited by the complementary expertise of the candidate and other scientists at the institution and felt that this would provide great potential for innovation.