CIRM RESEARCH LEADERSHIP AWARDS – RFA 09-04 (Cycle 12)

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

Application #	Title	SCORE	Median	SD	Low	High	BUDGET	TIER
LA1-06920	Recapitulating development of the musculoskeletal axis in vitro with pluripotent cells	94	95	3	90	98	$5,745,859	1
LA1-06917	Generation of functional cells and organs from iPSCs	93	95	2	90	95	$6,152,065	1
LA1-06918	MicroRNA Regulation in Stem Cells, Development, and Disease	80	80	6	65	85	$5,380,705	1
LA1-06915	Epithelial progenitors and the stromal niche as therapeutic targets in lung disease	80	80	7	70	90	$4,841,830	1
LA1-06919	Molecular Imaging for Stem Cell Science and Clinical Application	77	80	5	70	85	$6,443,455	1
LA1-06916	Engineering Cardiac Tissue for Regeneration and Drug Development	75	78	10	50	85	$7,480,036	3

COMPILATION OF PROGRAMMATIC REVIEW SUMMARIES PRESENTED IN RFA 09-04 REVIEW REPORTS

Listed below are the Programmatic Discussion sections from the respective Review Reports that contained a programmatic element and are assembled here for your reference.

LA1-06915
A motion was made to recommend this application for funding. The motion carried without discussion.

LA1-06916
A motion was made to move this application into Tier 1, Recommended for Funding. It was noted that the applicant rose quickly from assistant to full professor, has many publications in her/his area of expertise and has good letters of recommendation. However, there was some concern about the narrow focus of the application. The motion failed due to a tie vote.

LA1-06917
A motion was made to recommend this application for funding. The motion carried without discussion.

LA1-06918
A motion was made to move this application into Tier 1, Recommended for Funding. The motion carried. Because more than 35% of GWG members opposed the motion, opponents have exercised their right to have that position reported to the ICOC.

Key points of the minority report are:
-uncertainty as to whether the proposed project, while having recognized merit, would be transformative or particularly relevant for the stem cell biology field.
-concern that some of the proposed approach was too reductionist in scope.

LA1-06919
A motion was made to move this application into Tier 1, Recommended for Funding. Discussion centered favorably on the additive value that the PI would bring to the existing regenerative medicine group at the sponsoring institution. There was some disagreement among the panelists regarding the potential impact of the PI's research proposal; while some felt it exemplified a series of leading-edge, possibly transformative approaches to a critical translational bottleneck (imaging stem cell-based therapies), others felt that improved MRI technologies were not a critical near-term need for the field. The motion carried.

LA1-06920
A motion was made to move this application into Tier 1, Recommended for Funding. The motion carried.

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

LA1-06915: Epithelial progenitors and the stromal niche as therapeutic targets in lung disease

Recommendation: Recommended for Funding **Final Score:** 80
Total Funds Requested: $4,841,830

Public Abstract (provided by applicant)

Chronic lung disease is an enormous societal and medical problem in California and the nation as a whole, representing the third most likely cause of death. Treatment costs were $389.2 billion in 2011 and are expected to reach $832.9 billion in 2021 according to the Milken Institute. Chronic lung diseases cover a spectrum of disorders that include pulmonary fibrosis, a disease that makes it difficult to breathe due to the accumulation of scar tissue in the lung, and chronic obstructive pulmonary disease (COPD), a disease that makes breathing difficult due to loss of critical structures that allow oxygen to enter the blood. According to Breathe California, COPD is the 4th leading cause of death in the United States and 1.6 million Californians are diagnosed with COPD. Treatment options vary by disease but are particularly ineffective for patients with COPD and fibrotic lung diseases. One fibrotic lung disease termed idiopathic pulmonary fibrosis (IPF) can only be treated by lung transplantation and this option is limited to those who meet specific age and health criteria. Without transplantation the majority of IPF patients die within three years of initial diagnosis.

Our research team being recruited to California is led by an international expert in lung stem cell biology and includes a leading physician in pulmonary fibrosis research and clinical management. Goals of research outlined in this proposal are to understand how lungs are damaged by diseases and to develop new treatment options to help prevent, arrest, or repair damage leading to improved patient health. Specifically, we will show how cells that line airspaces of the lung generate new cells that function to protect the lung from injury and facilitate gas exchange during breathing. Through this work it will be possible to determine how lung disease is caused and this will lead to new therapies that will prevent either initiation or progression of lung disease.

Statement of Benefit to California (provided by applicant)

Lung disease has an enormous societal impact. For the period from 1990-2008 chronic lower respiratory diseases were the third most likely cause of death in the US, accounting for approximately 6% of deaths and an annual rate of approximately 0.1% of the total population (NHLBI report, 2010). Lung diseases can be caused by either genetic and/or environmental factors, and are compounded by age-related declines in lung function. Poor air quality in and around major California cities are well documented and have been conservatively estimated to account for 10,000 hospital visits per year (RAND Corporation report, 2010). Ozone and particulate airborne pollutants are a significant concern due to chronic effects on lung tissue remodeling in otherwise healthy individuals. They also trigger exacerbations in patients with existing lung disease leading to more serious illness and death. Interventions can include imposing strict air quality standards and improving therapies for patients either with or who are at risk of developing lung disease. Pulmonary fibrosis in particular represents a major unmet medical need in California and lung transplant is the only effective therapy at present. Accordingly, defining mechanisms of lung fibrosis and developing cures for otherwise intractable lung diseases has the potential to significantly benefit the population of California.

This CIRM Research Leadership Award application will develop a transformative program aimed at applying new discoveries in basic mechanisms of lung disease towards development of new interventions to help patients. This will be accomplished by integrating the applicant's

expertise in lung stem cell biology and regenerative medicine with basic and translational research strengths at the destination institution. Previous work has shown that signaling interactions between epithelial progenitor cells and their associated stromal microenvironment are critical for normal development and tissue homeostasis in adulthood. These interactions are dysregulated in many lung diseases including fibrotic lung diseases, chronic obstructive pulmonary disease and asthma. This proposal will focus on fibrotic lung diseases in particular due to the poor prognosis that results from lack of effective therapies. Through identifying mediators that regulate epithelial progenitor-stromal interactions in the normal adult lung, and how changes in their activity contribute to disease, we will gain new insights into disease mechanisms and therapies. We expect that discoveries will be broadly applicable to many lung diseases and will significantly impact Californians through novel drug discoveries that improve the health and quality of life of patients with early onset or established lung disease.

Review Summary
The candidate principal investigator (PI) is a tenured, mid-career professor and an established leader in lung science whose pioneering discoveries have laid the groundwork for the nascent field of lung stem cell/lung regeneration research. The general goal of the proposed research program is to identify determinants of lung epithelial maintenance and repair so that they might be exploited for therapeutic purposes. The PI will test the hypothesis that cellular communications between epithelial progenitors and their surroundings are essential for normal tissue homeostasis and repair, and that dysregulation of these signals leads to lung disease such as idiopathic pulmonary fibrosis (IPF) and bronchiolitis obliterans syndrome (BOS). In addition, the PI plans to establish efficient methods for deriving bronchiolar and/or alveolar progenitors from human embryonic stem cells (hESC) or induced pluripotent stem cells (iPSC) for patient-specific drug screens and therapeutic applications. The applicant institution will provide support in the form of protected research time, appropriate space, access to core services, matching funds for equipment, and an expanding intellectual infrastructure in the areas of lung regenerative medicine and stem cell biology.

Research Vision and Plans
- The proposed research program addresses mechanisms of lung regeneration, which, compared to other organ systems, represents a highly understudied area of stem cell biology.

- The large amounts of data to be obtained from these studies would lead to improved understanding of the cellular and molecular mechanisms underlying lung maintenance and repair, affording a unique opportunity for therapeutic innovation.

- Chronic lung diseases represent a significant medical burden for both California and the nation as a whole. In particular, IPF and BOS are poorly understood and untreatable. New therapeutic options are sorely needed to address this critical unmet need.

- The experimental approaches draw heavily on routine laboratory techniques that, while not particularly innovative, are technically feasible and applied to new research areas.

- While the research plan is very detailed, there is little discussion of how outcomes would be analyzed, or how pitfalls would be addressed. Similarly, there were few details provided as to how data from the different aims would be integrated.

- Some reviewers questioned the extent to which the data from murine studies would prove relevant to the human condition and advised the applicant to explore additional, more creative options for testing human cells in the context of a living organism.

PI Accomplishments and Potential
- Reviewers considered the PI to be perhaps the top lung stem cell researcher in the world today, having pioneered a number of key discoveries in the pulmonary field. His/her

achievements have been published in respected journals and have proven highly reproducible by others.

- The PI's laboratory has repeatedly brought new technologies from other fields into the lung research arena for the first time, thereby creating many of the essential tools and reagents that have proven enabling for his/her seminal work.

- The PI's leadership in the broader lung community is evidenced by continued participation in study sessions for peer review as well as organization of national meetings and conferences.

- While reviewers disagreed over the extent to which the PI's success in the specialized area of lung science would translate to outstanding contributions in stem cell biology per se, many were convinced the PI's work would have significant impact on the understanding of lung regeneration.

Institutional Commitment and Environment
- Reviewers considered the institutional commitment to be outstanding, as evidenced by extremely positive letters of support as well as matching funds and additional resources for relocation of the PI's laboratory.

- The applicant organization is a well-regarded research institution with a continued and growing presence in stem cell research and regenerative medicine.

- In addition to providing an excellent research environment, the applicant institution has recruited the PI's key collaborator, an established lung scientist with complementary expertise in IPF and related areas.

PROGRAMMATIC DISCUSSION
A motion was made to recommend this application for funding. The motion carried without discussion.

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

LA1-06916: Engineering Cardiac Tissue for Regeneration and Drug Development

Recommendation: Not Recommended for Funding **Final Score:** 75
Total Funds Requested: $7,480,036

Public Abstract (provided by applicant)

The 'valley of death' in scientific parlance refers to the time period where biomedical discovery in the laboratory fails to result in a cure for a disease. While the last decade has seen extraordinary developments in regenerative biology, the translation to regenerative medicine will require successful negotiation of the 'valley of death.' In most cases, the scientific field has yet to prepare a model of stem cell manufacturing that will meet the Food and Drug Administration's requirement of Good Manufacturing Practices and produce sufficient quantities of quality stem cells to meet patient need. This critical step requires the development of manufacturing technology and quality control standards for stem cell production. Using cardiac muscle cells as our model, this proposed project will develop these standards and practices to enable industry to meet regulatory requirements and produce safe and effective cures for heart disease. These lessons learned will be broadly applicable to quality production of stem cells for a broad range of pathological conditions which warrant a regenerative therapeutic option.

Statement of Benefit to California (provided by applicant)

Protecting California's investment in Regenerative Medicine includes prudent development of the techniques and methods required to meet regulatory requirements and the development of safe and effective cell-based therapeutics. The collapse of Geron Corp's stem cell development program and the difficulties facing current stem cell manufacturers suggest that the lack of a defined set of Quality Control standards and methods for cardiac stem cell production are representative of a broader problem that could impede efforts to exploit bench discoveries, traverse the 'valley of death,' and industrialize the production of cellular therapeutics. In our proposed study, we will use stem cell-derived cardiac muscle cells as a model to develop protocols and standards for determining cell quality and their applicability for disease models in drug discovery and as cellular therapeutics in the clinical environment. The cardiac stem cell quality index we will develop benefits the State of California by facilitating safe and effective therapeutics for ailing Californians and enabling the California stem cell industry with the manufacturing practices required to meet regulatory requirements and achieve market dominance.

Review Summary

The candidate principle investigator (PI) is a recently promoted full professor recognized in the bioengineering field for her/his work on biomaterials and tissue mimetics. The goal of the proposed research is to develop scalable methods and quality standards for the GMP (Good Manufacturing Practices)-compliant derivation of mature and fully functional human cardiomyocytes from human pluripotent stem cells (PSC). The PI proposes to achieve this by optimizing use of biomaterials in addition to soluble factors to mimic the cellular environment in heart muscle. The resulting production process should allow consistent production of sufficient quantities of well-characterized cells to be used for regenerative medicine purposes.

Research Vision and Plans

- While the ability to manufacture functional cardiomyocytes at scale was felt to be a significant challenge in the field, it was felt that developing GMP quality standards for production of cardiomyocytes was not a key bottleneck for developing these therapies.

- The proposed work didn't seem particularly innovative since the general approaches to be taken are commonly used by others. Not enough information was given to assess whether the applicant would approach the problems in novel ways.

- It was felt that understanding the effects of mechanical stimuli on cardiomyocytes and heart function is an important area of study that could lead to insights about heart disease as well as ability to manufacture cells at scale. It was acknowledged that the applicant is an important contributor in this area.

PI Accomplishments and Potential
- The applicant has multiple publications in high impact journals in both engineering and biomedical sciences, has generated substantial independent funding, and manages a large laboratory group.

- The applicant is not widely recognized as a leader in stem cell research or regenerative medicine, but is known within the field of biomedical engineering for her/his experience in the development of systems to create tissue mimetic structures.

- Reviewers noted that the applicant has shown that she/he is a big thinker who comes up with unique, clever and creative ideas and would have a positive impact on the applicant institution.

- While some reviewers were impressed with the leadership potential of the applicant, others felt that most of her/his scientific track record is as a member of a team, rather than a leader.

- Recognized leaders in the fields of cardiac regenerative medicine and tissue engineering acknowledge the impact the applicant has already had on the field, her/his capacity for innovative thinking and her/his potential to contribute to the development of transformative technologies in the field of regenerative medicine.

Institutional Commitment and Environment
- The institutional commitment was considered to be adequate, although not overly generous, including laboratory space with most major equipment provided and startup support with matching funds for new laboratory purchases. In addition, the applicant would have access to relevant core facilities.

- The rich environment at the applicant institution was viewed as likely to be beneficial to the principal investigator and would provide opportunities to take his/her current research program in new directions.

- While the potential for complementarity with other investigators working at the applicant institution was recognized, reviewers were disappointed that specific plans for collaborations were not made clear in the application or institutional support letter.

PROGRAMMATIC DISCUSSION
A motion was made to move this application into Tier 1, Recommended for Funding. It was noted that the applicant rose quickly from assistant to full professor, has many publications in her/his area of expertise and has good letters of recommendation. However, there was some concern about the narrow focus of the application. The motion failed due to a tie vote.

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

LA1-06917: Generation of functional cells and organs from iPSCs

Recommendation: Recommended for Funding **Final Score:** 93
Total Funds Requested: $6,228,068

Public Abstract (provided by applicant)

The development of induced pluripotent stem cell (iPSC) technology may be the most important advance in stem cell biology for the future of medicine. This technology allows one to generate a patient's own pluripotent stem cells (PSCs) from skin or blood cells. iPSCs can then be reprogrammed to multiply and produce high quality mature cells for cell therapy. Because iPSCs are derived from a patient's own cells, therapies that use them will not stimulate unwanted immune reactions or necessitate lifelong immunosuppression. If organs can be generated from iPSCs, many patients with organ failure awaiting transplants will be helped. The goal of this project is to further develop iPSC technology to bring about personalized regenerative medicine for treating intractable diseases such as cancers, viral infections, genetic blood disorders, and organ failure. Specifically, we would like to establish three major core programs for generating from iPSCs: personalized immune cells; an unlimited supply of blood stem cells; and functional organs.

First, we will generate iPSC-derived immune cells that kill viruses and cancer cells. Current immunotherapy uses immune cells that are exhausted (have limited ability to function and proliferate) after they multiply in a test tube. To supply active nonexhausted immune cells, iPSCs will be generated from a patient's immune cells that target tumor cells and infections and then redifferentiated to mature immune cells with the same targets.

Second, we aim to develop iPSC technology to generate blood stem cells that replenish all blood cells throughout life. Harvesting blood stem cells from a leukemia patient for transplantation back to the patient after chemotherapy and radiation has been challenging because few blood stem cells can be harvested and may be contaminated with cancer cells. Alternatively, transplanting blood stem cells from cord blood or another person requires genetic matching to prevent immune reactions. However, generating blood stem cells from a patient's iPSCs may avoid contamination with cancer cells, immune reactions, and the need to find a matched donor. Furthermore, we aim to generate iPSCs from a patient with a genetic blood disease, correct the genetic defect in the iPSCs, and generate from these corrected iPSCs healthy blood stem cells that may be curative when transplanted back into the patient.

Lastly, we will try to generate from iPSCs not just mature cells, but organs for transplantation, to potentially address the tremendous shortage of donated organs. In a preliminary study, we generated preclinical models that could not develop pancreases. When we injected stem cells into these models, they developed functional pancreases derived from the injected cells and survived to adulthood. We hope that within 10 years, we will be able to provide a needed organ to a patient by growing it from the patient's own PSCs in a compatible animal.

Statement of Benefit to California (provided by applicant)

Cancer is the second leading cause of death, accounting for 24% of all deaths in the U.S. Nearly 55,000 people will die of the disease--about 150 people each day or one of every four deaths in California. In 2012, nearly 144,800 Californians will be diagnosed with cancer. We need effective treatment to cure cancer.

End-stage organ failure is another difficult disease to treat. Transplantation of kidneys, liver, heart, lungs, pancreas, and small intestine has become an accepted treatment for organ failure. In California, more than 21,000 people are on the waiting lists at transplant centers. However, one in three of these people will die waiting for transplants because of the shortage of donated organs. While end-stage renal failure patients can survive for decades with hemodialysis treatment, they suffer from high morbidity and mortality. In addition, the high medical costs for increasing numbers of dialysis patients is a social issue. We need to find a way to increase organs that can be used for transplantation. In our proposed projects, we aim to use iPSC technology and recent discoveries to develop new methods for treating cancers, viral infections, and organ failure. More specifically, we will pursue our recent discoveries using iPSCs to: (1) multiply person's T cells that specifically target cancers and viral infections; (2) generate normal blood-forming stem cells that can be transplanted back into a patient to correct a blood disease (3) regenerate tissues and organs from a patient's cells for transplantation back into that patient.

These projects are likely to benefit the state of California in several ways. Many of the methods, cells, and reagents generated by this research will be patentable, forming an intellectual property portfolio shared by the state and the institutions where the research is performed. The funds generated from the licensing of these technologies will provide revenue for the state, will help increase hiring of faculty and staff (many of whom will bring in other, out-of-state funds to support their research), and could be used to ameliorate the costs of clinical trials--the final step in translation of basic science research to clinical use. Most importantly, this research will set the platform for stem cell-based therapies. Because tissue stem cells are capable of lifelong self-renewal, these therapies have the potential to provide a single, curative treatment. Such therapies will address chronic diseases that have no cure and cause considerable disability, leading to substantial medical expenses and loss of work. We expect that California hospitals and health care entities will be first in line for trials and therapies. Thus, California will benefit economically and the project will help advance novel medical care.

Review Summary
The goal of this proposal is to enable human induced pluripotent stem cell (iPSC)-based cell therapies in three specific areas. The applicant intends to work out methods for the generation of iPSC-derived immune cells to eliminate cancer cells and viruses, for the generation of iPSC-derived blood-forming (hematopoietic) stem cells (HSC) to overcome limitations of current methods of bone marrow transplants, and for the generation of whole replacement organs from iPSC.

Research Vision and Plans
- The proposed research is of the highest significance. It is directed toward three key areas of high translational importance in stem cell biology, addressing several unmet clinical needs. All three proposed projects align well with CIRM's mission.

- All three proposed projects involve novel approaches and are indicative of the PI's vision and translational insight.

- The most significant project is the generation of human autologous organs through a unique and very innovative approach that addresses many shortcomings of in vitro organ generation. If successful, this would revolutionize tissue engineering and provide autologous organs for those in need.

- The proposed strategy for the generation of autologous HSC is unique and highly significant. However, reviewers noted that the applicant did not address a limitation of autologous HSC transplants, the fact that they do not provide important anti-tumor responses inherent in allogeneic bone marrow transplantation.

- The proposed strategy for generating autologous immune cells against cancers is based on an interesting concept and would be paradigm changing. However, the proposal did not provide context regarding other approaches currently under investigation to overcome T-cell exhaustion.

- Although, as acknowledged by the applicant, these projects will require a relatively long time before reaching clinical translation, the PI has accomplished much already and has the skills to push these projects forward. All three projects are progressing with promising data and evidence of proof of principle, and the PI seems poised to succeed where others have failed.

PI Accomplishments and Potential
- The PI is a preeminent stem cell biologist with an extraordinary track record of innovation in stem cell biology and numerous high impact papers in high profile journals.

- Throughout his/her career, the applicant has consistently demonstrated innovative thinking and creativity with remarkable results.

- The PI's seminal contributions have been recognized internationally.

- The applicant has an outstanding record of both academic and scientific leadership.

- Although the PI is a relatively senior scientist, his/her accomplishments appear to be on an upward trajectory and his/her greatest impact in the fields of cellular therapeutics and tissue/organ engineering is yet to be appreciated.

Institutional Commitment and Environment
- The applicant institution has made a strong commitment to the applicant's recruitment.

- The applicant will be recruited as a full tenured professor, with significant research-protected time. Appropriate start-up, salary, renovation and equipment funds will be provided, as well as a large lab space in a CIRM-funded Major Facility and other adequate support space. Importantly, the PI will have access to an extensive list of shared resources and cutting-edge technologies, many of which were developed at the applicant institution.

- The PI's recruitment is closely aligned with the goals of the Stem Cell Institute within the applicant institution. His/her appointment will complement the existing faculty very well.

- The research environment consists of one of the most outstanding stem cell institutes in the world and offers excellent collaborative opportunities. It has tremendous draw for recruitment of top level scientists and trainees.

PROGRAMMATIC DISCUSSION
A motion was made to recommend this application for funding. The motion carried without discussion.

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

LA1-06918: MicroRNA Regulation in Stem Cells, Development, and Disease

Recommendation: Recommended for Funding **Final Score:** 80
Total Funds Requested: $5,380,705

Public Abstract (provided by applicant)

Pluripotent embryonic stem cells (ESCs) have the remarkable capacity to differentiate into any specialized cell type in the human body and are therefore of potential therapeutic value for neurodegenerative diseases, spinal cord injury, diabetes, heart disease, and numerous other degenerative diseases. Moreover, several of these same stem cell pathways are hyperactivated in tumorinitiating/ cancer stem cells. Therefore identifying novel gene regulatory pathways required for both the growth of these unique cells, as well as their differentiation into specialized cell types is key to developing novel therapeutic approaches for the treatment of degenerative disease and cancer. Our goal is to further develop a specialized, high-impact research program focused on understanding the mechanisms of gene regulation in pluripotent stem cells. With this information, we will design and develop assays to identify new drugs that regulate the differentiation of stem cells into specialized cell types and that suppress tumor growth by eradicating tumor-initiating/cancer stem cells. Our comprehensive and integrated research program will maximize the likelihood of realizing our goal of identifying chemical compounds that can specifically control cellular fates for therapeutic use.

Statement of Benefit to California (provided by applicant)

To fully benefit from the potential of regenerative medicine to treat injury and degenerative diseases we need to be able to effectively control and manipulate cellular fates on demand. This will require the successful translation of basic knowledge gained from understanding the molecular mechanisms controlling stem cell differentiation into specific cell fates, such as specialized cells of organs (e.g. insulin producing pancreatic beta cells) or specific types of neurons.

In order to more effectively accomplish this, it will be necessary to understand the molecular circuitry that operates in stem cells and bestows these remarkable cells with their unique ability to become any cell type. My laboratory has been successful in identifying novel stem cell pathways that regulate this fundamental capacity of stem cells and that can be targeted therapeutically. In the short term, the benefit to California will be the relocation of my specialized research program to the state, and, with the support of CIRM, the further development of this world-class, high-impact research program, which will perfectly complement the existing research strengths in genomics, RNA biology, and stem cells at the University. In the longer term, the citizens of California will benefit from my laboratory's efforts aimed at the identification of new drugs that will target these crucial, stem cell pathways and stimulate the body's own repair mechanisms. We anticipate that these new drugs will heal diseased tissues and organs previously considered irreparable. Moreover, our research has the potential of identifying new chemotherapeutic agents that target cancer stem cells, a recently identified cell that is likely to be responsible for incidences of tumor recurrence following treatment. The State of California will benefit by being at the heart of these clinical advances and the resulting economic impact as they translate to the market.

Review Summary

The candidate principal investigator (PI) is an early- to mid-career scientist whose research focuses on the role of microRNAs (miRNA) in stem cells, developmental processes and disease. The PI has already made major contributions to the field by identifying and

characterizing a number of key regulators of miRNA function. The planned research program will focus on understanding mechanisms underlying the pluripotency and differentiation of embryonic stem cells (ESC) by finding novel miRNA regulators and characterizing their molecular and cellular roles. The PI will further identify small molecule modulators of miRNA dynamics and explore their use in manipulating ESC regulatory pathways and their potential for therapeutic approaches involving alteration of stem cell fate.

Research Vision and Plans
-The proposed research program addresses an important but poorly studied topic: the translational control of pluripotency.

-The proposed work is likely to have high significant impact with implications for both ESC biology and cancer biology.

-The approach is innovative and relies on state-of-the-art techniques.

-A concern was expressed that the research program is too reductionist and narrowly focused and might lack adequate relevance to human ESC differentiation. A differing view was also expressed that the work could be transformative.

PI Accomplishments and Potential
-Reviewers considered the candidate's accomplishments and overall potential as outstanding.

-The PI has made seminal contributions to an understanding of miRNA regulation.

-The PI has been extremely productive, publishing a number of important articles in high impact journals including Cell, Nature and Science.

-The candidate is well funded with research grants from National Institute of Health and the American Cancer Society.

-The PI has demonstrated leadership by service on editorial boards and grant review committees, participation in scientific organizations and directing a major graduate core course.

-The PI is a recognized leader in the field of stem cell research and has received a number of honors and awards.

-Letters of recommendation were generally outstanding, including a particularly strong one from a Nobel laureate, although one letter seemed rather tepid.

Institutional Commitment and Environment
-The institutional commitment is substantial and appears to be conducive to a successful and productive career for the PI.

- The candidate's research fits well with the established programs at the applicant institution.

-The PI's projected leadership role should be a boost for stem cell research at the applicant institution.

PROGRAMMATIC DISCUSSION
A motion was made to move this application into Tier 1, Recommended for Funding. The motion carried. Because more than 35% of GWG members opposed the motion, opponents have exercised their right to have that position reported to the ICOC.

Key points of the minority report are:
-uncertainty as to whether the proposed project, while having recognized merit, would be transformative or particularly relevant for the stem cell biology field.
-concern that some of the proposed approach was too reductionist in scope.

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

LA1-06919: Molecular Imaging for Stem Cell Science and Clinical Application

Recommendation: Recommended for Funding **Final Score:** 77
Total Funds Requested: $6,443,455

Public Abstract (provided by applicant)

Stem cells offer tremendous potential to treat previously intractable diseases. The clinical translation of these therapies, however, presents unique challenges. One challenge is the absence of robust methods to monitor cell location and fate after delivery to the body. The delivery and biological distribution of stem cells over time can be much less predictable compared to conventional therapeutics, such as small-molecule therapeutic drugs. This basic fact can cause road blocks in the clinical translation, or in the regulatory path, which may cause delays in getting promising treatments into patients. My research aims to meet these challenges by developing new non-invasive cell tracking platforms for emerging stem cell therapies. Recent progress in magnetic resonance imaging (MRI) has demonstrated the feasibility of non-invasive monitoring of transplanted cells in patients. This project will build on these developments by creating next-generation cell tracking technologies with improved detectability and functionality. Additionally, I will provide leadership in the integration of non-invasive cell tracking into stem cell clinical trials. Specifically, this project will follow three parallel tracks. (1) The first track leverages molecular genetics to develop new nucleic acid-based MRI reporters. These reporters provide instructions to program a cell's innate machinery so that they produce special proteins with magnetic properties that impart MRI contrast to cells, and allow the cells to be seen. My team will create neural stem cell lines with MRI reporters integrated into their genome so that those neural stem cell lines, and their daughter cells, can be tracked days and months after transfer into a patient. (2) The second track will develop methods to detect stem cell viability in vivo using perfluorocarbon-based biosensors that can measure a stem cell's intracellular oxygen level. This technology can potentially be used to measure stem cell engraftment success, to see if the new cells are joining up with the other cells where they are placed. (3) The third project involves investigating the role that the host's inflammatory response plays in stem cell engraftment. These studies will employ novel perfluorocarbon imaging probes that enable MRI visualization and quantification of places in the body where inflammation is occurring. Overall, MRI cell tracking methods will be applied to new stem cell therapies for amyotrophic lateral sclerosis, spinal cord injury, and other disease states, in collaboration with CIRM-funded investigators.

Statement of Benefit to California (provided by applicant)

California leads the nation in supporting stem cell research with the aim of finding cures for major diseases afflicting large segments of the state's population. Significant resources are invested in the design of novel cellular therapeutic strategies and associated clinical trials. To accelerate the clinical translation of these potentially live saving therapies, many physicians need method to image the behavior and movement of cells non-invasively following transplant into patients. My research aims to meet these challenges by developing new cell tracking imaging platforms for emerging stem cell therapies. Recent progress in magnetic resonance imaging (MRI) has demonstrated the feasibility of non-invasive monitoring of transplanted cells in patients. This project will build on these developments by leading the integration of MRI cell tracking into stem cell clinical trials and by developing next-generation technologies with improved sensitivity and functionality. Initially, MRI cell tracking methods will be applied to new stem cell therapies for amyotrophic lateral sclerosis and spinal cord injury. In vivo MRI cell tracking can accelerate the process of deciding whether to continue at the preclinical and early clinical trial stages, and can facilitate smaller, less costly trials by enrolling smaller patient

numbers. Imaging can potentially yield data about stem cell engraftment success. Moreover, MRI cell tracking can help improve safety profiling and can potentially lower regulatory barriers by verifying survival and location of transplanted cells. Overall, in vivo MRI cell tracking can help maximize the impact of the State's investment in stem cell therapies by speeding-up clinical translation into patients. These endeavors are intrinsically collaborative and multidisciplinary. My project will create a new Stem Cell Imaging Center (SCIC) in California with a comprehensive set of ways to elucidate anatomical, functional, and molecular behavior of stem cells in model systems. The SCIC will provide scientific leadership to stem cell researchers and clinicians in the region, including a large number of CIRM-funded investigators who wish to bring state-of-the-art imaging into their clinical development programs. Importantly, the SCIC will focus intellectual talent on biological imaging for the state and the country. This project will help make MRI cell tracking more widespread clinically and position California to take a leadership role in driving this technology. An extensive infrastructure of MRI scanners already exist in California, and these advanced MRI methods would use this medical infrastructure better to advance stem cell therapies. Moreover, this project will lead to innovative new MRI tools and pharmaceutical imaging agents, thus providing economic benefits to California via the formation of new commercial products, industrial enterprises, and jobs.

Review Summary

The candidate principal investigator (PI) is a relatively early career academic scientist with an active research lab and a demonstrated leadership role in directing core facilities for medical imaging. The PI's focus has been on developing new magnetic resonance imaging (MRI) methods and tools to visualize cellular and molecular processes, and to track cells in tissue with increasing sensitivity. The candidate is a founder, board member, and scientific advisor for a biotechnology company that was created to further develop and commercialize his/her inventions. The PI's research proposal focuses on the development of new tools to monitor cell location, fate and survival after delivery into the body, major challenges in the path toward clinical translation of stem cell-derived therapeutics. The applicant plans to develop new, non-invasive cell tracking methods for MRI and to collaborate with CIRM-funded investigators to incorporate these new methods into preclinical and clinical studies of neural stem cells for amyotrophic lateral sclerosis (ALS), spinal cord injury and other disease states. The sponsoring institution has recently built a comprehensive, multi-modal molecular imaging core facility for which the candidate will provide scientific direction and oversight. The institution will provide a full-time faculty position, matching funding and dedicated blocks of effort and equipment usage in the imaging core to support the PI's research on this award.

Research Vision and Plans

- Reviewers described the PI's research as highly innovative, focused on a very important area that spans across all applications of stem cell regenerative medicine, and potentially transformative for researchers in California.

- Reviewers were enthusiastic about the PI's plans to train new users on state-of-the-art equipment and methods and to collaborate with researchers to facilitate progress on stem cell-based projects already under CIRM-funded development.

- While reviewers expressed interest in the research projects proposed by the applicant, there was some disagreement about whether improvements in MRI technology were needed to advance the clinical translation of stem cell-based therapeutics.

PI Accomplishments and Potential

- The applicant is viewed as an authority in development of MRI reporters and as an emerging leader in stem cell research. His/her work is viewed as highly innovative and widely applicable, as evidenced by publications and collaborations in a number of disciplines, including physics, developmental biology, neuroscience, immunology and clinical translation.

- Previous inventions by the PI have become widely used in the MRI field. Additional work proposed by the PI to develop tools for analysis of cells at a single-cell level was viewed as likely to advance the field significantly.

- The PI has successfully established an independent research program and concurrently directs an imaging service core facility.

- The PI has published extensively, has received considerable press coverage for his/her inventions and innovations, and is invited frequently as a seminar presenter (both nationally and internationally). While some reviewers noted there were relatively few publications in the highest profile journals, others commented that the publication record was appropriate for a leader in the development of new MRI technologies and tools. It was also noted that the PI is an inventor on 8 patents, which is an uncommon accomplishment for an academic scientist.

- While the PI has received funding from the National Institutes of Health (NIH) and industry grants, and is the Project Leader on an active NIH Program Project Center Grant, some reviewers expressed concern that much of the PI's funding was ending soon and/or up for renewal.

- Reviewers commented that the letters of support for the PI were strong, but some expected inclusion of letters from a broader range of individuals.

Institutional Commitment and Environment

- The PI would join an active regenerative medicine group that has a focus on imaging stem cells and would assume strategic leadership of an existing imaging core facility. Reviewers predicted that both the PI and the team would be strengthened by the collaborative environment, with resulting progress in cell tracking capabilities made across multiple platforms.

- The molecular imaging facilities, which the PI would direct, and have dedicated access to, have been recently completed and provide modern research equipment and extensive infrastructure for preclinical and clinical applications. The PI would have access to multiple core facilities for nuclear magnetic resonance (NMR), pluripotent stem cell culture and preclinical research. In addition, the institution has provided adequate office and laboratory space.

- It was not clear from the application if the institution's offer included the purchase and relocation of the PI's current MRI equipment.

- Some reviewers judged the startup package and commitment provided by the institution to be adequate but not overly impressive.

PROGRAMMATIC DISCUSSION

A motion was made to move this application into Tier 1, Recommended for Funding. Discussion centered favorably on the additive value that the PI would bring to the existing regenerative medicine group at the sponsoring institution. There was some disagreement among the panelists regarding the potential impact of the PI’s research proposal; while some felt it exemplified a series of leading-edge, possibly transformative approaches to a critical translational bottleneck (imaging stem cell-based therapies), others felt that improved MRI technologies were not a critical near-term need for the field. The motion carried.

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

LA1-06920: Recapitulating development of the musculoskeletal axis in vitro with pluripotent cells

Recommendation: Recommended for Funding **Final Score:** 94
Total Funds Requested: $5,745,859

Public Abstract (provided by applicant)
Muscle dystrophies are a family of degenerative diseases in which groups of muscles progressively degenerate with age. Duchenne Muscular Dystrophy is the most common muscular dystrophy (affecting 1 in 3,500 boys) and one of the most common human genetic diseases. The number of patients is estimated at 26,500 in US and Europe with an average life expectancy of 20-30 years. Duchenne muscular dystrophy is caused by mutations in the dystrophin gene, the largest gene of the human genome, located on the X chromosome. These mutations prevent the production of a functional protein and lead to muscle weakness and wasting. In the early stages of the disease, degeneration stimulates the regeneration of new fibers, a physiological response that counterbalances fiber loss and maintains normal muscle function. As the disease progresses, regeneration capacity slows down leading to the first clinical symptoms. There are currently no cures for human dystrophies and the only effective drugs target the symptoms of disease without slowing its fatal course. Restoring muscle populations by cell therapy is a promising approach to cure the disease. Such an approach involves grafting healthy muscle precursors to reconstitute functional muscle. While muscles possess adult stem cells called satellite cells that in principle could be used for grafting, these are far too limited in number for any therapeutic application. We propose to use an alternative strategy. First, patient cells will be reprogramming to a pluripotent state. Cells will then be genetically corrected and differentiated into muscle precursors prior to being grafted in patients to regenerate the lost muscles. This method should allow the production of large amounts of healthy immuno-compatible muscle progenitor cells.

A first important bottleneck in the development of such therapies is the development of protocols to differentiate stem cells cells into muscle precursors. While the in vitro differentiation of cardiac cells or neurons from stem cells can be easily achieved today, there is currently no protocol for the efficient differentiation of muscle cells. Thus a major aim of this project will be to develop protocols to differentiate stem cells into muscle precursors. My laboratory has been studying the early stages of muscle and vertebrae differentiation for many years and we will use our knowledge of these processes to recapitulate the early development of these lineages in stem cells to produce the muscle precursors. This will constitute an essential step in the development of cell therapies for muscular dystrophy. In addition, since muscles and vertebrae share a common origin in the embryo, the protocols that we develop for the production of muscle precursors could also be used for the production of vertebral precursors. We also propose to generate vertebral precursors from healthy and diseased patients to study diseases of the human spine such as congenital scoliosis.

Statement of Benefit to California (provided by applicant)
Muscle dystrophies are a family of degenerative diseases in which groups of muscles progressively degenerate with age. Duchenne Muscular Dystrophy (DMD) is the most common muscular dystrophy (affecting 1 in 3,500 boys) and one of the most common human genetic diseases. The number of DMD patients is estimated at 26,500 in US and Europe. The pathology is very severe, with an average life expectancy of 20-30 years. In early stages, muscle degeneration stimulates the regeneration of new fibers, a physiological response that counterbalances fiber loss and maintains normal muscle function. As the disease progresses

the regeneration capacity slows, leading to the first clinical symptoms.

For this CIRM award, I propose to begin to develop new approaches for cell therapy for Duchenne muscular dystrophy. Such protocols once established should allow the production of healthy muscle precursor cells that could be safely grafted to restore muscle function. A first roadblock for the development of such therapies lies in the efficient production of human muscle cells in vitro from pluripotent precursors, which has not been reported yet. We intend to use our expertise of muscle embryonic development to recapitulate these processes in culture to produce large amounts of muscle precursors for grafting in patients. The strategies developed will also permit studies of the early stages of musculoskeletal axis development in humans, of which virtually nothing is known today. This will allow understanding of the pathology of diseases of the spine such as congenital scoliosis.

There is no cure for DMD (as well for other dystrophies in general) and current treatments are limited to palliative care, mainly consisting of supportive care to control the onset of symptoms, slow disease progression, and prevent the cardiac, respiratory, and orthopedic complications caused by the disease. Muscular dystrophies represent a heavy social burden due to the very significant medical costs necessary to care for the affected children. The successful development of stem-cell based therapies will place the state of California in a leading position for treatment of muscle dystrophies and diseases of the musculoskeletal axis in general. These advances could improve the treatment of diseases that affect the people of California, potentially reducing morbidity, mortality, and health care costs. Advances in our understanding of muscular dystrophies could also lead to the founding of new biotechnology companies that create high-paying jobs and economic development for California. Finally, the point of CIRM Leadership Awards 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 candidate principal investigator (PI) is an established developmental biologist leading a research program focused on the early development of skeletal muscle and the spine. The proposed research will build upon the applicant's previous work to generate in vitro systems of muscle and vertebral development using mouse and human pluripotent cells. These systems will be used to improve differentiation protocols, understand human development and explore disease mechanisms. The PI proposes to focus research efforts on scoliosis, a congenital disease of the spine, and muscular dystrophy using a variety of pluripotent cell lines, including patient-derived induced pluripotent stem cells (iPSCs).

Research Vision and Plans
- Reviewers had no doubt that this research program will provide significant contributions to the field of stem cell biology. The PI brings a developmental biology perspective to the challenges of stem cell translation that may be critical for success.

- The plan to develop in vitro model systems will provide unique tools for studying not only human development but also scoliosis and muscular dystrophy. Improvement in differentiation protocols for skeletal muscle could have an important translational impact.

- There was some concern regarding the PI's relative lack of experience with pluripotent stem cells and translational research but agreement that his/her work will have significant translational impact.

PI Accomplishments and Potential

- The PI is an extraordinarily talented scientist and has made fundamental discoveries that have revolutionized the field. One of these was recently cited by the journal Nature as one of the 24 most important discoveries in developmental biology over the past 100 years.

- The letters of support from world-class scientists are full of superlatives and unequivocal praise for the PI.

- The PI has spent twenty years defining the field of musculoskeletal development and his/her expertise and accomplishments are close to unrivaled in that field.

Institutional Commitment and Environment

- The institutional commitment is outstanding and beyond reproach. The institution is clearly doing everything possible to attract this candidate.

- The institution will provide the PI with generous start-up funds, space and resources to recruit additional investigators.

- The institution is one of the top medical centers in the country and has been successful in attracting top talent. The PI's research program will fit seamlessly with those of his/her new colleagues.

PROGRAMMATIC DISCUSSION

A motion was made to move this application into Tier 1, Recommended for Funding. The motion carried.