Application: CL1-00500-1

Title: Shared viral vector facility for genetic manipulation of human ES cell

Public Abstract:

Human ES (hES) cells offer the opportunity to be converted into replacement tissues for diseased organs and provide cures for diseases like Parkinson's, diabetes, and a host of neurological disorders. Unfortunately due to political considerations, scientific space containing equipment and other resources provided by the federal government are off limits for work on unapproved hES cell lines. Space where unimpeded hES cell work can be carried out is a major limitation for many scientists at our institute to initiate scientific inquiry in the very exciting field of regenerative medicine. We are applying for funds for a Shared Research Laboratory Grant to work on non-federal government-approved hES cells, which are superior to the approved hES cell lines. Eighteen faculty here have no laboratory space in which to do research in hES cells. We are requesting funds to renovate and equip ~2,000 sq ft of independently-operated, stand-alone space which will include laboratory space for generating lentiviral vectors (LV) capable of delivering genes and/or small interfering RNA (siRNA) to manipulate hES cells, and tissue culture facilities to grow and propagate non-NIH approved hES cell lines. To study and to induce differentiation of hES cells to different lineages we will require the availability of tools that activate or suppress gene expression. Furthermore to correct a genetic defect, for instance a defective insulin gene that leads to type I diabetes, one needs to introduce a functional insulin gene in the regenerated pancreas from the ES cells of a diabetic patient. If the introduced gene is not integrated in the genome, it will be lost in the subsequent progeny. Thus the need for a delivery vehicle that will become part and parcel of the chromosome in both the progeny cells and the self-renewing cells. We have developed delivery vehicles based on retro- and lentiviruses that can safely and efficiently deliver and transcribe genes in both the embryonic and adult stem cells. We believe that we can provide such vectors to all the stem cell researchers in the neighboring institutions working on CIRM related hES cell projects, which will not only be cost effective, but accelerate the pace of science in the exciting field of hES cells. We plan to hire a full-time core director and 3 research assistants who will be responsible for setting up and maintaining the stem cell facility and managing the core facility for generating viral vector. We will offer a hands-on laboratory course to all participants in CIRM related research to generate retro- and LV, safety associated with use of these vectors and state-of-the-art methods to utilize hES cells. We hope to train the next generation of human stem cell biologists who will play an essential role in bringing the fruits of regenerative medicine to the people of California and the world.

Statement of Benefit to California:

Human embryonic stem (hES) cells offer the opportunity to be converted into replacement tissues for diseased organs and provide cures for diseases like Parkinson's, diabetes, and a host of neurological disorders. To realize the potential of this revolutionary concept, scientists must understand the basic mechanisms of how ES cells can become a liver, pancreatic cell, muscle, or neuron. What are the signals that trigger differentiation to a specific cell lineage and what molecular events must transpire to allow self-renewal of the ES cells? Eighteen faculty here wish to pursue answers to these fundamental questions. Several scientists want to understand the maintenance and self-renewal capacity of hES cells. Other investigators are proposing ways to induce hES cells to spinal chord or dopaminergic neurons. Converting hES cells to a variety of cell types will require genetic manipulation; therefore we are proposing the generation of delivery vehicles (vectors) that can be used to introduce or inactivate genes into hES cells. Because most of the scientists here do not have a facility to work on non-federally funded hES cell lines, we are requesting funds to build such a facilty. We believe that scientific work carried on hES cells will help to cure diseases like Parkinson's, Lou Gehrig's disease, and diabetes. The work proposed here will lead to establishing biotech companies in California to expand basic research into products thereby not only improving the health of Californians, but also become a significant economic engine. The facility we are proposing will provide gene delivery vehicles to scientists from neighboring institutions working with CIRM funds that will be cost effective and establish collaborations. The facility will also train the next generation of stem cell biologists to continue this very important scientific work and keep California in the forefront of biomedical research.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Application: CL1-00501-1

Title: North Bay CIRM Shared Research Laboratory for Stem Cells and Aging

Public Abstract:

Age-related diseases of the nervous system are major challenges for biomedicine in the 21st century. These disorders, which include Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and stroke, cause loss of neural tissue and functional impairment. Currently, there is no cure for these devastating neurological disorders. A promising approach to the treatment of age-related neurological disorders is cell therapy, i.e., transplantation of nerve cells into the brain or spinal cord to replace lost cells and restore function. Work in this field has been limited however, due to the limited availability of cells for transplantation. For example, cells from 6-10 human fetuses obtained 6-10 weeks post-conception are required for one patient with Parkinson's disease to undergo transplantation.

Human embryonic stem cells (hESCs) offer a potentially unlimited source of any cell type that may be required for cell replacement therapy, due to their remarkable ability to self-renew (they can divide indefinitely in culture) and to develop into any cell type in the body. In this proposal, we will build out approximately 3400 square feet of shared laboratory space within our existing research facility for hESC research, as well as approximately 2400 square feet for classroom facilities dedicated to training in hESC culture and manipulation. We seek to understand how hESCs differentiate into authentic, clinically useful nerve cells and will use novel molecular tools to examine the behavior of cells transplanted in animal models of human neurological disease. We will also need to develop a noninvasive method of following cells after transplantation and we propose to develop luciferase-tagged (light-emitting) hESC lines for in vivo animal imaging. In addition, we will use hESC-derived nerve cells to screen drug and chemical libraries for compounds that protect nerve cells from toxicity, and to develop in vitro disease models. We believe that these experiments are critical to enhancing our understanding of neurological diseases and providing the tools that will be necessary to move cell therapy to the clinic.

Before a hESC-based therapy can be developed, it is essential to train scientists to efficiently grow, maintain and manipulate these cells. We propose to teach four 5-day hands-on training courses - two basic and two advanced hESC culture courses per year - to California scientists free of charge. These courses will provide scientists with an understanding of hESC biology and will enable them to set up and conduct hESC research after completion of training.

In summary, the goal of this proposal is to provide over twenty investigators at the home institute and neighboring institutions with the ability to culture, differentiate, and genetically manipulate hESCs - including clinical-grade hESC lines - to develop diagnostic and therapeutic tools.

Statement of Benefit to California:

We propose to build a Shared Research Laboratory and offer a Stem Cell Techniques Course for over twenty principal investigators at the home institute and neighboring institutes working collaboratively on stem-cell biology and neurological diseases of aging. We propose to: 1) Purify nerve cells at different stages of maturation from human embryonic stem cells and to develop transplantation strategies in animal models that mimic human diseases, including Parkinson's disease, stroke and spinal cord injuries; 2) Screen drug and chemical libraries for reagents that protect nerve cells from toxicity and develop in vitro disease models using nerve cells generated from human embryonic stem cells; and 3) Assess the long-term integration and differentiation of transplanted cells using a non-invasive imaging system.

We believe these experiments provide not only a blueprint for moving stem-cell transplantation for Parkinson's disease toward the clinic, but also a generalized plan for how stem-cell therapy can be developed to treat disorders like motor neuron disease (amyotrophic lateral sclerosis, or Lou Gehrig's disease) and spinal cord injury. As the only stem-cell research facility in California's 10-12 most northwest counties, we are uniquely positioned to extend the promised benefits of Proposition 71 to this large part of the state. The tools and reagents we develop will be made widely available to California researchers and we will select California-based companies for commercialization of any therapies that may result. We also hope that California-based physicians will be at the forefront of translating this promising avenue of research into clinical applications. Finally, we expect that the money expended on this research will benefit the California research and business communities, and that the tools and reagents we develop will help accelerate stem-cell research in California and worldwide.

Application: CL1-00502-1

Title: TSRI Center for hESC Research

Public Abstract:

The therapeutic use of stem cells in regenerative medicine will require the ability to control stem cell expansion and differentiation into specific tissue types, such as pancreatic β-cells, heart tissue, bone or specific neuronal lineages. We have taken a chemical approach toward this problem in which large collections of synthetic small molecules are being screened in cell-based assays to identify drug-like molecules that control stem cell processes. Preliminary experiments in our institute have demonstrated that we can identify molecules that control the self-renewal and directed differentiation of murine embryonic stem cells. The characterization of the biological mechanisms of the molecules has also provided new insights into the underlying biology of stem cells. We now propose to extend these studies to hESC lines not eligible for federal funding, for which our research activities have been restricted to date. In addition, such lines may be better suited for specific applications, including the use of small molecules to derive specific cell lineages and investigate ES derived cell-based models of genetic disease. To this end, we would like to establish a human embryonic stem cell core facility. This facility will house the necessary equipment to genetically manipulate and culture hESCs on a large scale for a variety of studies including cell-based screens of small molecule libraries, as well as screens of arrayed genomic cDNA and siRNA libraries. We anticipate that this facility will serve our faculty as well as other labs that would like to collaboratively exploit this chemical approach to the study and manipulation of stem cells.

Statement of Benefit to California:

Historically, small molecules have been more useful than genetic approaches in the treatment of human disease. However, much of our ability to control embryonic stem cell self-renewal and directed differentiation currently involves genetic manipulation of these cells or complex mixtures of protein factors. The demonstration that one can systematically identify, optimize and characterize the mechanism of action of small drug-like molecules that selectively control stem cell biology both in vitro and in vivo will: (1) provide important tools to manipulate stem cells in the lab; (2) provide new insights into the complex biology that regulates stem cell differentiation; and (3) provide an important first step which may ultimately lead to drugs that facilitate the clinical application of stem cells.

Application: CL1-00503-1

Title: The Cedars-Sinai International Stem Cell Research Institute Shared Laboratory Facilities

Public Abstract:

We have established the International Stem Cell Institue at Cedars-Sinai to facilitate stem cell research, including reesearch on human embryonic stem cells. The International Stem Cell Institute will advance both basic research and clinical applications of stem cell research. To aid in these goals, we have already established a central laboratory to isolate new human embryonic stem cell lines. Some of these cell lines will be normal cells, others will be genetically defective cells. In addition, we will develop “good manufacturing practice” (GMP) cell lines. All of these will be important for the stem cell research to succeed at Cedars-Sinai.

The California Institute for Regenerative Medicine has issued a Request for Proposals that seeks applications that propose to develop shared research laboratory facilities. Here we request funding for major equipment items, personnel, and renovation costs to create a shared tissue culture core facility that will be available both to investigators at Cedars-Sinai and also to investigators from other institutions in our area. Three specific institutions that have expressed desire to utilize our proposed core facility are California State University Northridge, Mount St. Mary’s College, and Occidental College. The proposed shared research lab will have four subsections: a cell derivation laboratory, an imaging laboratory, a cell sorting facility, and a laboratory that will produce cells free of animal products that could be utilized in human clinical studies. Our shared facility will enhance stem cell research at Cedars-Sinai, and will encourage partnerships with investigators at nearby institutions. Ultimately, our research efforts will develop and and test potential beneficial applications of stem cells in the treatment of human diseases.

Statement of Benefit to California:

The proposed CSMC Shared Stem Cell Research Laboratory will benefit the State of California and its citizens by facilitating development of translational stem cell research applications. Cedars-Sinai already has prominent stem cell investigators, and as a result, our facility will assure that CIRM funds are utilized in high quality stem cell research applications. Our outreach efforts to less well-developed stem cell research programs at neighboring institutions will help increase the number of investigators and institutions that can conduct quality stem cell research, and will thus expand the stem cell research community in California.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Application: CL1-00504-1

Title: UC Davis Translational Human Embryonic Stem Cell Shared Research Facility

Public Abstract:

The intent of the proposed shared research facility is to provide a state-wide resource for qualified scientists in California to study human embryonic stem cells (hESC) without federal restrictions. The shared facility will encourage a spirit of collaboration and include laboratories for investigators to culture, collect, store, and analyze hESC, provide necessary services that will be cost-effective and assist with research productivity, and ensure an environment that will facilitate the essential interactions among scientists. This approach will advance the use of hESC for regenerative medicine purposes and aid in developing new technologies and therapies for the treatment of human disease. Using established methods that have proven successful for other collaborative and service-based structures, this facility will encourage scientists to work together and provide the necessary resources to ensure their success. Investigators new to hESC research will benefit greatly by having this facility available because it will have a centralized supportive structure where experienced personnel will provide the necessary assistance and guidance. For those investigators with hESC research experience, new opportunities will be available to work with cell lines that can be obtained but not be used in laboratories that are supported by federal funding. This will greatly expand research programs that are focused, for example, on studying ways to differentiate hESC towards blood cells and vessels for the treatment of disorders such as sickle cell disease and vascular abnormalities associated with heart disease. In addition, regeneration of damaged organs such as the heart, lung, liver, or kidney may require methods to reconstruct these tissues using scaffolds on which to grow the cells. These approaches require the ideas of cell biologists, engineers, biomedical researchers, and clinicians working together, and testing these ideas to ensure the procedures are safe before considering treatments of human patients. Techniques such as those that focus on ways to monitor cells once they are injected into the body will provide a powerful tool to study the outcome of these therapies.

A techniques course will be offered to scientists, students, and staff which will result in more laboratories in California working with hESC. The cells are difficult to grow and specialized training is required by personnel that are highly skilled and can provide the necessary information and direction to ensure success. The course is designed to provide qualified applicants the training experiences that will reinforce the basics, and ensure they are able to establish these techniques in their laboratories. The training course will be offered 4 times during the calendar year and include presentations and 'hands-on' experiences. Continuing education through the facility will ensure trainees have the necessary support when they return to their respective laboratories.

Statement of Benefit to California:

The Translational Human Embryonic Stem Cell Shared Research Facility will serve the state and its citizens by providing unparalleled opportunities to investigators, and establish a model for the manner in which researchers throughout California can work together to advance the use of cellular therapies for the treatment of human disease. This facility will remove barriers preventing the transfer of promising stem cell therapies to human patients by connecting people with expertise and new ideas with the resources necessary to develop and to evaluate new technologies and therapies under the necessary conditions before they are assessed in humans. The California community will benefit from the results of this collaborative environment because it will facilitate and advance research findings, promote a culture of sharing, and educate and train a new generation of scientists in human embryonic stem cell research. This approach, the infrastructure and goals of the proposed facility, and the plans for the techniques course will all provide opportunities for scientists, students, fellows, and staff, and increase the number of qualified scientific and medical personnel that will be able to make new discoveries and ultimately improve health care for patients.

Application: CL1-00505-1

Title: CIRM Shared Research Laboratories

Public Abstract:

Our plan is to establish a ~4700 sq. ft. shared research laboratory dedicated to the experimental manipulation and ultimate clinical application of human embryonic stem cells (hESC). This Shared Research Laboratory (SRL) is centrally located on the main campus. The SRL will be used by researchers focused on understanding how hESCs are induced to generate specialized tissues used for regeneration of the blood forming, nervous, and musculoskeletal systems. The SRL will be a state of the art facility accommodating a hierarchy of functions that includes:

> ~1659ASF of general hESC, multi-user laboratory space will be assigned on a time share basis to investigators who do not have the capacity, or cannot due to federal restrictions, conduct research with hESC in their own research laboratory. In addition to cell culture facilities that will allow multiple groups to work simultaneously, space in this area includes an hESC analytic laboratory for the basic characterization of hESC and their derivatives.
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> ~2245ASF of space will be used to establish a hESC GTP suite in which hESC free of infectious agents can be experimentally manipulated in a manner commensurate with their future clinical use. In addition to equipment necessary for the growth and genetic manipulation of hESC under GTP conditions, this facility will be able to distribute GTP maintained hESC lines to investigators.

Adjacent to the hESC GTP suite is the GMP laboratory suite including a hESC GMP derivation laboratory and bank. These facilities will allow hESCs to be derived and their progeny manipulated under conditions that meet federal guidelines for patient use. We have a strong track record of applying basic research findings to patients, and the adjacent location of multi-user, GTP, and GMP laboratories is an important factor that will allow basic hESC research findings to be developed and used to treat various human diseases.

The space for the SRL is part of our commitment to hESC research that includes 12 new stem cell faculty positions and matching funds for laboratory development. A committee comprised of faculty with extensive experience in the growth and manipulation of hESC is currently planning the development of the Shared Research Laboratory, and once it is established, they will provide regulatory oversight and supervise three staff responsible for the quality control of all equipment, ordering supplies, and scheduling access. The CIRM Shared Research Laboratory will be a state of the art facility in which intra- and extra-mural investigators can conduct hESC research not allowed due to federal restrictions or not technically feasible in their own laboratories.

Statement of Benefit to California:

The establishment of a hESC Shared Research Laboratory will make it possible for UCLA and non-UCLA investigators to conduct hESC research that is either not allowed due to current federal restrictions or not technically feasible in their own laboratories. As a result, investigators who would otherwise not be able to conduct hESC research will be able to become active in this area. This increase in the number of hESC scientists will in turn lead to new insights that will further increase the prominence of California as a leader in hESC research. A second benefit of the shared research laboratory is that the number of researchers trained to work with hESC will be increased, and this will ensure the availability of a skilled workforce available to fill jobs in the private biotechnology and pharmaceutical industry. These individuals will be a valuable resource for companies already located in California and will be an important incentive for others to relocate here. The plan to establish a Shared Research Laboratory designed to facilitate the translation of basic science to patients is a third benefit to the State. As described in the application, separate laboratory areas have been dedicated to the maintenance and manipulation of clinical grade hESCs, and this in turn will decrease time and costs of translating basic science discoveries to the clinic. This “bench to bedside” philosophy is consistent with our established track record of applying basic research to treat diseases. Thus, in addition to the direct benefit to patients and their families, the use of hESC to treat chronic diseases could reduce health care costs.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Application: CL1-00506-1

Title: UCSC Shared Stem Cell Facility

Public Abstract:

We have assembled a team of researchers with the aim of elucidating the molecular and cellular mechanisms that regulate stem cell self renewal and differentiation. Drawing on their broad range of expertise in development, genetics, genomics, molecular, cell and computational biology, these researchers will use interdisciplinary approaches to tackle problems concerning how genes are regulated in human embryonic stem cells (hESCs), and how this regulation influences their ability to both self-renew and differentiate into specific cellular subtypes. Defining and ultimately controlling this process is an essential step in designing stem cell-based therapies. These projects are aimed at providing insights and tools for neurological and genetic conditions such as Parkinson's Disease, ALS, CHARGE Syndrome, and Down Syndrome, and in aiding the development of gene therapy strategies. The work is funded in part from CIRM SEED grants to our faculty. In addition, we are committed to campus growth in this area, with faculty hires slated for expertise in various aspects of stem cell biology. Supported by a CIRM Training Grant, we are also committed to training a new generation of stem cell researchers – graduate students and postdoctoral fellows who will gain the knowledge and skills to embark on their own careers in this field.

To achieve these goals, we propose to build a Shared Stem Cell Facility (SSCF) by renovating 2000 square feet of space in the building where hESC research currently occurs. Our institution currently has no stem cell facility - hESC research is currently limited to NIH-approved lines because of the lack of separate, appropriately funded space. In addition, this facility will significantly expand and enhance the research space available for experimentation with hESC, in general, at our institution. The creation of a central facility dedicated to hESCs is essential for both on-going and new research, as well as for training. The resources and expertise provided by the SSCF will encourage additional faculty to use hESCs in their research and create new opportunities for faculty already committed to hESC research. For example, our faculty are eager to initiate projects that involve the use of non-approved cell lines that are free of the biological limitations of the approved lines, such as new hESC lines in which the mechanisms of self renewal and differentiation are altered, and in lines bearing disease causing mutations. This work will not be possible without a facility dedicated to hESC research that is free of federally-imposed restrictions.

Statement of Benefit to California:

The California Institute for Regenerative Medicine came about because of a mandate from the citizens of California who voted to invest state money into human embryonic stem cell research. Supporters of Proposition 71 waved signs reading "Save Lives with Stem Cells" and news reports predicted that the measure's passage would "put California at the forefront of the field." While individual projects such as the shared stem cell facility in this proposal will not directly save lives or put California at the forefront, the work that will take place promises to move the field towards successful stem cell-based therapies, and to help give rise to technologies and intellectual property that can serve as the basis for new companies in California. The research to take place in the proposed facility will contribute to the characterization of stem cell lines that will populate an envisioned stem cell bank in California. By allowing advanced hESC research, this facility will strengthen pre-existing international collaborations and stimulate more, thus bringing together worldwide efforts in a common cause. Finally, the ability to perform hESC research at this and other CA institutions that is not restricted to the federally approved lines will attract highly talented researchers from around the country. The research to be carried out in these facilities will greatly accelerate the rate at which we acquire new knowledge about the properties and uses of stem cells. Californians will be proud of this investment in infrastructure to facilitate new discoveries and the training of new researchers, positioning California to lead the way to improving and saving lives through regenerative medicine.

Application: CL1-00507-1

Title: The Childrens Hospital Los Angeles hESC Facility

Public Abstract:

Our institution is a tertiary-care academic pediatric medical center that combines care of severely ill children, research into the causes and treatments of childhood disorders, and training of the next generation of pediatric clinical physicians, nurses and allied health care professionals and biomedical scientists. A unique focus of the research in our institution is on applications to pediatric disorders such as diabetes, inherited disorders (cystic fibrosis, muscular dystrophy, sickle cell disease, etc), cancer and congenital birth defects. It is our central hypothesis that childhood disorders will be especially responsive to therapies produced by the use of stem cells; advances in the use of stem cells to treat childhood illnesses will then lead the way to treatments for the many disorders that occur later in life. For over a decade, the Stem Cell Program at our institution has been at the leading edge of translational research for cell and gene therapy and tissue engineering, with outstanding research programs in stem cells, gene therapy, developmental biology, organogenesis and transplantation immunology. Active research programs studying adult stem cells (hematopoietic, mesenchymal, pancreatic, hepatic, pulmonary, amniotic) and human and murine embryonic stem cells, interact closely with clinical Centers of Excellence in organ and hematopoietic stem cell transplantation, diabetes, cancer and blood diseases, neonatology, as well as a full array of pediatric secondary and tertiary care programs. These academically-oriented clinical programs have a long-standing tradition of inter-weaving research and clinical trials with patient care, to develop and evaluate innovative new treatments for severe pediatric and adult disorders. A Core Laboratory for studies with human embryonic stem cells (hESC) was established in 2005, using institutional funding. The hESC Core has supported initial studies and developed a formal training program in methods for the growth of hESC; 40 scientists from 5 research institutions in Southern California have attended the training course to date. However, the technical and regulatory burdens inherent in hESC research, have significantly restricted further development of individual hESC research projects within the limited existing laboratory space at our institution. Funding is thus requested to remodel and equip approximately 3000 sq ft of existing space (2500 sq ft of usable laboratory space) to create a suite of laboratories for dedicated use as an hESC Core facility alongside shared laboratory space for investigators involved in hESC research. We anticipate the laboratories and equipment established using this grant will support the research of at least 20 scientist investigators at our institution and will be also made available to researchers at nearby institutions across Southern California.

Statement of Benefit to California:

Development of methods for regenerative medicine using human embryonic stem cells (hESC) will have wide-spread applications to improve the health for millions of Californians and tens of millions of people world-wide, by providing novel, effective therapies. Regenerative medicine may provide new treatments for diseases including diabetes mellitus, Parkinson's disease, organ failure and injuries, inherited diseases and cancer and leukemia. The major challenge facing the field of regenerative medicine is to increase knowledge of the processes by which the mature cells of tissues (pancreas, brain, bone marrow, etc.) develop from stem cells, so that clinical approaches can be developed to produce cells suitable for transplantation. It is essential to establish laboratory facilities that can be used for research on hESC in a centralized manner that complies with all California and Federal guidelines. The hESC Core Laboratory and shared facilities to be developed based on this application will provide a resource to support research in stem cells by investigators from our institution, as well as investigators from across the Southern California region.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Application: CL1-00508-1

Title: A Stem Cell Core Facility for Studying Human Embryonic Stem Cell Differentiation

Public Abstract:

This application proposes to develop a Stem Cell Core Facility of ~1700 square feet to support the use of human embryonic stem cells (hESC) for a growing consortium of stem cell scientists at the home institution as well as neighboring institutions. The facility will be built and managed so as to allow use of non-NIH-approved hESC cell lines as well as research funded by non-federal agencies including the California Institute for Regenerative Medicine (CIRM). The Facility will be centrally located adjacent to other existing, successful core facilities and within short walking distance of all the users at the home institution. The Facility will be managed by an Oversight Committee consisting of faculty experienced in hESC and associated technologies, as well as those with experience in managing shared core facilities. The Committee will have close contact with an established Biotechnology Impacts Center to address any ethical issues that may arise.

The users at the home institution consist of an energetic, interdisciplinary group of both young and established investigators who have made a substantial commitment to stem cell biology. Within the past several years, they have held workshops on embryonic stem cells with neighboring institutions, taught two graduate level courses in stem cell biology, including one in bioethics, established a Stem Cell Center, and applied for and received CIRM funding. They have recently hired an experienced hESC investigator and are currently recruiting others, demonstrating the home institution's commitment to the field of hESC. The group currently consists of 30 investigators from three different colleges within the home institution who have common interests in molecular mechanisms of pluripotency and differentiation of hESC.

Several investigators have joint projects, including collaborations with investigators at neighboring institutions who will also be using the facility. The proposed Stem Cell Core Facility will allow this dynamic group of accomplished investigators to bring the promise of stem cell biology to an expanding, culturally diverse region of California.

The research programs that would use the facility concentrate on various aspects of the molecular mechanisms underpinning the pluripotency of hESC, as well as their ability to differentiate into different types of tissues. The results generated by these programs will contribute to the development of tools, diagnostics, and therapies by laying the foundation for understanding hESC and identifying new compounds and methodologies that will allow researchers to maintain hESC and prepare them for use in therapies. This basic understanding of the molecular networks governing hESC biology is essential before any safe and effective treatment can be considered for use in humans.

Statement of Benefit to California:

When Californians resoundingly passed Prop 71, they demonstrated the importance of stem cell research to all the citizens of our state. However, the human embryonic stem cell (hESC) lines that are currently sanctioned by the federal government are limited by many factors including genetic stability, contamination, poor growth characteristics, and lack of genetic and disease diversity. Working with non-federally approved hESC lines, including new more robust lines that will be developed in the future, will be necessary for any eventual therapeutic use of stem cells. Also critical to that success will be a thorough understanding of the molecular mechanisms that govern the pluripotency and differentiation of hESC, as well as attracting new scientific expertise to the field of stem cell biology.

This proposal meets these challenges and benefits all Californians by establishing a Stem Cell Core Facility (SCCF) that will greatly expand both the scientific as well as the geographic base of stem cell research. The SCCF will allow research on non-federally funded hESC lines and service a group of highly accomplished investigators at the host and neighboring institutions in the most ethnically and culturally diverse and fastest growing region of California. The investigators are all at the top of their respective fields, have a range of hESC expertise and are committed to applying their experience to some of the most critical issues facing the hESC field today. The group is highly interdisciplinary and has an established history of productive interactions and collaborations. They have created a new Stem Cell Center which is aggressively fostering stem cell research and have secured extramural funding for that research. All proposed users have existing projects that directly impact our understanding of the basic biology of hESC and will generate data that will be essential to the successful development of stem cell-based therapies.

Application: CL1-00509-1

Title: City of Hope Shared Resource for Human Embryonic Stem Cell Research in Developmental Biology, Cancer and Regenerative Medicine

Public Abstract:

Researchers at our institution are increasingly including human embryonic stem cells (hESCs) in investigations of development, regeneration and disease. A hESC shared research resource (hESC Core) will be a valuable and cost effective mechanism to enable researchers to begin work with hESCs, facilitate ongoing efforts, provide a central source for high quality established and newly-derived hESC lines that are not on the list of federally approved lines, and assist researchers with evaluation and selection of hESC lines intended for specific purposes. The facility will also provide access to specialized equipment essential for conducting experiments with hESC lines, which would not otherwise be accessible to researchers working with non-federally approved lines.

The pilot projects described in this proposal are examples of efforts employing hESCs and originate in multiple parts of the institution. Projects to understand the origins of genetic abnormalities that accumulate in hESC lines in culture will help ensure that hESC-based therapies are safe. Projects that are developing models of human cancer are creating platforms for basic studies of cancer and for discovery of novel therapies. Projects that are designing strategies for differentiation of hESCs to specific fates will make possible use of hESCs in cell replacement therapies for patients with degenerative diseases, diabetes and cancer.

The hESC Core will be responsible for maintenance and propagation of existing hESC lines and derivation of new lines using strict quality assurance. The Core will also be devoted to facilitating studies involving genetic modifications of hESCs and directed differentiation by manipulation of microenvironmental cues. These functions will be required for creation of cancer models and development of cell replacement therapies. In addition, the Core will provide space for investigators constrained by federal funding restrictions or institutional resources. The Core will also provide cells and laboratory space for researchers from neighboring California State University Campuses who have submitted projects that would use this Core and that mesh well with existing programs.

Beyond being a starting point for investigators initiating hESC-based projects and an active partner in ongoing projects, this hESC Core will be a shared resource useful to all California scientists interested in hESC research. We anticipate collaboration with other CIRM-funded hESC shared research laboratories, sharing capabilities, techniques and cell lines to maximize leverage of CIRM funds.

Statement of Benefit to California:

The hESC shared resource will play an essential role in the study of hESC biology and investigations of their utility in understanding human disease and developing new therapies. Using hESCs, COH researchers aim to minimize the tumorigenic potential of hESCs and to develop a better understanding of human cancers of the blood and brain, and to develop innovative cell replacement therapies for treatment of diabetes, hematological disorders, skeletal disease and muscular abnormalities. The hESC Core will generate new hESC lines that may be better suited to specific applications compared with existing lines, and that will be derived and maintained under conditions consistent with potential future clinical application.

COH, as a leader in hematopoietic and islet cell transplantation, has unique scientific strengths. Our HCT Program is the largest in California and is at the forefront of developing new cellular and biologic treatment for hematological disorders. We also have demonstrated leadership in selection, culture and manipulation of cells under GMP conditions for application to investigator initiated IND-based trials. Our experience and expertise in taking discoveries from bench-to-bedside places us in an outstanding position to do the same for hESC-based discoveries. This experience directly benefits the proposed hESC Core, since its efforts to maintain and derive hESC cells require strict conditions of quality assurance.

As the key resource for planned and existing research projects, the Core will facilitate entry of talented new investigators into investigations and applications of hESCs. It is important to note that this facility will serve neighboring institutions (e.g., those in the California State University system), allowing these scientists access to hESC research which is otherwise not possible. We anticipate collaboration with other hESC core facilities—sharing technologies, capabilities and cell lines to maximize the application of CIRM funds.

Application: CL1-00510-1

Title: Shared facilities for the preclinical testing of embryonic stem cell therapies.

Public Abstract:

Blood Systems Research Institute (BSRI), located in San Francisco, has a 45-year history of research in transfusion medicine and related fields. BSRI has undergone a recent expansion in investigators, laboratory space and equipment to address the growing number of opportunities that exist in the broad field of cellular therapeutics, particularly in the area of human embryonic stem cell (hESC) technology. The notable strength of BSRI lies in the expertise of its investigators in clinical and translational research owing to its long history with cellular therapy in the form of blood cell transfusion.

Laboratory space at BSRI will be remodeled to support our program in hESC research. We request funds to improve two tissue culture rooms to support basic research and pre-clinical studies on hESC lines. A 3rd laboratory will be converted into a cell isolation and analysis laboratory housing equipment used in the isolation and analysis of hESC-derived cells and tissues. A 4th room will be converted into a vivarium to study stem cell transplantation.

The research facility will be used by scientists at BSRI and neighboring institutions in the San Francisco Bay Area to perform basic research and to develop methodologies appropriate for the clinical of application of hESC-based therapies. Therapies under investigations include developing blood and liver stem cells as a new source of tissues to treat birth defects and disease. A training program for research technicians is also included which will help train new workers in the stem cell field.

Statement of Benefit to California:

The shared stem cell facility will help develop a new cell therapies such as those based on blood and liver cells. Blood diseases such as sickle cell anemia and thalassemia as well as liver diseases caused by viral infection, drugs or inherited disease affect many thousands of Californians. Often, transplanting healthy cells offers treatment or a cure for many of these diseases, but a lack of available or suitable donor tissue prevents such therapy in many cases. Embryonic stem cells offer the hope of generating a sufficient supply of tissues for cellular therapy. The successful outcome of this work will offer new hope to many Californians suffering from blood or liver diseases. This will improve lives and save money on long-term health care costs associated with these diseases.

Additionally, a training program has been included to help train research technicians for work in the stem cell field, therby helping to creat high paying jobs and provide the workforce needed for California to be the leader in stem cell research.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Application: CL1-00511-1

Title: COLLABORATIVE LABORATORY AND TRAINING COURSE FOR HUMAN EMBRYONIC STEM CELL RESEARCH AT BURNHAM INSTITUTE FOR MEDICAL RESEARCH

Public Abstract:

We are proposing to expand our "safe haven" human embryonic stem cell laboratory to accommodate the enormous interest in scientific research in this field, and to provide an environment that is conducive to the goals of the CIRM's Strategic Plan. Our collaborative Shared Laboratory will support the research of all of our institution's many stem cell researchers, including the new investigators who have been recently approved for funding under the CIRM's SEED grant program. In addition, we will cooperate will neighboring institutions to minimize overlap in strategic technological areas and maximize the value of CIRM's investment in our scientific community. The scientists in our program will share their special expertise in the areas of human ES cell derivation and molecular analysis.

All aspects of the Shared Laboratory will be directed by the Program Director, a well-established senior stem cell scientist who has experience in laboratory design and management of large groups of researchers. An Oversight Committee, composed of leading scientists, ethicists, and institution management will meet regularly to monitor and oversee the activities of the Laboratory.

We will also offer a series of Basic and Advanced Stem Cell Techniques Courses on behalf of our local scientific community. A Public Education Program will provide non-scientists with the opportunity to have hands-on experience with hESC research. Alumni from the courses will have access to an interactive web-based discussion group, and will meet once a year to share their scientific discoveries and insights. By closely collaborating with other California institutions, we plan to take full advantage of CIRM's investment in stem cell research and speed the translation of stem cell-based therapies to the clinic.

Statement of Benefit to California:

Californians are a large and diverse population that poses unique challenges for the future of medical care. Fortunately, California has a tradition of taking the lead in technology and medical breakthroughs and following through from the first idea to the final product. A major goal for California's supporters of stem cell research is development of stem cell-based products that have medical use, and the mandate for the research community is to provide the best possible fundamental information to help guide clinical applications. We have already laid the groundwork for research that encompasses both federally approved and non-approved human embryonic stem cells (hESC) by establishing a privately funded safe haven stem cell laboratory and founding a non-profit IRB-approved storage facility for excess embryos that have been donated for research. We have created an informational website and generated the largest worldwide public database of molecular information from our analyses of approved and non-approved hESC. We have been offering hands-on comprehensive courses in hESC technologies for three years, and have launched popular programs for scientific and ethical discussions that are regularly attended by hundreds of Californians. We propose to build on this foundation and expand our breadth and depth in stem cell biology through creation of a CIRM-supported collaborative Shared Laboratory and Stem Cell Techniques Course. We have designed this program to maximize benefit to both our own and neighboring institutions, to enhance collaborative interaction and open doors for the next generation of stem cell scientists. The Laboratory and Course will be a magnet for other researchers to contribute their own expertise, which will leverage the power of the California stem cell community. The program will be a springboard to new commercial ventures and will speed the development of clinical applications for stem cells that will benefit all Californians.

Application: CL1-00512-1

Title: CPMC Shared Research Laboratory

Public Abstract:

Human Embryonic Stem (hES) cells have the capacity to become all of the cell types of the human body. However, clinical applications of these cells require an understanding of how to isolate the downstream embryonic progenitors (EPs) of specific tissues. The CPMCRI Shared Research Laboratory (SRL) proposes to utilize a new two-step single cell technique to rapidly isolate a large number of potentially useful EPs, expand the number of those cells, test them for quality, and then share those purified cell types with other medical researchers throughout California. Specifically, the SRL will:

1. Isolate uniform populations of novel EPs that can become different tissues directly from discarded human IVF embryos. Using the two-step technology, ~ 1000 novel cell lines will be isolated and analyzed for gene expression and quality, banking, and distribution.

2. Isolate uniform populations of novel EPs that can become different tissues from hES cells derived from discarded IVF embryos carrying disease genes. In collaboration with Pacific Fertility Center, embryos carrying disease genes will be used to generate hES cells or caused to change into cells that can become different tissues using the two-step technology. Novel disease-bearing EP lines will be provided to California researchers in parallel to the normal lines for drug discovery and inherited disease research.

To this end a 1500 sq/ft laboratory at CPMCRI will be renovated and dedicated as the SRL for stem cell research not sanctioned by the Federal Government. The facility will contain 3 cell culture hoods, 6 incubators, a cryopreservation system, microscopes, centrifuges, a robotics cell culture platform, and various equipment items necessary for cell culture.

The Principal Investigator will serve as the Director of the facility. A Facilities Manager will be responsible for the day-to-day supervision of the facility. Core personnel will be responsible for the culture, cryopreservation, and distribution of the cells to researchers at CPMCRI, neighboring institutions, and institutions throughout California. CPMCRI researchers have projects that include neurological disease (ALS and nerve cell regeneration), cancer (breast cancer stem cells and cell migration), cardiovascular disease (myocyte regeneration), and inherited disease-related organ repair (cystic fibrosis and sickle cell disease).

Statement of Benefit to California:

The proposed research at the CPMCRI SRL benefits the people of California by providing medical researchers in the state novel human cell lines useful in both basic scientific study and potentially for use in the treatment of numerous degenerative diseases. The CPMCRI SRL will provide its collaborators with human embryo-derived cells that are more differentiated than human embryonic stem cells, are closer in their characteristics to the actual tissue that they are intended to repair, and therefore are closer to therapeutic application. The role of the SRL at CPMCRI will be to generate, characterize, test, and distribute these cell lines derived from normal human embryos through a process of direct differentiation wherein human embryonic stem cell lines are not utilized. In addition, the CPMCRI SRL will generate EPs from embryos carrying inherited disease gene alleles. The novel method of deriving these cells and the unique genetic properties of those generated with abnormal genetic backgrounds, offer a unique service to California researchers, useful in understanding the biology of disease and early human development, cell based drug discovery, and for the cell-based treatment of degenerative disease.

Application: CL1-00514-1

Title: The Gladstone CIRM Shared Human Embryonic Stem Cell Core Laboratory

Public Abstract:

The CIRM Shared Human Embryonic Stem Cell Core Laboratory will provide shared research facilities for use by California scientists. This laboratory will be hosted by a research institution focused on basic research into three of the most important medical problems of modern times: cardiovascular disease, AIDS, and neurodegenerative disorders. Each of these research areas addresses promising targets for regenerative medicine. We propose to develop a laboratory (1108 sq ft) for hESC tissue culture with specialized microscopy, and an animal holding and procedure space (500 sq ft) for in vivo pre-clinical studies of hESCs in mouse models of disease. The proposed laboratory will also help to train students from a nearby college be become laboratory technicians. This facility will contain advanced equipment for analyses of hESCs and complement existing space and incorporate hESC work provided by other core laboratories such as the genomics and flow cytometry cores that serve a broad community of researchers.

The host institution is renowned for the quality and administration of its extensive core facilities. Highly productive cores have always been at the heart of this institution's culture and this continues to be a priority. Five years ago, the host institution founded an embryonic stem cell core, which allows investigators not familiar with ESC research to obtain training, expertise and knowledge regarding embryoid bodies and ESC differentiation. As a result, two-thirds of the current investigators have incorporated some aspect of stem cell research in their portfolio. The host institution is also located in close proximity to a major biomedical university, so that all stem cell services are being coordinated to provide the best possible array of services to all stem cell investigators.

The research interests of our investigators that are related to stem cells can be grouped into three areas: cardiovascular development and disease, neurodegeneration and repair, and mechanisms that control the genetic stability of the cells while they divide and develop. This research involves the creation of genetically altered ESCs that require maintenance, expansion, and characterization. To aid in the analysis of the cellular phenotypes, we propose to use advanced high-content microscopy equipment. Several leading laboratories that apply this technology to basic cell biological analysis are close to Gladstone. An important next step will be to examine the behavior, survival, and interactions of hESCs once they have been implanted into mice. Visualization of the cells in live animals will be greatly enhanced by the proposed imagining instrument that will allow us to examine living cells within animals by light signals transmitted from the implanted cells. This program represents a comprehensive basic approach to how stem cells develop into other kinds of cells and will form the foundation for future preclinical studies.

Statement of Benefit to California:

Contribution to the California Economy:
A major goal of regenerative medicine is to repair damaged tissue. Our research focuses on developing new methods to differentiate human embryonic stem cells (hESCs) into specific cell types for regeneration of diseased tissues. Our research could benefit the California economy by creating jobs in the biomedical industry by developing new technology. Ultimately, this study could help reduce diseases, including cardiovascular, immune, and neurological diseases. Thereby, we hope to increase the productivity and enhance the quality of life for Californians.

The results of our studies will help develop new technology that could contribute to the California biotechnology industry. Our studies will create multiple lines of hESCs that have genetic markers that turn on at specific time points. These cell lines could be valuable for biotechnology companies and researchers who are screening for drug compounds that will cause these developmental changes. Furthermore, we are working closely with California companies to develop new microscopes and analysis software that could be the basis for new product lines or new businesses. If therapies do come to fruition, we anticipate that California medical centers will be leading the way.

The most important contribution of this study will be to improve the health of Californians. Diseases that are the target of regenerative medicine are major causes of mortality and morbidity, resulting in billions of dollars in healthcare costs and lost days at work. As we continue our efforts in medical research, we hope to one day unlock the secrets of tissue development and repair. This knowledge will help medical researchers develop beneficial therapies beyond what is currently available and potentially improve the quality of life and life expectancy of patients who suffer from disease.

Application: CL1-00517-1

Title: RSI Stem Cell Biology Open Research Center

Public Abstract:

We propose the creation of "Regenerative Sciences Stem Cell Biology Open Research Center." The mission of this facility will be to create a value-added shared research facility that will provide a unique environment to conduct research on hESCs, and create and maintain hESCs. Regardless of whether RSI wins funds for a Stem Cell Techniques Course, our facility will not only offer shared research space for hESC research, but will provide training and courses in how to conduct such research for small groups, and make that training publicly available through multimedia presentations on the web and CD/DVD. Furthermore, our shared research facility will take advantage of our unique research environment in which people from the high school to faculty levels are brought together to collaborate on cutting-edge research, where the conventional hierarchical management structure is eschewed in favor of a collegial approach. We will actively encourage people with possible research interest in stem cell biology to propose exciting high risk/reward work. We will then select those meritorious proposals and workers who would best benefit from our unique environment. Should another stem cell research center be funded in our vicinity we will work with them to add value to their services by working with groups of workers who might not otherwise have the opportunity to conduct original work in human stem cell biology.

The facility will be managed by a committee consisting of staff from RSI, as well as representatives from the local universities and colleges. Decisions will be made by close adherence to the collegial principles already described. We will actively solicit research proposals from neighboring educational institutions at the faculty, postdoctoral, and graduate school levels. In addition, we will expand our existing fellows/interns program by selecting a group of fellows and interns from local colleges, universities and high schools to be trained in human stem cell biology and encouraged to propose and conduct original research in collaboration with the more senior researchers.

Statement of Benefit to California:

We propose the creation of "Regenerative Sciences Stem Cell Biology Open Research Center." The mission of this facility will be to create a value-added shared research facility that will provide a unique environment to conduct research on hESCs, and create and maintain hESCs. The center will not only act as a conventional shared facility for stem cell research, but will bring all the benefits of open biological research. The center will be open to all interested faculty, will promote education of young researchers and will pursue high risk, high reward scientific research. CA research infrastructure will benefit.

Application: CL1-00518-1

Title: "The Stanford University Center for Human Embryonic Stem Cell Research and Education"

Public Abstract:

The goal of this proposal is to establish a premiere center for human embryonic stem cell (hESC) research and education in the state of California. Our center builds on the established excellence of faculty with research organized into four thematic areas: 1) Human embryology, derivation of hESC lines, including disease-specific lines, and SCNT, 2) Cell fate specification and hESC reprogramming, 3) Cancer and cancer stem cells, and 4) Directed differentiation to cardiac and neural lineages..

Here, we seek funding to renovate facilities that will house a human embryo/oocyte resource center and database, hESC line derivation, as well as other research and educational training including a central repository for growth, characterization and distribution of hESC lines to scientists in our community. The success of the faculty in this Center in garnering funding for hESC research, including CIRM funding, mandates the expansion of our research facilities. In addition, an accompanying curriculum in Stem Cell Techniques Courses is complementary to the research efforts and builds on a history of teaching excellence. This curriculum will encompass three areas: 1) Basic hESC Biology covering core essentials of hESC biology for individuals with little or no previous experience in hESC research, 2) Advanced or Specialized Stem Cell Techniques courses that will provide individuals with tailored instruction to enhance forward momentum in selected scientific topics, and 3) Systems Biology that reaches across institutions to bring together scientists in hESC and computational research. We anticipate that the outcome of our training initiatives will be both an expansion of knowledge and the building of teams to tackle tough basic and clinical challenges.

Finally, we note that our human embryo/oocyte resource center will provide expertise, materials and a complete, decoded database for use of precious resources in hESC research. This will enhance efforts to provide early diagnostics for reproductive and somatic disorders, cancers and onset of disease. Thus, this Center builds on a regionally unique combination of scientific and clinical excellence of Stanford University and neighboring institutions to provide critical research and educational support to scientists in California.

Statement of Benefit to California:

This proposal provides real benefits and value to the citizens of California in that our Center is established with a foundation built on: 1) a scientific faculty that is unsurpassed in knowledge of human development and disease and dedicated to pushing forward in hESC research, 2) a program director with numerous publications on hESCs and extensive experience in the State of California in establishing and directing an hESC Center with both research and teaching components, 3) a Shared Tissue Resource that is supported by the largest, and most accomplished academic IVF (in vitro fertilization) Clinic in California to support research protocols, in an appropriate manner, that range from derivation of normal and affected or disease-specific lines to reprogramming of somatic cells via nuclear transfer, 4) an established, decoded database system that will allow data from hESC research to be translated back to improvements in assessing embryo health (and thus decrease adverse outcomes that impact women's health such as repetitive miscarriages), 5) a core curriculum that has been successfully implemented for group and individualized instruction, and 6) a central location in Northern California within Silicon Valley that allows us to draw additional expertise from neighboring institutions and open our doors to training diverse members of the scientific community on one contiguous campus. Thus, the combined facility and teaching resource proposed will benefit the citizens of California by consolidating and accelerating research within the northern and central California region as well as by providing advanced training opportunities for investigators and research personnel throughout the State. This will enable a broad range of stem cell applications, promote the rapid translations of new discoveries to the clinic and also provide well characterized clinical grade reagents to support these efforts.

Application: CL1-00519-1

Title: The Berkeley Human Embryonic Stem Cell Shared Research Laboratory

Public Abstract:

Investigators from three major regional research and clinical institutions have instituted a stem cell research center. Numerous collaborations among our community of investigators have successfully utilized both Federal registry and non-registry human embryonic stem cell (hESC) lines in the center; however, the available resources for the culture and maintenance of these lines place inherent limitations on the research. We therefore propose to establish a Human Embryonic Stem Cell (hESC) Shared Research Laboratory for cell culture and investigation, which will serve as a central resource to greatly enhance stem cell science and technology in the region.

This resource will greatly benefit numerous ongoing research project areas. First, the ability of human embryonic stem cells to self-renew, that is grow and maintain their ability to differentiate into presumably every cell type in the adult body, is a hallmark property this is incompletely understood. Investigations of self-renewal mechanisms will lead to improved approaches to mass produce these cells for numerous therapeutic and diagnostic applications. In addition, understanding how hESCs differentiate into blood cells will enhance the treatment of numerous disorders including cancer, diabetes, and infectious disease. Moreover, studying how hESCs differentiate into numerous types of neurons will have implications for neurodegenerative disorders, including Parkinson's Disease and Lou Gehrig's Disease. Furthermore, regenerative medicine efforts to engineer new cardiomyocytes and blood vessels will improve the treatment of heart disease and congestive heart failure, still the leading loss of life in the United States. Importantly, the ability to control and harness hESCs as a limitless source of differentiated blood cells, neurons, cardiomyocytes, and other cell types will also greatly enhance high throughput drug screening, toxicology screens, and diagnostics efforts. Finally, novel bioengineering approaches to create robust and scaleable technology platforms for expanding, differentiating, and grafting hESCs will benefit all such therapeutic and diagnostic applications.

The Shared Research Laboratory will be located in two nearby sites on the host institution, within a new building and a modern biological sciences building, to provide convenient access to all researchers on campus and in the surrounding community. The Laboratory will provide a central repository and resource for culture and maintenance of numerous lines, and imaging and cytometry analysis. The Laboratory will also build upon our strong tradition of and success with shared core facilities to synergistically enhance our stem cell research capabilities. The resulting culture and analytical facility will thus provide a strong, shared resource to benefit stem cell research in the regional community.

Statement of Benefit to California:

Our Human Embryonic Stem Cell (hESC) Shared Research Laboratory will strongly enhance the scientific, technological, and economic development of California. The most important net benefit will be to human health.

The Laboratory will meld three outstanding research institutions: a university with a history of major contributions to the scientific knowledge and technological capabilities of the State, a research institution that bridges basic science with clinical translation, and a national laboratory with leading research in genomics and cancer biology. This collective expertise is poised to make major advances in stem cell biology and engineering, which will be greatly stimulated by the establishment of a collaborative laboratory for hESC research.

Our proposed Laboratory includes leaders in cell biology, developmental biology, immunology, neuroscience, and bioengineering. This expertise is being applied to understand mechanisms that control hESC self-renewal and differentiation, and the resulting advances will help establish California as a leader in stem cell biology. Furthermore, our team has leaders in regenerative medicine and bioengineering who apply basic biological information to create technology platforms for expanding, differentiating, and grafting hESCs for therapeutic and diagnostic applications. Collectively, this work will impact the treatment of cancer, autoimmune disease, infectious disease, heart disease, and neurodegenerative disorders.

Furthermore, we have a long and successful tradition of translating science into practice through interactions with industry and the clinic. Continuing this history in the area of stem cells will enhance the technological strength and economic development of the State. Finally, this Laboratory will provide a collaborative training environment that will expose many students and fellows to leading, interdisciplinary science and technology, thereby creating valuable future employees of California.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Application: CL1-00520-1

Title: The University of California: Irvine Regional Human Embryonic Stem Cell Shared Research Laboratory and Stem Cell Techniques Course

Public Abstract:

A major goal of the Shared Research Laboratory (SRL) is to foster the development of new treatments for human diseases and disorders by serving as a leading regional center for human embryonic stem cell (hESC) research, clinical applications, and training. A critical component of this vision is a full service SRL. The SRL will provide space and equipment that is free of federal funding to allow pursuit of any study needed to discover the basic properties of hESCs, to understand disease processes, to accelerate drug development and to develop cell-based therapeutics. The research in the SRL includes a balance of studies into the basic biology of hESCs, disease mechanisms, and potential therapeutics. Results of these studies will increase our understanding of the causes and potential treatments of spinal cord injury, retinal disease, motoneuron diseases, Huntington's disease, diabetes, multiple sclerosis, muscular dystrophy, heart disease, and Alzheimer's disease. The SRL also hosts a hESC Techniques Course. This 5-day, intensive, hands-on course trains future stem cell researchers in techniques for cultivation, handling and differentiation of hESCs. We propose to develop new space for pre-clinical testing, to obtain key pieces of major equipment, and to support personnel in order to improve our ability to develop new FDA-compliant treatments for human diseases and disorders. The new space will allow us to expand our training effort to include procedures needed to conduct pre-clinical translational and transplantation projects. The expanded curriculum will include animal survival surgery, cell transplantation techniques, and methods for tracing transplanted cells in the animal. Currently few, if any, venues exist in which researchers can learn not only how to create potential hESC therapeutics, but also learn how to test potential treatments in animal models. Importantly, all treatment-oriented research will be done under strict FDA quality assurance guidelines, so researchers will not have to repeat experiments when they file with the FDA, streamlining processes and decreasing time to clinical trial. The research expertise and institutional support for hESCs puts us in a strong position to serve as a regional facility of excellence, bringing new researchers into the field, and leading the way toward realizing the potential of hESCs in treating human conditions.

Our institution is exceptionally strong in translating basic scientific discoveries to the clinic,and in particular, has FDA-compliant pre-clinical strength in translation of hESC discoveries. Indeed, preclinical studies undertaken through the SRL will be conducted under the guidance of existing Regulatory Quality Assurance Officers to ensure FDA-compliance. With the proposed additions to the SRL, our vision of serving as a regional resource for hESC research and training will bring us closer to hESC-based treatments.

Statement of Benefit to California:

Proposition 71's primary goal is to translate basic research to clinical applications. Our program is exceptionally strong in moving basic scientific discoveries to the clinic and has FDA-compliant pre-clinical strength in translation of hESC discoveries.

The disability and loss of earning power and personal freedom resulting from a disease or disorder are devastating and create a financial burden for California. Therapies using human embryonic stem cells (hESCs) have the potential to change the lives of millions, and hESCs as models of diseases will help us understand the underlying causes of disease. For the potential of hESCs to be realized, California researchers need the equipment, lab space, and personnel to develop hESCs into viable treatments. Shared research laboratories (SRL) allow researchers to access critical, expensive equipment and concentrate expertise under one roof providing a favorable environment for collaboration. The federal constraints on hESCs create a critical need for SRL equipped and staffed with non-federal funds.

Our SRL is a regional resource currently used by scientists from 4 institutions, and hosts the quarterly hESC Techniques Course. Additional investment will result in a full service regional SRL where researchers can derive new hESC lines, develop cell-based treatments, and test potential therapeutics in animal models. Anticipated benefits of our SRL to the citizens of California include: 1) development of new cell-based treatments for a variety of human diseases and disorders; 2) improved methods for understanding normal development and the environmental risks to the early embryo; 3) development of intellectual property that could form the basis of new biotech startup companies; and 4) improved methods for drug development that could directly benefit citizens of the state. With the proposed additions, our vision of serving as a regional resource for hESC research and training will bring us closer to hESC-based treatments.

Application: CL1-00521-1

Title: UCSB Laboratory for Stem Cell Biology and Engineering

Public Abstract:

Regenerative medicine is an emerging area that will only realize its great potential through novel collaborative research approaches, and the University of California at Santa Barbara (UCSB) is well positioned to make significant contributions by leveraging fundamental biomedical research efforts with enabling technologies in materials, microfluidics and bioengineering. This proposal details plans for the development and renovation of shared-use laboratory facilities for the culture of human embryonic stem cells (hESC). The Laboratory for Stem Cell Biology and Engineering will be designed to promote stem cell research by investigators at UCSB, as well as those at neighboring universities and research institutions on the California central coast. Availability of a core stem cell laboratory will facilitate expansion of current stem cell studies at UCSB and stimulate new investigations into the biology and engineering of stem cells. The Laboratory will be embedded within a new UCSB Center for Stem Cell Biology and Engineering that is planned for the 3rd and 4th floors of Biological Sciences 2 building. Our clientele will include researchers in 13 different Departments and Institutes at UCSB, as well as nearby institutions. Research supported by the facility will include: investigations of the molecular mechanisms of hESC proliferation and differentiation; translational bioengineering to study novel methods of hESC culture, sorting, and delivery; and studies in regenerative medicine that test hESC derivatives in animal models of disease.

Statement of Benefit to California:

California, like much of the United States, is facing a staggering challenge to its health care system. Increasingly physicians are treating chronic, debilitating, and therefore expensive diseases with organ specific impairments. Examples include diabetes, cardiovascular disease, and Parkinson's disease. The demographic wave of the Baby Boomers will accelerate many of these issues. By 2020 they will average 64 years of age. As a result, the percentage of the elderly in California is expected to grow from what was 14 percent in 1990 to 22 percent in 2030.

Treatment of chronic degenerative diseases of an aging population, which is proportionally a high percentage along the Central Coast, is an imperative. Degenerative diseases are those diseases caused by the loss or dysfunction of cells. Examples include cardiovascular disease, osteoarthritis, Parkinson's disease, osteoporosis, and macular degeneration. Among these, stem cell work at UCSB would leverage a strong existing program in macular degeneration, a condition that is not being addressed in the stem cell field nationally or in California. Stem cell work for eye disease holds the promise of being a poster child for the entire field. There is no doubt that an early clinical success will benefit the state.

In terms of advanced biomedical research our geographic region is not well represented, but its engineering sector is primed with enabling technology. The area is ripe for growth in biotechnology that would serve as a pipeline to large pharmaceutical corporations as stem cell technologies move toward the clinic. The proposed Laboratory for Stem Cell Biology and Engineering will promote this movement and enhance the research stature of The University and attract leading researchers to California.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Application: CL1-00522-1

Title: Enhancing Facilities for Genetic Manipulation and Engineering of Human Embryonic Stem Cells at UCSD

Public Abstract:

Human embryonic stem cell (hESC) research promises to be of fundamental importance in the study and treatment of various human diseases, including cancer, neurodegenerative disorders and organ failure. In recent years we have made great strides in advancing hESC research as documented by the large number of successful, high-impact laboratories and breadth of research projects here. In addition, we are situated among several other first-rate institutions, all of which have joined in an unparalleled research environment for hESC research.

Since the creation of the California Institute for Regenerative Medicine, we have devoted both space and financial resources to promote hESC research. Our institutional commitment has as a cornerstone the creation of a core facility for hESC research to foster and promote hESC research at this and surrounding institutions. To date the facility has served to (1) train scientists in the basic methodologies to conduct hESC research (2) facilitate hESC research for many investigators, both established and beginning scientists, and (3) provide a “safe haven” that is sheltered from any federal funding sources thus allowing unimpeded hESC research. However, due to the high demand on space, equipment and technologies, the present facilities are insufficient to sustain the ongoing and proposed research projects.

We therefore request funding from CIRM to expand this facility and enhance its scientific output and creativity. In addition to providing expanded adequate facilities for our many scientists and clinicians embarking on hESC research, our major scientific goals for the shared research laboratory are (1) the development of protocols for the generation of genetically marked HESC lines, (2) the improvement of protocols for derivation of mature cell types, with an emphasis on neural differentiation, and (3) the development of novel surfaces and materials for the large scale growth and production of hESCs. These goals synergize the expertise of several departments, including the departments of Bioengineering, Materials Science, Biological Sciences, Pharmaceutical Sciences and the School of Medicine.

The support provided by this shared research grant will allow our institution to enhance our interdisciplinary stem cell program so that we may accelerate our goals of improving health and conquering diseases through regenerative medicine.

Statement of Benefit to California:

Human embryonic stem cells (hESC) provide the “raw material” that can potentially provide mature cell types for developing new disease therapies. Understanding how to control the growth and differentiation of hESCs, however, requires extensive research. Unfortunately, federal restrictions limit progress.

In 2005, our institution established a shared research laboratory which has provided essential training and has made space and technologies available to conduct hESC research without federal restrictions. However, the needs of researchers are beginning to exceed our limited resources. CIRM funding will allow expansion of the existing facility and the development of key technologies essential to ongoing and proposed projects at this and other institutions throughout California.

The proposed expansion includes creation of a satellite with emphasis on bioengineering technologies needed to develop therapeutic delivery vehicles and grow tissue engineered implants from hESC-derived cells. This satellite will leverage our international leadership in cell and tissue engineering and significant experience in translational research and technology transfer. The unique strength of interdisciplinary partnerships will accelerate translation of new scientific discoveries to clinical practice and new therapeutic agents that will benefit California’s healthcare system and global competitiveness.

CIRM funding will be enhanced by the investment already made by our institution in hESC research. The proposal integrates scientific need with the proposed expansion in cell biology and engineering abilities. Our request comes in direct response to needs of productive, experienced researchers in a context where professors, doctors, ethicists, social and political scientists can contribute to advancements in service of human health. Our context provides the teaching environment that will help engage California’s best young minds, and impart the latest discoveries to our students.

Application: CL1-00523-1

Title: The University of California San Francisco Shared Research and Teaching Laboratory: a Non-Federal Human Embryonic Stem Cell Resource for the Bay Area Community

Public Abstract:

The University of California, San Francisco (UCSF) has a long history of making innovative discoveries that change the way scientists and clinicians think about disease processes and their approaches to finding cures. Accordingly, researchers at this institution were quick to appreciate the enormous promise of human embryonic stem cells (hESCs) as research tools for understanding how the body normally works, thus laying the groundwork to identify disease-related aberrations. Therefore, in 2001, when the federal government decided to limit government funding to work with existing hESCs, which they banked, U.S. scientists were faced with a dilemma. Would we abide by these unprecedented restrictions, which meant that research would be limited to first-generation cells, or could we find ways to develop second-generation, higher-quality hESCs? Investigators on our applicant team took both approaches. Since UCSF contributed two hESC lines to the federal registry, our team members participated in the government's program to distribute these cells, which entailed teaching scientists how to use them. We also sought nonfederal funding sources to derive new hESC lines. Thus, we have a great deal of experience that is directly relevant to achieving the California Institute for Regenerative Medicine's (CIRM's) goal of establishing Shared Research Laboratories that also offer hands-on courses. We give the highest priority to teaching hESC techniques in the context of the ethical issues surrounding this work.

Here, we propose to expand the nonfederal laboratory space that already exists at UCSF. Renovating and equipping an adjacent lab will significantly increase our capacity for growing and analyzing second and subsequent generations of hESCs. Our goal is to make the existing space, renovated with UCSF funds, and the new lab to be created with this CIRM award, available to our colleagues. We also want to jump-start their work by teaching them how to grow and analyze hESCs. Thus far, 16 graduate- and postgraduate trainees are funded by our CIRM training grant; 32 UCSF scientists have applied for CIRM SEED and Comprehensive grants, and we expect many more will follow. We also want to support the work of our colleagues at 10 neighboring institutions. At the same time, we will use this lab to derive new and higher-quality hESC lines. We will also teach these techniques to highly motivated California scientists. Our work is important because the researchers who use our laboratory are studying the causes of major human diseases that occur as the result of trauma (e.g., paralysis), cell death (e.g., Parkinson's and Alzheimer's diseases, diabetes, cardiac failure), or cell malfunction (e.g., cancer). Thus, by sharing our laboratory space, scientific equipment and technical expertise with colleagues at UCSF and other institutions, we will play an important role in helping scientists accomplish CIRM's ultimate goal of finding cures for human diseases.

Statement of Benefit to California:

By voting in favor of Proposition 71, which funds research involving human embryonic stem cells (hESCs) that is not supported by the federal government, the citizens of California sent a clear message that they want scientists in our state to play an important role in research that could revolutionize medical treatments and render significant economic benefits. Currently, these treatments largely consist of surgical or pharmacological interventions, and transplantation approaches that involve significant hurdles. For example, human cells carry unique identifiers—molecular "bar codes"—that must be closely matched or the transplant will be rejected. And, unless the bar codes match perfectly, the recipient has to take powerful drugs to suppress rejection. Finally, there are major shortages of cells and organs for use in transplantation procedures. With the advent of hESCs, researchers are envisioning new therapeutic approaches. In theory, these cells, the building blocks of the entire body, can become any cell type. Thus, there is a great deal of excitement about using hESC-based transplantation techniques to cure human diseases.

Why haven't these approaches moved forward full throttle? In 2001 the federal government limited hESC research to existing cell lines. This unprecedented move created additional barriers. If scientists want to make new hESC lines or work with higher-quality cells that were established after 2001, they have to use labs that are completely devoid of government funding—that means building materials, equipment and supplies. Therefore, these labs must be created with funds from nonfederal sources, one of the reasons that the California Institute for Regenerative Medicine was created. We envision that our proposed Shared Research Laboratory and Teaching Facility will help us create a major center for conducting the most exciting aspects of hESC research that will ultimately lead to cures for many of the most devastating human diseases.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Application: CL1-00524-1

Title: USC Center for Stem Cell and Regenerative Medicine: Shared Research Laboratory and Course in Current Protocols in Human Embryonic Stem Cell Research

Public Abstract:

To realize the potential of human embryonic stem cells (hESC) in research and medicine, it is essential to disseminate state of the art technology in this field to the scientific community at large. The Shared Research Laboratory (SRL) of the Center for Stem Cell and Regenerative Medicine (CSCRM) at the University of Southern California will aim to provide a comprehensive support service for hESC researchers at our University and at neighboring institutions. The mission of the SRL will include the following goals: 1) to supply scientists with quality controlled stem cell lines for use in their research, including cell lines that are not eligible for use in NIH-funded projects; 2) to provide space and equipment for scientists new to the field to carry out pilot projects, in order to help them to integrate the hESC platform technology into their own research programs; 3) to develop and validate new and improved methods for growing hESC in the laboratory; 4) to operate a formal practical course in hESC laboratory techniques to scientists from throughout the region.

The facility will be situated in the new Harlyne Norris Cancer Center tower on the USC medical school campus. The laboratory will have sufficient work stations to support training, collaborative projects, and research and development programs for evaluation of new stem cell culture techniques, and it will be equipped with specialized instruments required to monitor stem cells. The operation of the facility will be overseen by the Program Director and the Manager of the CSCRM Core Facility. Advice on access and management will be provided by a subgroup of the CSCRM Stem Cell Advisory Group comprising stem cell researchers from USC, Children's Hospital of Los Angeles, and California Institute of Technology.

The SRL will support the work of CSCRM scientists and their colleagues at neighboring institutions involved in basic research on hESC, including international collaborations on standards for this research. The facility will also enable many groups involved in translational work at the USC medical school to gain experience and training in the use of hESC in their work in areas such as neurology, liver disease, cardiology, and ophthalmology. These scientists will be able to conduct preliminary studies in the facility under the guidance of experienced staff.

The SRL will offer a 5-day course on Current Protocols in Human Embryonic Stem Cell Research, to provide a comprehensive practical training for investigators wishing to use hESC lines in their research programs. Laboratory instruction will include demonstration of the most commonly used methods for cultivating hESC, methodology for assessing the purity and quality of hESC cultures, and methods for converting hESC into specific cell types such as nerve or blood cells. The training course will be available to scientists from institutions throughout the Los Angeles area and will be held 3-4 times per year.

Statement of Benefit to California:

The California Institute of Regenerative Medicine has as its goal the development of stem cell and related research for the treatment of disease. Human embryonic stem cells (hESC) could provide an indefinitely renewable source of any type of healthy human cell for use in research and therapy, and are therefore the focus of widespread scientific excitement. However, because the development of hESC technology is still at an early phase, significant technical barriers exist for new workers entering the field. The proposed Shared Research Laboratory (SRL) in the Center for Stem Cell and Regenerative Medicine (CSRCM) at the University of Southern California will act as a hub for dissemination of state-of-the-art technology in hESC research throughout the region. By training students and established investigators in the practical skills required for hESC use, and by providing shared space for pilot and collaborative projects, the SRL will vastly accelerate stem cell research in Southern California. The SRL will also carry out research and development aimed at evaluating new technologies for hESC research, and will incorporate new discoveries by participanting scientists into validated protocols for maintenance and differentiation of hESC. This role, which will include participation in international collaborative efforts for assessment of hESC methodology, will ensure that the SRL scientists benefit from the most recent advances in hESC research, and that their own discoveries are integrated into best practice for hESC research globally. California, and the greater Los Angeles area, will thus become an international focal point for hESC research. As workers involved in translational and clinical research learn to apply hESC in their studies, basic discoveries in stem cell biology by SRL trained researchers will move towards clinical application. The availability of the SRL will also provide a needed boost to the development of biotechnology in the Los Angeles area.