CIRM ALPHA STEM CELL CLINICS AWARDS: RFA 13-06

Tier 1 - Recommended for funding = ☐
Tier 2 - Moderate scientific quality or consensus on scientific merit cannot be reached, and may be suitable for programmatic consideration by the ICOC= ☐
Tier 3 - Not recommended for funding at this time = ☐

TIER 1 BUDGET $33,578,323

TIER 2 BUDGET $11,000,000

Application #	Title	SCORE	Range Median	SD	Low	High	Budget	Tier
AC1-07659	**The Innovation-Alpha Clinic for Cellular Therapies (I-ACT) – A Program for the Development and Delivery of Innovative Cell-based Treatments and Cures for Life-threatening Diseases.**	**85**	85	8	70	100	**$10,975,088**	**1**
AC1-07764	**Alpha Stem Cell Clinic for the Development of Regenerative Therapies**	**77**	76	7	65	85	**$11,673,826**	**1**
AC1-07675	**Alpha Stem Cell Clinic (ASCC) Consortium**	**75**	75	9	50	85	**$10,929,409**	**1**
AC1-07650	**The Regenerative Medicine Alpha Stem Cell Clinic Program Proposal**	**68**	64	8	60	85	**$11,000,000**	**2**
AC1-07788	**Stem cell clinic for the treatment of genetic and chronic diseases, and injury**	*					**$10,904,643**	**3**
AC1-07637	**Alpha Clinic - a Hub for Stem Cell Therapies**	*					**$10,779,909**	**3**
AC1-07742	**CIRM Alpha Clinic**	*					**$10,963,076**	**3**

REVIEW REPORT FOR CIRM RFA 13-06: ALPHA STEM CELL CLINICS AWARDS

AC1-07637: Alpha Clinic - a Hub for Stem Cell Therapies

Recommendation: Not recommended for funding **Final Score:** --
Total Funds Requested: $10,779,909

PUBLIC ABSTRACT (provided by applicant)

A clinical trial is designed to evaluate the effectiveness and safety of medications or medical devices by monitoring their effects on groups of people. Clinical trials represent an avenue for patients to receive promising new therapies that would not otherwise be available and to determine that a proposed method to heal or alleviate a medical condition will pass strict standards for safety first, and then efficacy in clinical use.

Once a proposed therapy reaches the first step in human clinical trials- the “Phase I study”, it will have already passed the Food and Drug Administration’s scrupulous requirements for safety and efficacy in animal models. A Phase I Clinical Trial will then look at the safety of the component introduced to the human body, and will ensure that the method of administration is safe. The initial Phase I study for cellular therapies will involve a few people- often around 20- and is designed only to test the safety of the proposed cell product.

Phase II trials continue to examine safety, in a larger group of patients, and will also look at efficacy, to see if the product does what it claims. The Phase II trial will include a control group who not receive the experimental treatment.

Phase III trials are the last round needed to show promise for the new method before the FDA will approve the product for use in the routine clinical setting. This phase will involve a large group of patients, a standard treatment control group, and often involve several different hospitals or treatment centers working together- called a “multicenter trial”. This is the final stage before the cellular therapy can become a standard of care which can be prescribed and reimbursed by insurance.

Our institution, and others across the state of California, are committed to developing novel treatments using stem cells and regenerative medicine to treat diseases and injuries, including many for which there are no or few other options. These novel treatments would be made available to the public through clinical trials conducted at medical centers throughout the state. Therefore, CIRM has proposed the concept of setting up a network of centers with Alpha Clinics, through which these trials can be safely conducted, to enable the novel therapies to reach the residents of the entire state of California.

We are developing these regenerative therapies to treat our human patients, and at our institution they can also benefit companion animal patients. We work in teams of basic and clinical scientists, including those from the School of Medicine and the School of Veterinary Medicine. We currently have nearly twenty disease teams focused on bringing Regenerative Therapies to the clinic, with the goal of making improving health.

With ten regenerative medicine clinical trials already ongoing, and two dozen in the pipeline at our institution, we are making major strides in this new field, which we believe is the future of medicine.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)
Clinical trials are designed to evaluate the effectiveness and safety of medications or medical devices. They represent an avenue for receiving potentially promising new therapies that would not otherwise be available and to determine that a proposed method to heal or alleviate a medical condition will pass strict standards for safety first, and then efficacy in clinical use.

In the state of California, due in large part to the efforts and funding provided via grants from the California Institute for Regenerative Medicine (CIRM) there are stem cell/regenerative medicine clinical trials at our institution that are ongoing or recently completed in the following areas: Critical limb ischemia, retinal disorders, heart disease, non-healing ulcers, vertebral disc repair, lateral vertebral body fusion for spine pain, acute burn injuries, cartilage repair, spinal cord injury and traumatic brain injury.

CIRM is now proposing the concept of the Alpha Clinic network where these trials, and others like them, can be conducted at other medical centers across the state, which would be coordinated through the proposed Alpha Clinic Network. An Alpha Clinic program would be at our institution and at 4 other medical centers throughout various regions in the state, ensuring that all residents will have equal access to these very exciting and innovative therapies.

All Alpha Clinic participants would conduct FDA approved stem cell therapy clinical trials which would involve qualified candidates, usually people who are already under the care of a doctor or are recruited from a population in order to be trial participants. Through the Alpha Clinic Network there would be the potential for community and regional, as well as state-wide referrals, to allow for all Californians to participate in the novel stem cell therapy and regenerative medicine clinical trials established throughout the state.

The goal of these novel clinical trials is to generate approved therapies that can be prescribed to all patients who need them. By regenerating damaged and diseased tissues through the use of stem cell therapies, health care costs in our state could be dramatically reduced.

At our institution we currently have stem cell therapy clinical trials recruiting or in development for the treatment of: Retinal Disorders, Critical Limb Ischemia, Huntington's disease, Osteoporosis, Traumatic Brain Injury, Hypoplastic Left Heart Syndrome, Cerebral Palsy, Non-healing ulcers, Bone Damage, Spina Bifida, Burns, HIV, ALS, Vertebral Fusion: Pain and Disc Degeneration, Cartilage Degeneration, Heart Attack, Stroke, Lung disease, Swallowing disorders, Tracheal damage, Lichen Planus, Scleroderma, Multiple Sclerosis, Crohn's Disease, Lymphoma, Leukemia, Myelodysplastic syndrome, Multiple Myeloma, Liver disease, Bladder disease, Kidney disease, Cardiac Pacemaker, and Parkinson's disease.

REVIEW SUMMARY
This CIRM Alpha Stem Cell Clinic (CASC) application comes from an already busy clinical program seeking to use CASC resources to build upon their existing activities and infrastructure to accelerate the enrollment and completion of clinical trials. There are five lead trials proposed that use stem cell-based therapies to treat eye disease, peripheral vascular disease, traumatic brain injury, pediatric heart disease, and neurodegenerative disease. Two of these trials already have regulatory approval and are enrolling patients. In addition, the applicant institution has ten trials of stem cell and regenerative medicine approaches currently ongoing or recently completed and eighteen additional therapies in the pipeline. A key area of activity proposed for the CASC would be to use CIRM resources to accelerate the enrollment of patients into the institution¹s existing pipeline of clinical trials through an outreach and education program and creation of a network of affiliates throughout CA.

Responsiveness to the RFA
- This is a very active clinical program with many stem cell-based clinical trials already ongoing

or in the pipeline, such that the applicant describes the current program as the equivalent of an Alpha Clinic. While some reviewers felt that the large number of trials ongoing or planned would clearly benefit from additional resources, others questioned the added value of establishing a CASC at this site and did not think the application clearly conveyed how CIRM funds would be used to leverage and enhance the already ongoing activities.

- Applicants stated that CASC resources would be used to triple the rate of patient enrollment primary through marketing and outreach efforts, but no information was provided to support the estimated increase in enrollment.

Institutional Support and Sustainability Plan
- The application has outstanding infrastructure already in place, including a large manufacturing facility, with a busy clinical program and a strong patient base. However, it was noted that the patient base will vary by disease indication and for some trials it may be necessary to recruit outside the current patient pool.

- Most reviewers felt that there is a significant institutional commitment to conducting clinical trials using stem cell-based therapies; however, the overall sustainability plan was not strong and lacked detail. The applicant plans to fund the next 5-10 years through grants and contracts, and beyond that through a recharge mechanism, which is similar to the existing approach.

Alpha Stem Cell Clinic Team
- While reviewers agreed the team is well qualified, there was concern that the Program Director is already heavily committed on other activities and may have difficulty being able to meet the effort requirement of the RFA.

- Many personnel are existing employees who would transition to cover CASC activities with unclear impacts on the prior existing infrastructure.

- There was concern that the Program Manager does not have adequate experience given the central role played within the CASC.

Alpha Stem Cell Clinic Structure and Operational Plan
-Reviewers had difficulty differentiating proposed activities from those existing activities already in place at the institution, raising the possibility of overlapping roles. The application did not clearly articulate how additional infrastructure would make the existing clinical activities more efficient.

- The application did not describe how the many trials in the pipeline would be prioritized for support by the CASC and whether there was a vision for the center to focus on a particular scientific area, nor did it mention the need to establish and articulate a set of standard policies and procedures for the CASC.

- Reviewers felt the budget as stated on a price per clinical trial basis was very high and did not appear to be an efficient use of funds.

Lead Clinical Trials for the Alpha Stem Cell Clinic
- The lead trials, several of which are already CIRM-funded, span a variety of disease areas. While the trials were generally viewed as well chosen to address unmet medical need and to be a good fit with the CASC mission, questions were raised about the ability to impact the target diseases based on the level of preclinical scientific evidence to support the therapeutic candidates as well as the fact that there are other products in development.

- Reviewers expressed concern about whether the results of one of the lead clinical trials would

be interpretable, given that it will include patients with a wide range of disease etiologies.

- For one of the proposed lead trials the CASC would serve as only one site of a multi-center trial that is being led by an industry sponsor. It was unclear how much the CASC could singlehandedly have an impact on that trial.

REVIEW REPORT FOR CIRM RFA 13-06: ALPHA STEM CELL CLINICS AWARDS

AC1-07650: The Regenerative Medicine Alpha Stem Cell Clinic Program Proposal

Recommendation: Tier 2 **Final Score:** 68
Total Funds Requested: $11,000,000

PUBLIC ABSTRACT (provided by applicant)
Our proposal seeks to create the [Redacted] Alpha Clinic. Our institution is the largest private academic medical center in the western United States. We have all the components needed to succeed in this endeavor: 1) outstanding resources for innovative patient care and research; 2) a distinguished and prolific track record in clinical investigation; 3) major successful programs in basic, translational and clinical regenerative medicine; 4) a highly-integrated organizational structure focused on the doctor-patient interaction; 5) superior leadership with unparalleled experience in clinical trials of cell therapy.

The initial focus of the Alpha Clinic will be on cardiovascular and neurological diseases. The focus on heart is motivated by our track record and capability in that area. Our institution is a world leader in heart research and cardiovascular care. It is in the top 10 nationally recognized cardiovascular programs, and ranks as one of the top heart and heart surgery programs in the western USA according to U.S. News & World Report.

Our 2 Lead Trials are trying to address two diseases that have major public health impact: large heart attacks and ALS. Both these diseases appear to be excellent targets for stem cell therapy.

Our newly-opened [Redacted] will be the home of the Alpha Clinic. We will operate multispecialty Regenerative Medicine Clinics to care for cell therapy research subjects and patients, in a state-of-the-art building which contains all relevant outpatient facilities and procedure suites, as well as research laboratories of the [Redacted] and [Redacted]. The shared spaces and open laboratory concepts are envisioned to bring clinicians and scientists together to promote synergistic approaches and increase the probability of major medical breakthroughs. The President and CEO has committed $10 million of direct institutional support to the Alpha Clinic during the grant funded period with further commitments to sustain it beyond.

With a unique combination of experienced leadership and clinical investigators, competent staff, a broad spectrum of current and planned CTx clinical trials and a very strong institutional support, [Redacted] provides the optimal environment for a CIRM Alpha Stem Cell Clinic. We will be very privileged to receive funding from CIRM to establish the Alpha Clinic and execute our plan to be of service to the citizens of California.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)
[Redacted] is applying to be one of five California Institute for Regenerative Medicine Alpha Stem Cell Clinics (CASC). Regenerative medicine has been a major institutional focus of ours over the last several years. Our vision of a Regenerative Medicine Alpha Stem Cell Clinic is to provide a unique programmatic umbrella structure for a cross-specialty delivery of stem cell therapy that our researchers, clinicians, healthcare givers and patient educators can use in delivering scientifically sound and regulatory compliant clinical research and patient education. We have ongoing or planned cell therapy clinical trials in heart disease, vascular disease and stroke. Additionally, we have investigators making preparations to conduct clinical trials in Lou Gehrig's disease (amyotrophic lateral sclerosis, [ALS]), and in segmental bone fractures. We

will be able to provide the necessary infrastructure and support for our clinical research teams involved in stem cell research.

It is common for the public to get conflicting reports about stem cell therapy. We will use the grant funding for the Alpha Clinic to provide Californians access to reliable information about stem cells and its potential use in treating disease. We will also provide information about current clinical trials investigating the safety and efficacy of stem cell products. These clinical trials will hopefully lead to regulatory approvals that will allow for commercialization of approved clinical stem cell therapies. We are committed to using the grant support for a comprehensive approach to education and dissemination of information to patients, their families or social supports.

We will actively work with the entire CASC network and the Coordinating and Information Management Center (CIMC) to provide, analyze, publish and disseminate data in a timely and scientific manner. These activities will further our understanding of the role of stem cells in treating diseases and further the body of work to advance the field.

We hope that the citizens of California will be the direct beneficiaries of the Alpha Clinic.

REVIEW SUMMARY
This CIRM Alpha Stem Cell Clinic (CASC) application describes a plan to build on its institution¹s strong commitments to regenerative medicine and delivery of stem cell therapies to patients. The institution has recently opened a new building in which outpatient facilities and procedure suites for a regenerative medicine clinic are located, along with research laboratories and core facilities to support stem cell clinical research, and has committed additional financial resources to sustain an CASC if one is funded by CIRM at its site. The proposed CASC will act as a central operational group to support core activities that can be applied across all of the institution¹s regenerative medicine clinical trials, such as providing regulatory support, negotiating contracts and budgets, supporting clinical operations and coordinating clinical trials. In addition, the CASC intends to provide information and education to patients about stem cells and ongoing clinical trials. It will focus first on clinical trials that will deliver stem cell-based therapies to patients who have had a heart attack (myocardial infarction) or are afflicted with neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS). The proposed pipeline of additional clinical trials will also be focused on stem cell-based clinical trials for cardiovascular, ophthalmic and neurologic indications.

Responsiveness to the RFA
- One of the identified lead clinical trials is currently enrolling patients and the second is likely to be enrolling patients within 12 months of the award date.

- Reviewers found insufficient information regarding how the CASC would share information and interact with other CASCs in the network.

- Reviewers commented that it was not obvious how the CASC would accelerate the lead trials, but predicted that its activities could build value for future studies in the clinical trial pipeline.

Institutional Support and Sustainability Plan
- The institution has made a significant commitment to clinical regenerative medicine and the CASC has excellent resource allocation and assured future financial contribution, during and beyond the 5-year duration of this award.

- Much of the sustainability for the program hinges on the impressive strength of the pipeline for the CASC, as many of the trials under consideration have industry sponsors.

Alpha Stem Cell Clinic Team

- The Program Director (PD) has extensive leadership experience and is regarded as a leading investigator in stem cell clinical research. Reviewers noted this would likely help recruit patients and clinical trial sponsors, but they expressed concern that the PD will be very over-committed and likely not able to commit the minimum 30% effort required by the RFA.

- The leadership team consists of recognized leaders in cardiovascular disease and neurological indications. However, the exact contribution that the named Associate PD would make to the CASC is not very clear.

- The current members of the broader CASC team have appropriate experience in conducting clinical trials and reviewers agreed with identified roles and areas of expertise for planned new hires.

Alpha Stem Cell Clinic Structure and Operational Plan

- Reviewers thought the CASC was well structured and would be well integrated into ongoing regenerative medicine activities at the institution.

- Given the large expansion into regenerative medicine that the institution has undertaken, many of the activities described as elements of the CASC have already been initiated or will soon be put in place. Some reviewers questioned whether the additional resources provided by CASC funding would substantially supplement ongoing activities and if the CASC would add significant value.

- Reviewers disagreed whether the funding request was appropriate, or excessive, for the proposed CASC activities.

Lead Clinical Trials for the Alpha Stem Cell Clinic

- One lead trial is in cardiovascular stem cell medicine and reviewers noted it fits very well into the expertise of the clinical team. However, the applicant institution is only one enrolling site in this large, multi-site trial and reviewers questioned whether the accelerating efforts of an active CASC at a single site would have significant effects on the overall trial.

- The second lead trial is a first-in-human clinical safety trial for a stem cell-based therapeutic intended to treat a neurodegenerative disease for which there is no cure. While the trial will address a great medical need, reviewers questioned whether an active CASC would have much impact on this small trial.

- The PD and institution have ties to one of the lead clinical trials, which could result in the appearance of a conflict of interest. Reviewers commented that policies should be in place to ensure that the relationships are clearly defined and separated.

REVIEW REPORT FOR CIRM RFA 13-06: ALPHA STEM CELL CLINICS AWARDS

AC1-07659: The Innovation-Alpha Clinic for Cellular Therapies (I-ACT) – A Program for the Development and Delivery of Innovative Cell-based Treatments and Cures for Life-threatening Diseases.

Recommendation: Recommended for funding **Final Score:** 85
Total Funds Requested: $10,975,088

PUBLIC ABSTRACT (provided by applicant)
As the largest provider of bone marrow cell transplants in California, and the second largest in the nation, our institution has great expertise and an excellent record of safety in the delivery of stem cell treatments. We now propose to create the Alpha Clinic for Cell Therapy and Innovation (ACT-I) in which new, state-of-the-art, stem cell treatments for cancer and devastating blood-related diseases will be conducted and evaluated. As these experimental therapies prove to be effective, and become routine practice, our ACT-I Program will serve as the clinical center for delivery of these treatments. ACT-I will be an integral part of our Hematologic Malignancy and Stem Cell Transplantation Institute, placing it in the center of our institutional strengths, expertise, infrastructure and investment over the next decade. To move quickly once the CIRM award is made, ACT-I can be launched within our institution's Day Hospital, a brand new, outpatient blood stem cell transplantation center opened in late 2013 with California Department of Health approval for 24 hour a day operation. This will ensure that ACT-I will have all the clinical and regulatory expertise, trained personnel, state-of-the-art facilities and other infrastructure in place to conduct first-in-human clinical trials and to deliver future, stem cell-based therapies for cancer and blood-related diseases, including AIDS. When our new Ambulatory Treatment Center is complete in 2018, it will double our capacity for patient visits and allow for expansion of the ACT-I pipeline of new stem cell products in a state-of-the-art facility.

Beyond our campus, we operate satellite clinics covering an area that includes urban, suburban and rural sites. More than 17.7 million people live in this area, and represent some of the greatest racial and ethnic diversity seen in any part of the country. Our ACT-I is prepared to serve a significant, diverse and underserved portion of the population of California.

CLINICAL TRIALS. Our proposal has two lead clinical trials that will be the first to be tested in ACT-I. One will deliver transplants of blood stem cells that have been modified to treat patients suffering from AIDS and lymphoma. The second will use neural stem cells to deliver drugs directly to cancer cells hiding in the brain. These studies represent some of the new and exciting biomedical technologies being developed at our institution. In addition to the two lead trials, we have several additional clinical studies poised to use and be tested in this special facility for clinical trials. In summary, ACT-I is well prepared to accommodate the long list of clinical trials and begin to fulfill the promise of providing new stem cell therapies for the citizens of California.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)
California's citizens voted for the California Stem Cell Research and Cures Act to support the development of stem cell-based therapies that treat incurable diseases and relieve human suffering. To achieve this goal, we propose to establish an Alpha Clinic for Cellular Therapies and Innovation (ACT-I) as an integral part of our Hematological Malignancies and Stem Cell Transplantation Institute, and serve as the clinical center for the testing and delivery of new, cutting-edge, cellular treatments for cancer and other blood-related diseases. Our institution is uniquely well-suited to serve as a national leader in the study and delivery of stem cell

therapeutics because we are the largest provider of stem cell transplants in California, and the second largest in the country. According to national benchmarking data, our Hematopoietic Cell Transplantation program is the only program in the nation to have achieved survival outcomes above expectation for each of the past nine years. This program currently offers financially sustainable, research-driven clinical care for patients with cancer, HIV and other life-threatening diseases. CIRM funding will allow the ACT-I clinic to ramp up quickly, drawing upon institutionally established protocols, personnel and infrastructure to conduct first-in-human clinical trials for assessment of efficacy. As CIRM funding winds down, ACT-I will have institutional support to offer proven cellular therapeutics to patients. The lead studies at the forefront of the ACT-I pipeline of clinical trials focus on treatments for HIV-1 infection and brain tumors, two devastating and incurable conditions. These first trials are closely followed by a robust queue of other stem cell therapeutics for leukemia, lymphoma, prostate cancer, brain cancers and thalassemia.

Our long list of proposed treatments addresses diseases that have a major impact on the lives of Californians. Thalassemia is found in up to 1 in 2,200 children born in California; prostate cancer affects 211,300 men, and HIV-1 infection occurs in 111,000 of our citizens. From 2008 to 2010, 6,705 Californians were diagnosed with brain cancers, 4,580 of whom died. In considering hematological malignancies during this same period, 2,800 patients were diagnosed with Hodgkin lymphoma (416 died), 20,351 with non-Hodgkin lymphoma (6,241 died), 13,358 with leukemia (6,961 died), 3,900 with acute myelogenous leukemia (2,972 died), 2,129 with acute lymphoblastic leukemia (648 died) and 4,198 with chronic lymphocytic leukemia (1,271 died). Standard of care fails in many cases; mortality rates for patients with hematological malignancies range from 25% to 76%. Successful stem cell therapeutics hold the promise to reduce disease-related mortality while improving disease-related survival and quality of life for the citizens of California, and for those affected by these diseases worldwide.

REVIEW SUMMARY

The overall goal of the proposed CIRM Alpha Stem Cell Clinic (CASC) is to conduct and evaluate clinical trials using stem cell therapeutics for cancer and blood related disorders. Building upon a large and successful bone marrow transplantation program, the Clinic will leverage existing infrastructure and resources, including a pipeline of therapies in development, a diverse patient base, and a financial commitment of matching funds from the applicant organization to help sustain the program beyond the projected period of CIRM funding. Two lead clinical trials are proposed, comprising 1) the use of neural stem cells to deliver localized chemotherapy to brain tumors; and 2) the use of autologous, gene-modified blood stem cells for treating patients with Acquired Immune Deficiency Syndrome (AIDS) and lymphoma. Additional program activities are to establish advisory and oversight committees to ensure effective coordination between the various components of the Alpha Clinic, and to maintain its productivity in the longer term.

Responsiveness to the RFA

- The proposed Alpha Clinic, which will be located within the umbrella of larger hematopoietic transplant center, will benefit from a very solid pre-existing infrastructure that should accelerate its implementation and augment its effectiveness.

- The applicant adequately and appropriately describes how the proposed Alpha Clinic will accelerate cell-based therapies in development through their expert staff and efficient processes.

- The proposal does not clearly articulate the merits of the proposed Alpha Clinic as an independent entity so much as an extension of ongoing activities within its umbrella organization.

Institutional Support and Sustainability Plan

- The proposed Clinic is well designed to integrate within an existing physical and administrative infrastructure, with a robust pipeline of therapies in development, and an excellent track record of conducting early phase clinical trials.

- Within the hematopoietic transplantation field, the applicant institution is nationally recognized and has significant access to a diverse and relevant patient base through a network of satellite centers and collaborative relationships with a major health maintenance organization.

- Although lacking specific details around expected revenues, the applicant described a balanced plan for sustainability including matching funds from the applicant organization, with appropriate milestones and criteria for gauging the success of the Alpha Clinic.

- The proposal does not include clear plans to distinguish the Alpha Clinic from its umbrella organization, which is similarly centered on hematopoietic transplantation and malignancy. While reviewers questioned the extent to which clinical trials from fields other than hematological disorders and cancer would be attracted to the Alpha Clinic, they acknowledged that this narrow focus could be interpreted as either a strength or a weakness.

- Reviewers would have appreciated greater emphasis on describing inpatient aspects of the Alpha Clinic, since many early stem cell trials will likely need to be inpatient as opposed to outpatient programs.

Alpha Stem Cell Clinic Team

- The Program Director (PD) is highly recognized in his/her field, with relevant expertise in gene therapy development and its associated regulatory challenges, and a successful track record of leading consortium projects.

- The supporting team members bring a wide range of direct and relevant experience to the proposed Alpha Clinic, including subject recruitment, medical expertise, clinical trial operations, and business development.

- The proposal lacked clear designation of a formal project management office to ensure operational preparedness for meeting milestones and timelines.

Alpha Stem Cell Clinic Structure and Operational Plan

- The proposal appropriately addresses activities such as clinical operations, data safety monitoring, patient coordination and patient outreach. Team structures, including oversight committees, are well defined.

- The proposed timelines and milestones are feasible and within expectations of the Alpha Clinic grant award. Metrics for success are well considered.

- Some reviewers considered the estimated capacity of the Clinic to treat 70 new research patients/year to be low and questioned whether adjustments in trial design or addition of trial sites might increase this capacity.

- While the overall budget is reasonably aligned with proposed activities, several areas appear inflated and could benefit from further scrutiny, such as travel funds, the costs of a web platform, and the overall number of personnel outlined in the organizational plan.

- The proposal lacked details on how multi-center trials would be effectively managed, and how operations would be standardized. While not critical flaws, such considerations could enhance delivery of program outcomes and make them more predictable.

Lead Clinical Trials for the Alpha Stem Cell Clinic

- Both lead trials address important, unmet medical needs and have achieved regulatory clearance for initiating clinical studies within 12 months of the grant award start date.

- Reviewers were satisfied that the proposed trials were evaluated for funding with sufficient rigor to merit their designation as Lead Trials in this Alpha Clinic proposal.

- Reviewers acknowledged that Lead Trial 2 includes some unique technical aspects that could potentially increase potency of the therapeutic candidate. However, based on description in the proposal, they were uncertain why the trial could not be extended into a broader population of AIDS patients, thereby increasing the likelihood of enrollment.

- While the lead trials are a good fit for the expertise of the applicant team, the proposal does not clearly describe how hiring of new, required personnel would be efficiently managed.

REVIEW REPORT FOR CIRM RFA 13-06: ALPHA STEM CELL CLINICS AWARDS

AC1-07675: Alpha Stem Cell Clinic (ASCC) Consortium

Recommendation: Recommended for funding **Final Score:** 75
Total Funds Requested: $10,929,409

PUBLIC ABSTRACT (provided by applicant)
Two world renowned research universities with their regional partners will join forces to create the CIRM Alpha Stem Cell Clinic (ASCC) Consortium. We are uniquely qualified by our respective institutional knowledge and collective experience to establish best practices for the delivery of stem cell therapies and education as we combine: 1) world class state-of-the-art medical centers and related health-care systems; 2) highest caliber stem cell research and education; 3) long established and successful gene medicine programs; and 4) robust and varied clinical trial infrastructure.

Our institutions provide the best in healthcare and the latest in medical technology. We are located in neighboring counties that together constitute ~34% of the total California population giving the ASCC access to a significant socially, economically and ethnically diverse population. The ASCC will employ a mobile model of management for the in- and out-patient operations, linking the institutions with their affiliated clinical care facilities, thus permitting the multi-directional flow of resources, personnel and study subjects.

The ASCC includes significant institutional commitments that will leverage substantial existing infrastructure to ensure its long term sustainability:

- NIH-funded Clinical and Translation Science Awards (CTSAs).

- A powerful consortium that provides:

    - On-line central IRB review,

    - Clinical Trials Management System,

    - Biobank and processing labs,

    - Sophisticated informatics to identify the best qualifying subjects, in an IRB-compliant manner, from among the 2M patients in the care system,

    - Drug and Device Discovery and Development initiative focusing on the early translation of academic discovery into valuable and impactful therapies.

- History of translating scientific discoveries to ground breaking clinical therapies including decades-long track record of successful GMP manufacturing and delivery of novel gene/cell therapies, notably the only FDA approved hESC based clinical trials accruing subjects.

- Stem Cell Research Centers provide critical state-of-the-art resources, dedicated, trained, technical staff, and GMP level human pluripotent stem cell derivation laboratories and banks as well as other cutting edge critical core resources,

- Exemplary education and public outreach programs to address the unique challenges of stem cell medicine.

Our lead clinical trials will develop multi-use platforms that can be used to deliver cell therapeutics across multiple trials (e.g., gene transfer and engineered immunity), providing new therapies for a wide range of life-threatening diseases.

The ASCC is built on 3 central principles: 1) commitment to the development of platforms using stem cells for multiple therapies; 2) training the next generation of stem cell scientists in the use of the platforms; and 3) using intra-and extra-institutional resources to rapidly move the most promising discoveries from the laboratory to clinical trials.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)
Two world renowned research universities and our regional partners will join forces to create the CIRM Alpha Stem Cell Clinic (ASCC) Consortium. The ASCC will be a center of excellence for the development and delivery of stem cell therapies, accelerating the availability of treatments to the population of California. We are uniquely qualified by our respective institutional knowledge and collective experience as we combine:

- World class medical centers and related health-care systems;
- Highest caliber stem cell research and education;
- Long established and successful gene medicine programs; and
- Robust and varied clinical trial infrastructure.

We are located in neighboring counties that together constitute ~34% of the total California population representing a significant socially, economically and ethnically diverse population. The ASCC will maximize availability of our clinical trials through a mobile model of in- and out-patient operations that permits the multi-directional flow of resources and personnel in the service of a range of patients from those entering Phase I clinical trials to those seeking FDA approved treatments.

The ASCC will provide the foundation for our lead clinical trials to deliver new cell therapies for cancer and blood diseases. Our lead clinical trials developed multi-use platforms that, if successful, will be used to deliver cell therapeutics across multiple trials (e.g., gene transfer and engineered immunity), providing new therapies for a wide range of life-threatening diseases in children and adults, including genetic disorders (e.g., sickle cell disease), HIV/AIDS, and many forms of cancer.

The ASCC will provide the necessary infrastructure and medical and operational expertise to effectively and efficiently drive novel stem cell therapies to clinical trials and ultimately change clinical practice. We will achieve 6 goals:

- Create a center of excellence for cell-based therapies, addressing the unique challenges of testing and delivering novel products by integrating and building upon our extensive experience and many strengths;

- Build interactive and highly trained teams and electronic data sharing systems to accelerate and translate discovery to improve human health;

- Transform the delivery of cell therapeutics through our proven GMP manufacturing;

- Advance, expand, and integrate the educational opportunities that informs patients, families, communities, and clinicians of the full range of scientifically sound and medically

appropriate, regulated stem cell-based clinical trials while providing objective information about potentially dangerous and unproven procedures;

- Identify and promote technologies for the rapid commercialization of promising new therapies, consistent with the CIRM mission to provide return on investment to the state, and

- Serve as a regional, national and international resource for evidence-based best practices in stem cell treatments.

REVIEW SUMMARY
This Alpha Stem Cell Clinic (CASC) application proposes to create a consortium between two research universities and several regional partners. This consortium would have access to a large, diverse patient population and significant existing infrastructure for patient care, stem cell research and clinical trials. The applicants propose that their CASC would establish a center of excellence for cell-based therapies to support activities such as clinical trial operations, data monitoring and coordination, patient outreach and education, and regulatory compliance. The CASC¹s proposed lead clinical trials are gene-modified hematopoietic stem cell therapies for cancer and blood disease. These trials involve potential platform technologies that could be applied to future trials for other diseases.

Responsiveness to the RFA
- Reviewers agreed that the consortium approach would create synergies. They felt that the award would particularly benefit the smaller of the two research universities.

- Reviewers noted that the value of the proposed CASC would lie predominantly in expanding access to patients, attracting national and international clinical trials and accelerating future trials in the pipeline. They cautioned that it may be difficult or impossible to accelerate the progress of the two lead clinical trials.

- Some reviewers questioned whether the CASC would provide more than incremental benefit over existing infrastructure at the applicant institutions, noting that many of the proposed personnel are being re-assigned from current NIH-funded Clinical and Translational Science Awards (CTSAs). Other reviewers found the presence of CTSAs and experienced staff already in place at the applicant institutions to be particular strengths of the proposal.

- Reviewers would have appreciated more detail regarding objective metrics for measuring success of the CASC.

Institutional Support and Sustainability Plan
- The application has outstanding infrastructure in place to support the proposed CASC, including CTSAs, GMP manufacturing facilities and stem cell research centers.

- Reviewers praised the institutional support for this application, which includes a significant financial commitment to new space development, overhead, inpatient and outpatient services, and salary for program directors and key staff.

- The proposed CASC would have access to a large patient base, estimated at 36% of the California population.

- The sustainability plan is reasonable and includes a capital campaign, a pipeline of clinical trials with funding in place, and a plan for attracting additional national and international trials.

Alpha Stem Cell Clinic Team

- Reviewers noted that the applicants have put together an impressive and multidimensional team of experienced personnel to facilitate all aspects of CASC function in development and support of clinical trials including study coordinators, patient care coordinators, patient care advocates, a data monitoring team, information technology managers, education and training coordinators, regulatory managers, compliance managers, industry and hospital liaisons, and administrative and financial support staff.

- Some reviewers cited the program directors[1] lack of specific stem cell experience as a key weakness, while others argued that this would be compensated for by their colleagues and is outweighed by the directors[1] extensive experience in translational research and administration.

Alpha Stem Cell Clinic Structure and Operational Plan

- Reviewers praised the clear organizational structure with appropriate space, personnel, clinic activities, and prioritization. The existing infrastructure, personnel, and the status of the lead trials suggest a high likelihood of successful implementation of CASC operations in the proposed timeline. The plan for integration of personnel and organization between the two research universities is reasonable and realistic.

- Some questions were raised about the budget and particularly support for personnel performing activities that may be out of the scope of the RFA.

- The applicant proposes that CASC trials will be required to use a specific data management software solution, but a reviewer worried that this would be too restrictive, and trial sponsors should be able to choose.

Lead Clinical Trials for the Alpha Stem Cell Clinic

- Reviewers agreed that the two lead clinical trials meet the scope and priorities of the RFA and address unmet medical needs. They appreciated that both are based on potential platform technologies that could be utilized in future trials at an accelerated pace.

- Lead Trial #1 has FDA clearance to begin enrolling patients. Reviewers did not find the approach to be particularly novel but felt that it has a good probability of success. The trial should provide signals of short-term safety and biological activity but will require extensive patient follow-up to monitor long-term safety.

- Lead Trial #2 is anticipated to file an Investigational New Drug (IND) application with the FDA in 2015. Reviewers found the approach to be complex, perhaps overly so, and noted significant regulatory risks that could affect the timeline. But, if successful, reviewers agreed that the platform technology could be applied to other cancers.

REVIEW REPORT FOR CIRM RFA 13-06: ALPHA STEM CELL CLINICS AWARDS

AC1-07742: CIRM Alpha Clinic

Recommendation: Not recommended for funding **Final Score:** --
Total Funds Requested: $10,963,076

PUBLIC ABSTRACT (provided by applicant)
\This Alpha Clinic will combine the expertise and resources of two medical institutions to help implement unique clinical stem cell trials. In 2007, California voters supported an initiative to promote research of stem cells to help to cure or treat various diseases. Some of those therapies are ready to be tested in people. Both our institutions have extensive experience in the use of stem cells for blood disorders, organ transplant, and genetic diseases. We now aim to use stem cells as possible treatments for these diseases and others which include sickle cell anemia, life-threatening lung problems, and disorders found during pregnancy involving abnormal fetal brain development. Clinical study of stem cells requires a strong infrastructure to provide scientific and administrative support, and our institutions are well poised to support the work of this clinic due to their history of successful complicated clinical trials. We have a dedicated clinical trials office to implement stem cell research that is staffed with personnel with experience in complex clinical trials. In addition, the recent affiliation of our two institutions provides extensive expertise in managing health problems found in children. Joining forces and utilizing the clinical and research strengths of both hospitals, working with children and adults, will be a valuable resource for the people of California and beyond.

This Alpha Clinic will support two Lead Clinical Trials: (1) A Phase II multicenter trial that uses mesenchymal stem cells for acute respiratory distress syndrome (ARDS). The Alpha Clinic will provide research nursing, technician, research assistant, and data management support. (2) A Phase I study of gene therapy for the treatment of beta-thalassemia. The complexity of implementation involves both inpatient/outpatient care, prolonged hospitalization, and necessitates relocation of patients.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)
The proposed Alpha Clinic will promote clinical testing of cell-based therapies, with a particular focus on pediatric populations affected by leukodystropies, fatal lung disorders, Type 1 Diabetes, and sickle cell anemia. We will pioneer new approaches for ARDS and solid organ transplant. The inherited blood diseases sickle cell anemia and thalassemia afflict significant numbers of individuals in California, particularly in underserved populations; affected individuals require expensive treatment and experience severe tissue damage that degrades quality of life and is often fatal. Individuals afflicted by these disorders can be cured by transplantation of blood stem cells. Nevertheless, the application of this treatment is limited because the supply of donated bone marrow stem cells is limited, and because it is necessary to match certain characteristics of the donor's and host's immune systems. In order to expand the application of transplantation for sickle cell anemia and thalassemia, we have assembled a team of clinical and basic scientists with collaborations in the biomedical industry with the goal of developing and conducting clinical trials of novel cellular therapies for these disorders. We will use support of the CIRM Alpha Stem Cell Clinic mechanism to formulate a feasible path to carry out early phase clinical trials dedicated to the expansion of cell-based therapies that use hematopoietic and other types of stem cells aimed at curative outcomes. The over-arching aim of this application is to test pre-clinical advances in human trials so that many more people might be able to receive this curative therapy. The enhanced and extended lives of these individuals will represent a direct benefit. Ultimately, the knowledge and experience produced by the research will contribute to the growing biotechnology efforts in the State and promote to overarching goal

of making novel cellular therapies available to a much broader group of patients, thus greatly extending the benefits to the affected individuals and to the taxpayers of California.

REVIEW SUMMARY

This application proposes to combine the resources and expertise of two affiliated medical centers to create a CIRM Alpha Stem Cell Clinic (CASC) that would support efficient implementation of stem cell based clinical trials in both adult and pediatric populations. The CASC would have teams at each site to oversee stem cell based clinical research and training programs, and to select projects for scientific and administrative support. The clinic would draw upon a diverse patient population from Northern and Central California and beyond, and would initiate with two lead clinical trials, both of which are currently enrolling patients: 1) a phase 2 multicenter trial that uses mesenchymal stem cells for acute respiratory distress syndrome (ARDS), and 2) a phase 1 study of gene therapy for the treatment of the blood disorder beta-thalassemia. Future CASC clinical studies are expected to include both industry sponsored and investigator-initiated studies.

Responsiveness to the RFA

- The added value of the proposed CASC to the existing capabilities and plans for coordination between the two centers was not clear or convincing.

- Some out-of-scope activities were proposed, including the use of CASC funds to pay patient support costs (housing) for one of the lead clinical trials.

- A clinical trial in the pipeline does not appear to be based on stem cells.

- The plan to use CASC funds to retain research nurses who would otherwise be laid off due to Clinical Translational Sciences Institute (CTSI) funding cuts sustains existing efforts but does not achieve CIRM¹s goal to accelerate stem cell clinical trials.

Institutional Support and Sustainability Plan

- The applicant proposes to sustain the CASC with a combination of fundraising, use of an endowment, income from 2-3 clinical trials per year, and income from indirect costs associated with federal grants or industry-sponsored studies. However, reviewers felt the plan was somewhat vague about how much would come from each source.

- The proposed clinical trial pipeline was disappointing given the depth and breadth of stem cell research expertise at these medical centers. It was not clear that a CASC would be able to accelerate some of the trials that have small patient populations and competition with other trials.

Alpha Stem Cell Clinic Team

- The Program Director (PD) has experience leading one small but complex stem cell-based clinical trial and has some administrative experience leading a clinical fellow training program. However, she/he has not led an organization comparable to the proposed CASC.

- The lead investigators on the two lead clinical trials are highly experienced with clinical development.

- The Patient Coordinator has an excellent background for that role.

Alpha Stem Cell Clinic Structure and Operational Plan

- Reviewers felt that the operational plan was not robust and needed improvements in the data management and data sharing plans. There was some concern that the data-sharing tool is different than what most others use.

- The role of the smaller medical center in implementation and operation of the CASC was largely overlooked in the application.

Lead Clinical Trials for the Alpha Stem Cell Clinic

- Reviewers were skeptical that either of the proposed lead trials would be accelerated by the formation of a CASC, given that rate of enrollment in each of those trials is limited by patient eligibility criteria and small patient populations.

- Reviewers felt that the lead beta thalassemia trial was not an ideal selection for CASC support since there are few California patients (the trial is recruiting patients from Thailand), and since the sponsor has already published results for the same product studied in a clinical trial in France.

- The ARDS trial appeared to be poorly planned, and is understaffed now due to cuts in their CTSI funding.

REVIEW REPORT FOR CIRM RFA 13-06: ALPHA STEM CELL CLINICS AWARDS

AC1-07764: Alpha Stem Cell Clinic for the Development of Regenerative Therapies

Recommendation: Recommended for funding **Final Score:** 77
Total Funds Requested: $11,673,826

PUBLIC ABSTRACT (provided by applicant)

The proposed alpha clinic will bring together an outstanding team of physician-scientists with substantial clinical trials experience including stem cell and other cellular treatments of blood diseases and others. This team will also draw on our unique regional competitive advantages derived from our history of extensive collaboration with investigators at many nearby first-class research institutions and biotech companies. We propose to include these regional assets in our plans to translate our successful research on basic properties of stem cells to stem cell clinical trials and ultimately to delivery of effective and novel therapies. We propose to build an alpha clinic that serves the stem cell clinical trial needs of our large region where we are the only major academic health center with the needed expertise to establish a high impact alpha clinic. Our infrastructure will initially be developed and then used to support two major high-impact stem cell clinical trials: one in type I diabetes and one in spinal cord injury. Both are collaborations with established and well known companies. The type I diabetes trial will test embryonic stem cell derived cells that differentiate to become the missing beta cells of the pancreas. The cells are contained in a semipermeable bag that has inherent safety because of restriction of cell migration while allowing proper control of insulin levels in response to blood sugar. These hybrid devices are implanted just beneath the skin in patients in these trials. In a second trial of stem cell therapy for spinal cord injury, neuronal stem cells that have been shown to have substantial safety and efficacy in animal models of spinal cord injury and other types of spinal cord trauma or disease will be tested in human patients with chronic spinal cord injury. Both of these trials have the potential to have very substantial and important impact on patients with these diseases and the families and society that supports them. Following on these two trials, we are planning stem cell clinical trials for heart failure, cancer, ALS, and other terrible deadly disorders. Our proposed alpha clinic also benefits from very substantial leveraged institutional commitments, which will allow for an alpha clinic that is sustainable well beyond the five-year grant, which is essential to continue to manage the patients who have participated in the first trials being planned since multi-year followup and tracking is essential scientifically and ethically. We have a plan for our proposed alpha clinic to be sustainable to 10 years and beyond to the point at which these therapies if successful will be delivered to patients in our healthcare system.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)

Many terrible diseases that afflict the citizens of California and cause substantial economic and emotional disruption to California families can potentially be treated with novel stem cell therapies. These therapies need to be tested in a rigorous and unbiased fashion in clinical trials, which is the focus of our proposed alpha clinic. Our clinic proposes to begin with clinical trials in two major diseases in need of improved treatment: type I diabetes and spinal cord injuries. The type I diabetes clinical trial will test a novel hybrid embryonic stem cell-derived pancreatic cell/encapsulation technology that is implanted just beneath the skin in an out-patient procedure, and is inherently safe because the cells are confined to a semi-permeable bag. The spinal cord injury trial will test the benefit of neural stem cells delivered to the site of injury. Both have substantial positive evidence in animal models and have the potential of leading to major breakthroughs. In addition to providing the infrastructure for these two trials, our proposed alpha clinic will also take advantage of very substantial regional expertise at our partner institutions to test stem cells in other diseases of importance in California including heart failure, ALS, cancer,

and many others. Our proposed alpha clinic will also be a major economic as well as medical driver as it leverages substantial institutional and private sector commitment, and has the potential to deliver breakthrough therapies that will be marketed either in a health care system or by private sector companies.

REVIEW SUMMARY

The overall goal of this proposal is to develop a regional center for stem cell clinical trials at a major California university. The proposed CIRM Alpha Stem Cell Clinic will harness research performed in both academia and the biotechnology industry. The clinic will leverage existing clinical trial infrastructure as well as integrate preclinical facilities to support translation. In addition to the host institution, a private donor has committed financial support to this stem cell clinic. The applicant plans to accelerate clinical trial start up and support clinical trial operations. The center anticipates initiating its two lead, industry sponsored, stem cell clinical trials in spinal cord injury and type 1 diabetes within a year. The applicants propose a process to select future trials from a pipeline of stem cell programs across a broad range of indications, including hematologic malignancies, neurological disorders, cardiovascular disease, ophthalmology and endocrinology.

Responsiveness to the RFA

- The proposal will leverage very impressive existing infrastructure and philanthropic investment at the host institution to accelerate stem cell clinical research.

- Reviewers identified the applicant¹s plan to forge collaborations with regional research institutes and the biotechnology community as a strength of the proposal.

- The proposed metrics for success were poorly selected. The most useful of these is the number of trials launched and completed. Other proposed metrics, such as IND filing, are less informative since the site will have little control over IND filing. A reviewer suggested that the numbers of patients screened and enrolled and percentage of screened patients enrolled to be better success metrics.

Institutional Support and Sustainability Plan

- Reviewers were universally enthusiastic about the outstanding existing infrastructure at the host institution as well as local research institutes and the strong biotechnology sector within the host city. This critical mass of researchers should help populate the center¹s study pipeline.

- The clinic, if approved, will be generously funded by commitments from both the host institution and an additional donor.

- Given the large patient base, trial pipeline, and institution¹s commitment to stem cell research, reviewers found the clinic¹s proposed sustainability plan to be feasible.

- The host institution has a track record in executing stem cell clinical trials and experience successfully recruiting patients at the national and international level.

Alpha Stem Cell Clinic Team

- The Program Director (PD) is an extremely active and productive stem cell researcher with experience leading multiple stem cell clinical trials. The PD occupies a position appropriate to run the center.

- Collaborators are world class and provide expertise in multiple disciplines. Reviewers appreciated the incorporation of faculty experts on each clinical trial team to both advise the trial PI and complement the trial PI¹s expertise.

- The PD hasn¹t run a large center. Concern was expressed that between launching the clinic and demands imposed by the construction of a new facility, s/he may be overcommitted.

- Reviewers suggested that staffing could benefit from adding a dedicated contracts person and from more efficient allocation of tasks to appropriate personnel. A reviewer cautioned that more study coordinators could be needed once the center ramps up. The panel further observed that over commitment of effort could become an issue for many of the key team members.

Alpha Stem Cell Clinic Structure and Operational Plan

- Reviewers appreciated that clinic¹s planned project selection process and its ability to draw from multiple institutions and diverse indications. Timely clinic set up is likely as many staff members are already in place or identified.

- The applicant¹s proposal to harmonize and accelerate Institutional Review Board (IRB) approval and clinical trial contract execution would likely accelerate clinical trial start up. However, the panel would have appreciated more detail regarding how the applicants would achieve this across all participating institutions. Similarly, reviewers found insufficient detail provided as to how accelerated patient enrollment timelines could be achieved.

- Reviewers questioned some specifics of the staffing plan. Some proposed functions appear redundant with traditionally sponsor-funded activities, while other potentially accelerating functions do not appear adequately staffed or budgeted.

- Reviewers struggled to understand the budget and to link proposed activities to specific proposed personnel.

Lead Clinical Trials for the Alpha Stem Cell Clinic

- The panel was very enthusiastic about Lead Clinical Trial 2 (LCT2) in type 1 diabetes (T1DM), which includes strong biomarkers for early efficacy signals. Further, the multisite trial has an active IND, will likely initiate within 12 months and addresses an unmet medical need. Reviewers felt the Alpha Clinic could accelerate LCT2, particularly at the host city site. Of note, however, a reviewer noted a minor criticism that the LCT2¹s lead PI¹s experience is primarily in a related clinical indication (T2DM), but not the identical clinical indication to be studied in the lead trial (T1DM).

- Lead clinical trial 1 (LCT1) in spinal cord injury has an active IND and should initiate within 12 months. The trial leverages existing transplantation and surgical expertise gained in early clinical trials using the same cell type in a different clinical indication. LCT1 addresses a dire unmet medical need and reviewers agreed the Alpha Clinic could accelerate this single site trial.

REVIEW REPORT FOR CIRM RFA 13-06: ALPHA STEM CELL CLINICS AWARDS

AC1-07788: Stem cell clinic for the treatment of genetic and chronic diseases, and injury

Recommendation: Not recommended for funding **Final Score:** --
Total Funds Requested: $10,904,643

PUBLIC ABSTRACT (provided by applicant)
The [Redacted] Stem Cell Clinic will marry science and medical expertise to accelerate the development of medical stem cell products that can be used to treat patients. The mission of Stem Cell Clinic is to optimally support clinical trials with stem cells for the treatment of genetic and chronic diseases, and injury. The Stem Cell Clinic plans to establish an infrastructure to provide critical resources to facilitate and accelerate such trials, to create a centralized home for investigators who want to perform these trials, and to develop interdisciplinary teams who share know-how and expertise for the best and appropriate use of stem cell products. The ultimate goals are to advance stem cell therapy from the early testing stage to standard of care treatment, and to train the next generation of physician scientists in the area of stem cell therapy.

Many stem cell studies that aim to translate knowledge from the laboratory to patients are in progress within the applicant institution, including trials already underway, and others which are being evaluated by the FDA. These therapies cover a broad range of disorders and regeneration of tissues such as skin, nervous system, heart and blood vessels, and blood formation in children and adults. We selected 3 trials as lead trials because they are at an advanced stage of development, they will provide proof of concept data, and they are addressing debilitating unmet medical needs. The first trial focuses on treatment of spinal cord injury with specialized neural stem cells called oligodendrocytes derived from embryonic stem cells; the second on corrective gene therapy of patient's skin stem cells to treat a severe genetic blistering disease which is presently incurable; and the third on the use of purified rare blood forming stem cells to treat deadly genetic disorders of blood formation with a new protein (antibody) that will make space in the patient's bone marrow.

Establishing a core infrastructure of clinical and regulatory management will ensure that clinical trials are standardized, planned within the context of society bioethics and policy, and conducted with improved efficiency, quality and patient safety. The three institutions that constitute [Redacted] are prepared to utilize their collective resources to support and sustain the Stem Cell Clinic by providing the necessary core facilities, ancillary infrastructure, and access to patient populations. Importantly, current fund raising campaigns will help to ensure long-term maintenance of the Stem Cell Clinic. Our institution is fully committed to providing the necessary resources and talents to fully support the entire Alpha Stem Cell Clinics Network.

In summary, we embrace the vision of CIRM to bring efficacious stem cell therapies to patients, and we believe that the Stem Cell Clinic will make a difference in finding a cure for severe and currently intractable human diseases.

STATEMENT OF BENEFIT TO CALIFORNIA (provided by applicant)
New stem cell therapies hold tremendous promise for treatment of debilitating human diseases that cannot be treated by any other means e.g. Alzheimer's disease, spinal cord injuries, cardiovascular disease, genetic diseases and cancer. Our proposal describes the formation of a new CIRM-sponsored Stem Cell Clinic that will facilitate and accelerate clinical trials of novel stem cell therapies within the public guidelines of bioethics and policy, and with the added goal

of reducing the economic burden of these diseases. Our focus will be stem cell trials that treat and even cure genetic diseases, chronic diseases and injury.

The proposed Stem Cell Clinic will consist of a highly experienced internationally renowned Program Director, a leadership team of clinicians who will conduct novel stem cell clinical trials associated with the Stem Cell Clinic, and a core infrastructure that will provide shared clinical and regulatory support to standardize trials, optimize efficiency, and reduce costs. Of the numerous emerging stem cell technologies that currently exist within [Redacted], we have selected three lead trials that will be facilitated and accelerated by the Stem Cell Clinic during the first two years of our program. The remainder provides a pipeline that will be prioritized for Stem Cell Clinic support in the subsequent 3 years.

Plans for the initial three trials are at an advanced stage. The first trial focuses on spinal cord injury (SCI) which affects an ~1.3 million people in the US. Individuals with SCI have many symptoms including loss of movement and/or sensation, spasms, increased infections, ulcers and chronic pain. This trial tests if specialized nerve cells called oligodendrocytes generated from embryonic stem cells can aid in repair of the injured spinal nerves. The second trial treats children born with a skin disease call dystrophic epidermolysis bullosa which is caused by the lack of the collagen type VII (C7) protein. These children suffer from large, severely painful blisters, and open wounds. A normal C7 gene is introduced into the patient's skin stem cells which are developed into skin grafts subsequently attached to the patient's wounds with the goal to repair the damaged skin and alleviate pain. The third trial will treat children with a deadly genetic disorder called severe combined immune deficiency (SCID). Children with SCID lack blood immune cells to fight infections, and without treatment, most die before the age of two. This trial will transfer highly purified blood forming stem cells from healthy donors to enable SCID patients to develop their own protective immune system.

These trials are examples of the kinds of pioneering therapies that Californian citizens and others will be offered via the SSCC to alleviate human suffering, with an added goal of reducing the economic burden of disease and injury.

REVIEW SUMMARY

The goal of the proposed CIRM Alpha Stem Cell Clinic is to advance stem cell therapy from the exploratory stage to standard of care treatment, and to train the next generation of physician scientists in the area of stem cell therapy. The Alpha Clinic will build upon the existing clinical and translational research resources and facilities in order to i) establish an infrastructure to facilitate and accelerate clinical trials with stem cells, ii) create an institutional home for investigators who will perform stem cell trials, and iii) the develop interdisciplinary teams with expertise instrumental for advancing stem cell therapies. Three lead clinical trials were initially proposed focused on i) the use of human embryonic-derived specialized neural stem cells to treat spinal cord injury, ii) the use of corrective gene therapy to treat a severe blistering skin disease called dystrophic epidermolysis bullosa (DEB), and iii) the use of blood forming stem cells to treat children with a potentially lethal disease called Severe Combined Immune Deficiency (SCID). The applicant reassigned the third trial as a pipeline trial after the original submission. The Clinic will leverage its existing patient referral base and pipeline of additional stem cell-based therapies under development to complete at least six additional trials within the five-year timeframe of the award.

Responsiveness to the RFA

- It was not clear to reviewers that the Clinic proposal would accelerate the already well-funded, early-stage trials which are proposed as lead trials, or whether tangible benefits will result from the additional CIRM funds.

- Reviewers noted that the proposal primarily builds for the future. Reviewers differed widely in their judgment of the potential impact on future trials; comments ranged from “incremental” to “paradigm changing” benefits.

- Proposed metrics were judged to be meaningful.

Institutional Support and Sustainability Plan
- Additional proposed support appears to overlap appreciably with existing resources at the applicant institution.

- The existing infrastructure is excellent to support clinical trial operations, manufacturing and monitoring of patients/subjects.

- The applicant institution has an outstanding track record in stem cell biology and an extraordinary history of biomedical innovations leading to patents and industry start-ups.

- The applicant institution draws on a large patient base, and the lead trials are in areas of recognized excellence.

- The proposed plan for sustainability and the institutional commitment were noted as strengths of the application. The approach to sustainability was viewed as a strength, and is a combination of philanthropy, a fee-for-service model, and a pipeline built on both institution-based and industry-based future trials.

Alpha Stem Cell Clinic Team
- The proposed Program Director (PD) is a world-recognized expert who was recently recruited to the applicant institution. The PD¹s track record and relevant experience in setting up a similar entity was recognized as a key strength of the application.

- The proposed PD¹s scientific leadership in regulated trials in stem cell and gene transfer therapy are directly relevant to the goals of the clinic.

- Reviewers differed in their judgment of a new recruit to execute an ambitious plan. Some reviewers noted that a new recruit to an established institute may encounter administrative or operational challenges. Others countered that this PD has many existing relationships and will be able to deliver on the plan based on prior strong track record.

- The team has experience in clinical trial operations and patient recruitment. The lead trials are in areas for which the applicant institution is recognized for its leadership.

Alpha Stem Cell Clinic Structure and Operational Plan
- The implementation and operational plan are solid, contain well thought-out approaches, and will likely succeed in addressing the goals of the CIRM Alpha Stem Cell Clinics network.

- Reviewers praised the fee-for-service model proposed for future trials.

- The budget was judged to be excessive for the proposed trial support given current existing trial funding and proposed lead trials.

- Reviewers differed in their judgment of the proposed staff positions and justifications. Some felt the positions were well justified, appropriate, and clearly fit with the vision for the Clinic. Others felt the positions were not well considered, targeted late-stage trials, and may substantially overlap with existing positions.

- Some reviewers considered that the proposed clinic would not become a “well oiled clinical trials machine” that appeals to industry-sponsored trials.

- Reviewers noted uncertainty about the applicant¹s commitment to engaging in multi-center trials. This section of the application was judged to be a weakness, with a plan to “consider” centralized resources but little commitment to this type of endeavor.

Lead Clinical Trials for the Alpha Stem Cell Clinic

- Reviewers considered the proposed lead trials to be a major weakness of the proposal. Concerns included the extremely small number of patients in two of the target indications, which is not ideal if the goal is to build “a machine” for stem cell trials.

- Reviewers differed in the strengths and weaknesses of selecting small trials as the lead trials. Some saw value in the rare disease as an entry point for achieving clinical proof-of-concept, and as a starting point to move into larger indications. Some criticized that one of the lead trials was not powered to detect important outcomes.

- One trial, originally designated as the third lead trial but later reassigned as a pipeline trial by the applicant, was judged to be unnecessarily complicated, and recent protocol changes make the timeline to completion uncertain for this trial.

- While all of the proposed lead trials address important unmet medical needs, reviewers questioned whether one of the proposed candidate therapeutics is truly stem cell-based, and hence responsive to the RFA.

- Two lead trials meet the criteria for active IND.

- Some elements of the proposed Clinic are relevant to late-stage trials, and therefore would not impact the current lead trials.

- All lead trials were rigorously reviewed by funding agencies; two have CIRM funding and one has NIH funding.