

TIMOTHY D. HENRY, M.D. Director, Division of Cardiology Cedars-Sinai Heart Institute

October 21, 2014

Independent Citizen's Oversight Committee c/o Maria Bonneville Executive Director California Institute of Regenerative Medicine 210 King Street San Francisco, CA 94107

## Re: (AC1-07650) The Cedars-Sinai Medical Center Regenerative Medicine Alpha Stem Cell Clinic (CSMC-α) Program Proposal

Members of the Independent Citizen's Oversight Committee:

As Project Director of the proposed Cedars-Sinai Medical Center Regenerative Medicine Alpha Stem Cell Clinic, I am writing to underscore our commitment to expanding our already active and productive regenerative medicine clinic for the benefit of the citizens of California. As outlined in our application and supported by the initial review, we have the proven expertise and infrastructure to conduct scientifically sound cell therapy clinical trials. Funding for the CIRM Alpha Stem Cell Clinics is essential to enable us to expand our program to meet current demands of California residents, as well as to enhance our ability to provide cellbased therapies for clinical use through rigorous clinical research. CIRM funding will also enhance our ability to train and educate health professionals, patients and the public about regenerative medicine.

Our application received positive reviews and was recommended on a discretionary basis for funding as a 4<sup>th</sup> Alpha Clinic Center. *We respectfully urge ICOC to exercise its discretionary ability to fund this meritorious proposal.* The stated purpose of the Alpha Clinic RFA was to encourage development of regenerative medicine clinics that facilitate enrollment in well-designed, scientifically sound clinical trials and to provide a resource for physicians, health care professionals, patients and the citizens of California. Our proposal is responsive to these laudable precepts. The following bullet points highlight our strengths and outline why our center would advance CIRM's mission.

- 1) Cedars-Sinai Medical Center Institutional Strengths:
  - a) Cedars-Sinai Medical Center is one of the largest medical centers in California (~1000 inpatient beds) with an extensive patient referral network throughout California as well as the broader southwest United States.
  - b) Cedars-Sinai Medical Center is a major training institution with over 500 medical residents and fellows in medical and surgical specialties and sub-specialties.

- c) Cedars-Sinai Medical Center has a new state-of-the-art Advanced Health Sciences Pavilion which is ideally suited to expand the influence of our current Regenerative Medicine Clinic, which is limited to heart patients but is poised to expand to other specialties.
- d) Cedars-Sinai Medical Center has extensive institutional resources to support regenerative medicine including an experienced cell therapy Institutional Review Board, Investigational Drug Services, NIH funded Clinical and Translational Science Institute, and Bioinformatics Core.
- 2) Focus on **Cardiovascular** and **Neuromuscular disease**, which makes our application uniquely suited to complement the three tier 1 applications:
  - a) Cardiovascular disease is the #1 cause of morbidity and mortality in California, the United States and throughout the world.
    - i) Over 50% of the deaths in California and the United States are from cardiovascular disease.
    - ii) A large number of cardiovascular diseases are ideally suited for cell therapy; these include heart failure, myocardial infarction, refractory angina, peripheral arterial disease and stroke.
    - Cedars-Sinai Heart Institute is ranked the #1 Heart Program in the west by U.S. New & World Report (2013-2015).
    - iv) Cedars-Sinai Heart Institute has the largest Advanced Heart Failure center in the world. In 2013, 119 heart transplants (most ever in the United States), the largest total artificial heart program and one of the largest Left Ventricular Assist Device programs.
    - v) As described below, we have extensive experience in the successful design and completion of Cardiovascular Cell Therapy clinical trials.
  - b) Neuromuscular disease
    - i) One of our two lead clinical trials targets ALS.
    - ii) There are no effective treatments at all for ALS, a disease that affects approximately 50,000 Americans.
    - iii) ALS is thought to be caused in part by lack of support cells called astrocytes which can readily be made from neural stem cells.
    - iv) Combining this with release of powerful growth factors such as GDNF can have dramatic effects on motor neuron survival.
    - v) We have one of the world's leading ALS clinics with >150 patients.
    - vi) Dr. Clive Svendsen has over 15 years of experience in the ALS stem cell field and has pioneered combined gene and stem cell therapy approaches to neurological disease.
- 3) Strong leadership:
  - a) The Cedars Alpha Clinic Project Director, Timothy Henry, MD, has arguably more experience in cell therapy trials than any other investigator in the U.S., having served or serving on the Steering Committee for over 20 cell therapy trials including 8 trials as the National Principal Investigator or Co-Investigator.
  - b) The project director has overseen the enrollment of >400 patients in 34 ongoing or completed clinical trials at the Minneapolis Heart Institute and the Cedars-Sinai Heart Institute.
  - c) This includes experience with 12 different cell types (8 autologous and 4 allogeneic) with multiple different methods of delivery.

d) The project director is 1 of the initial 5 Principal Investigators for the NIH-sponsored Cardiovascular Cell Therapy Network (CCTRN). As Principal Investigator of the Minnesota research network, we enrolled more than 50% of the patients for CCTRN. After the successful initial 5-year grant the program was expanded to 7 sites for 7 years, he continues as one of the seven Principal Investigators in this network.

## 4) Both Lead Clinical Trials at Cedars-Sinai at Cedars-Sinai are CIRM Funded

- a) Lead Trial One: ALLSTAR: Randomized, Double-Blind, Placebo-Controlled Phase II Study of the Safety and Efficacy of Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells (CDCs, CAP-1002) in Patients With an Anterior Myocardial Infarction and Ischemic Left Ventricular Dysfunction. The Phase 1 ALLSTAR Trial (NIH sponsored) has completed enrollment and the (positive) results were reported in October at Transcatheter Cardiovascular Therapeutics (TCT) in Washington, D.C. The large, multicenter Phase 2 trial (CIRM-sponsored) *is enrolling and Cedars-Sinai is the lead enrolling site*. Having the Alpha Clinic would enable better recruiting and follow-up of this key trial, which is the largest and furthest advanced clinical trial in the CIRM portfolio.
- *b)* Lead Trial Two: A Phase I Multicenter Two-Dose Escalating Study of CNS10-NPC GDNF in Patients with Amyotrophic Lateral Sclerosis. This is a critically important trial for ALS, a fatal disease without treatment options. *The trial is on target to begin enrollment in 2015.*
- c) Our 2 lead trials are consistent with the overall mission of CIRM in fulfilling unmet medical needs by bringing stem cell therapies to patients of California and beyond.
- d) Both trials are of high quality and relevant to CIRM's mission
- e) Both trials address important unmet medical needs
- f) Given the institution and team, there is a high likelihood of successful trial conduct
- *g)* Not only is feasibility of an active trial within the first year likely, it is a given, as one of the two trials is already recruiting patients and is the furthest advanced of any CIRM-funded trials.
- h) Alpha Clinic funding is essential to accelerate the completion of both of these critically important CIRM-funded trials.
- 5) Extensive Pipeline
  - a) We have five IRB-approved cardiovascular cell therapy studies (ALLSTAR, ixCELL-DCM, Athena-II, DYNAMIC, RENEW).
  - b) We have two additional trials that are currently undergoing regulatory/contracts review (DREAM-HF, CHART-2).
  - c) We are 1 of 7 sites in the NIH Cardiovascular Cell Therapy Network.
  - d) Alpha Clinic funding will enable us to apply our very successful cardiovascular disease model to neuromuscular disease followed by orthopedics, and ophthalmology.
  - e) Timothy Henry, MD and Joseph Cosico (Alpha Clinic Operations Director) were awarded a unique NIH grant to train clinical research nurse coordinators and personnel. This training grant is fully operational and can be used to support the CIRM Alpha Clinic Network.
  - f) The Regenerative Medicine Institute at Cedars-Sinai is pioneering the use of iPSC derived cells and other stem cells for treating macular degeneration (Dr. Wang), lung diseases (Dr. Stripp, CIRM funded)

and bone diseases (Dr. Gazit, CIRM funded). This provides a strong pipeline for future stem cell therapies coordinated through the Alpha Clinic.

- 6) Congruence with CIRM's overall mission
  - a) Our Alpha Clinic will accelerate the development of stem cell treatments.
  - b) Our Alpha Clinic will increase the likelihood of developing a successful treatment for patients.
  - c) Our Alpha Clinic will fill an unmet medical need, as it targets refractory advanced heart disease as well as ALS.
  - d) The approach described is efficient, in leveraging existing strengths and resources.
- 7) Value Proposition to being a key member of CIRM Alpha Clinic Network.
  - a) We will be able to share our resources with other Alpha Clinics and also serve as extension portals for recruitment and follow-up for their clinical trials in other disease targets and for educational initiatives for cell therapy.
  - b) Reciprocally, we can provide other Alpha Clinics with access to our robust cardiovascular and neuromuscular cell therapy trials from Phase I-Phase III.
  - c) Cedars-Sinai Medical Center already has a successful regenerative medicine clinic, one of the first of its kind in the U.S (press release attached).
  - d) The Cedars-Sinai Medical Center has an active regenerative medicine clinic website. <u>http://cedars-sinai.edu/Patients/Programs-and-Services/Heart-Institute/Centers-and-Programs/Regenerative-Medicine-Clinic/index.aspx</u>

In summary, Cedars-Sinai provides unique strengths to enable success for the CIRM Alpha Clinic Program. We will be excellent stewards of CIRM funds and will deliver by meaningfully contributing to the advancement of cell therapy through enrolling, follow-up data analyses and reporting of our results in peer-reviewed scientific meetings and publications as well as lay educational initiatives. My colleagues and I look forward to briefly sharing our vision with you on October 23, 2014.

Thank you for your consideration.

Sincerely,

Timothy D. Henry, MD Director, Division of Cardiology Professor, Department of Medicine Lee & Harold Kapelovitz Endowed Chair Cedars-Sinai Medical Center