CHAIRMAN'S LETTER

ROBERT N. KLEIN, J.D.

"[we] have promises to keep, and miles to go before [we] sleep"[1]; but, the Milestones of Progress of California's stem cell scientists are undeniable, as they advance toward stem cell therapies for chronic disease and injury. Proposition 71, the California Stem Cell Research and Cures Initiative, approved by the voters in 2004 drives this stem cell research progress. Although its initial scientific funding was almost entirely delayed from 2005 to May 2007 by litigation brought by ideologically motivated plaintiffs, an extraordinary body of research is under way with more than 800 scientific discoveries published, FDA-approved human trials in progress, and nine nations and two international states joined together with California as international funding partners. Proposition 71 projects have generated 25,000 job years and attracted over $1 billion in matching funds from private donors, institutions, industry and foreign governments; these matching funds almost equal the $1.25 billion in funding commitments made by CIRM's Governing Board, after peer review, to stem cell research and facilities.

EXTERNAL REVIEW AND VALIDATION

Beyond the validation of the scientific importance of this work, implicit in attracting over $1 billion in matching funds and the 11 foreign governments electing to join stem cell research with California, an independent external advisory panel, including some of the world's most distinguished medical research leaders, evaluated CIRM's performance in 2010. The review panel members included:

Dr. Alan Bernstein, Dr. George Daley, Professor Sir Martin Evans, Dr. Igor Gonda, Dr. Judy Illes, Dr. Richard A. Insel, Dr. Richard Klausner, and, Dr. Nancy Wexler[2].

The External Advisory Panel concluded that, "CIRM has already delivered extraordinary results in a remarkably short period of time. This accomplishment is especially noteworthy given the limited administrative budget and correspondingly small staff. The agency has awarded 364 grants and loans for research and facilities to 54 institutions totaling $1.07 billion."

> *To date, the agency has issued 22 rounds of funding. CIRM has established systems and processes for soliciting, evaluating, and monitoring high quality, targeted research projects and has done this in an ethically sound manner. CIRM has established a rigorous peer review process that engages world experts in stem cell research who are called upon for their advice and recommendations. In a short few years, CIRM has created a robust, world-class stem cell research effort in California, with a greatly expanded workforce, state of the art facilities and the requisite physical and intellectual infrastructure needed to accomplish its scientific goals.*
>
> *In summary, progress during this first stage of CIRM's development has been remarkable…"*
>
> (Report of the External Advisory Panel, p. 8)[3]

MILESTONES OF PROGRESS

Proposition 71 funding has built an extraordinary human and physical infrastructure to develop stem cell therapies in California, while driving the frontiers of the field into human trials and a broad spectrum of discoveries that promise to revolutionize medicine (see pages 16 to 25).

Here, in outline, I highlight a few major accomplishments, by category:

Building The Research Leadership Infrastructure: To build the research leadership opportunities for the best and brightest young faculty of this country, the New Faculty Awards Program has awarded 45 new faculty positions; each of these individual leaders has attracted an average of six to eight post docs and graduate students to their labs, building an aggregate discovery force of approximately 315 brilliant young researchers.

Building The Research Technical Work Force: The vast expansion of stem cell research and therapy development efforts require a concurrent and rapid development of the research technician workforce. To meet this need and provide an entry platform for students from every economic background to enter the stem cell field, CIRM developed the Bridges Program, conceived by the Governing Board, to bring together 32 of the leading stem cell research institutions and companies with 28 state colleges, city colleges and independent regional colleges' best and brightest young students who seek a career in the stem cell research and therapy field. In the first five years, this program should reach 750 students.

Constructing The Research Facilities Infrastructure: To develop the world-class research platforms to launch this new field, CIRM has funded 12 Institutes, Centers of Excellence and Specialized Research Centers —bringing nearly a million square feet of new research space on line by the end of 2011.

Advancing The Therapy Candidates Through Phase 1 and Phase 2 Human Trials: Seven human trials have been approved by the FDA and/or are seeking a final release to commence their human trials. These trials have benefited from the contributions of CIRM either in the initial development of the science driving the trial (through research, shared facilities, or GMP facilities funding), the trial itself, or in the case of brain cancer the second phase of the trial's development will be funded by CIRM.

Developing A Therapy Pipeline For Human Trials: An additional 14 Disease Teams are proceeding toward human trials for diseases ranging from AIDS to Diabetes to Age Related Macular Degeneration and Stroke.

Supporting A Broad Portfolio Of Preclinical Advances: A broad portfolio of preclinical therapy candidates (or development bottlenecks) is in development supported by 37 separate grants.

Broadening The Base Of Knowledge Necessary To Identify And Develop Therapy Candidates: More than 800 discoveries have been published in the four years since the full funding began after the defeat of litigation that attempted to block implementation of the initiative's programs.

Leveraging California's Internal Scientific Capacity And Global Collaborations: Leveraging the scientific capacity of California's Stem Cell Research by a) connecting with the world's leading scientists and b) building internal California structures and incentives for sharing discoveries, shared facilities and collaboration is a strategic goal with progress best illustrated by focusing on three examples:

1) First, 11 international government funding agencies have now signed collaborative agreements with CIRM—pledging to fund their scientists on teams with California scientists, if they succeed in obtaining an approval from both CIRM's peer review process and the Governing Board review. This program brings international scientific leverage to California's mission.

2) Second, The Shared Research Laboratory Program at 17 sites exemplifies the scientific leverage that can be gained by providing leading edge research equipment, training, and supplies at strategic locations within the state's leading research institutions, to drive minimally funded early discovery experiments targeting preliminary data to qualify for future research grants. Stanford University, for example, credits its $4.14 million Shared Research Laboratory grant, with providing the launch of new scientific studies that have now led to approximately $41 million in additional grants from the NIH and other leading funding sources, with another $14 million in pending grants (just in the three years after the lab's installation).

3) Third, CIRM's Intellectual Property Policies push the spread of new biomedical materials throughout the state, leveraging the immediate value of the discovery and speeding the propagation of the knowledge. For example, when a grantee publishes a discovery that includes biomedical research materials first produced by the CIRM-funded research, those materials must be shared for research in California, either: a) free or at actual cost; or b) the information necessary to reconstruct or obtain identical biomedical material must be provided.[4]

For a current list of Milestones of Progress, see the 2010 Annual Report page on CIRM's website: www.cirm.ca.gov/2010AnnualReport

California's modern Medici empowered the people of California, first giving them the opportunity to vote their vision and then leading the effort to raise $1 billion in matching funds to carry out the commitments of Proposition 71.

CHAMPIONS OF STEM CELL RESEARCH: CALIFORNIA'S MODERN MEDICI

The Medici of Florence, Italy of the 1650s and the 1660s protected and financially supported an empirically based Scientific Renaissance from religious suppression that lead to the creation of the Hand Book of Empirical Science from the Accademia Del Cimento and the birth of the Royal Academy of London in 1660 and the Royal Academy of Paris in 1661: the expansion of the Scientific Renaissance.

California's modern Medici of stem cell research are the great philanthropic patron families who committed resources at vital moments and, through their support, have led the stem cell revolution. These visionaries include the following, all of whom provided major support for the world-class discovery platforms embodied in CIRM's Major Facilities Program.

ELI AND EDYTHE BROAD	RAY AND DAGMAR DOLBY	EDWARD AND VIVIAN THROP	KAT TAYLOR AND TOM STEYER
LORRY LOKEY	T. DENNY SANFORD	THE KECK FAMILY TRUST	
LI KA SHING	WILLIAM AND SUE GROSS	REGINA AND JOHN SCULLY	

Their leadership followed the courageous intervention of the philanthropic individuals and foundations that bought CIRM bonds despite the overhang of litigation, which could have nullified the bond obligations; those champions included:

JOHN AND ANN DOERR	ELI AND EDYTHE BROAD	THE DAVID AND LUCILLE
RICHARD BLUM	GORDON AND BETTY MOORE	PACKARD FOUNDATION
WILLIAM BOWES	HENRY SAMUELI	STEWART AND LINDA RESNICK
JOHN MOORES	STEVEN AND MARY SWIG	HERB AND MARION SANDLER
J. TAYLOR CRANDALL	IRWIN AND JOAN JACOBS	GERSON BAKAR FAMILY

All of the great people and families listed above built their contributions upon the visionary commitments of the individual donors to the Proposition 71 campaign.

This extraordinary group of California's modern Medici empowered the people of California, first giving them the opportunity to vote their vision and then leading the effort to raise $1 billion in matching funds to carry out the commitments of Proposition 71. Without their vision, their commitment and their courage, Proposition 71 would have faltered, broken by political misrepresentations and litigation—all of which was designed to block the mandate of 7 million California voters. Without the decisive endorsements and financial backing of all of these modern day heroes, the stem cell revolution would have stopped, a broken vision of the potential to empower the understanding of chronic disease and injury. The world would have missed an historic opportunity to reduce human suffering.

One must also acknowledge with profound respect and appreciation, the critical contribution of the peer reviewers, from other states and countries, to this progress; without them the scientific quality achieved would not have been possible. (See list of reviewers on p. 44.)

REVENUE POSITIVE AND JOB GENERATING

The California Mandate: Revenue Positive to 2014. California's voters approved a bond-financed structure for stem cell research to permit the research and therapy development to drive forward from concept to human trials, even during times of intense economic stress for the state. In 2004, California experienced a period of maximum financial stress, similar to 2010–11, with the voters approving $15 billion in deficit funding bonds in April of 2004, to keep the state solvent before approving Proposition 71 in November of 2004. Proposition 71 was structured with the bond interest capitalized for the first five years, with no payments from the general fund; the original economic projections, reconfirmed by a December 2010 study, projected that the new state tax revenue generated from the research and development funding—just through 2010—would offset state general fund bond payments in the sixth through the eighth project year: 2010–2012.

After considering the new economic activity in the sixth through ninth project year, along with over $1 billion in donor and institution matching funds, current projections estimate that new state tax revenue will offset all state bond interest payments through the ninth project year and a portion of the (2014–2016) 10th through 12th project years.[5]

The first $2 billion of research funding, along with matching funds, is expected to produce 25,000 job

years and approximately $260 million in new state tax revenue and nearly $70 million in local government tax revenue, using a very conservative economic model. If the industry "clusters model"[6] initially developed by Michael Porter of Harvard is incorporated into the tax revenue model, the State and Local Government revenues should increase substantially. Three of the largest biotech clusters in the United States, one in the San Francisco Bay Area, one in San Diego and one in formation in the Los Angeles basin, could well produce a substantially greater economic synergy for California, than the conservative basic economic multiplier used in the current economic impact study.

THE LONG-TERM FUNDING MODEL: ESSENTIAL TO REACHING PATIENTS

Californians made a critical choice to authorize approximately 10 years of funding (which formally commenced in June of 2007), with the final funding commitments currently scheduled for the summer of 2017, financing research through 2020. It is only with this unbroken chain of funding commitments that new discoveries can be translated into therapies and carried forward to phase 1 and phase 2 FDA human trials; at that point, the biotech industry should pick up the promising new therapies and develop them for broad-based patient access.

California families made a commitment for the benefit of their own families, families of the country and families of the world, to empower research that actually reached patients and was not cut off by the episodic financial crises so typical of short-term state revenue and budget cycles. California families and businesses (all of the state Chambers of Commerce along California's coast—from San Diego to San Francisco—endorsed the initiative along with the State Chamber of Commerce) voted to invest today in developing Stem Cell Therapies that might intervene in chronic disease and injury—to reduce the severity or cure (in whole or in part) the condition, rather than being left with a health care system focused on financially crushing chronic therapies.

A primary objective of Stem Cell Research is to develop interventionist therapies that can substantially reduce or eliminate the long-term cost of chronic therapies and complications for patients, their families, employers and the State. The 10- to 15-year stable research funding commitment is possible because the bond structure of Proposition 71 spreads the cost of stem cell therapy development over 40 years and the multiple generations who will benefit from the new therapies.

CALIFORNIA AS A RESEARCH SANCTUARY

On Aug. 23, 2010, Judge Royce Lamberth of the Federal District Court for the District of Columbia issued a decision that served as a stark reminder of the importance of Proposition 71.[7] Judge Lamberth granted a preliminary injunction in a challenge to the Obama Administration's Guidelines for Human Stem Cell Research (the "Guidelines"), which authorizes federal funding for research using human embryonic stem cells that were derived from human embryos created for reproductive purposes[8] but which prohibits funding for research involving the *derivation* of human embryonic stem cells. The decision, before it was stayed by the Court of Appeals, effectively halted federal funding of human embryonic stem cell research, including funding that would have been permitted under President Bush's 2001 executive order.

Plaintiffs (two adult stem cell researchers, the Christian Medical Association and others) filed an action to prevent the Guidelines from taking effect. The plaintiffs argued, among other things, that the Guidelines violated the Dickey-Wicker Amendment, which prohibits the use of federal funds for "research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death . . ."

ON APRIL 29, 2011, THE U.S. COURT OF Appeals reversed the District Court's order, concluding that the National Institutes of Health (NIH) had reasonably construed the Dickey-Wicker Amendment to prohibit federal funding for research involving the derivation of human embryonic stem cell lines (hESCs), while permitting funding for research in which hESCs will be used.[9] Although the Court of Appeals' decision currently permits the NIH to continue to fund hESC research, it is just the first step in a long process. The case will now return to the District Court and is likely to be subject to additional appeals before the case finally concludes. **Because of Proposition 71, California is not subject to the NIH guidelines or to the courts' orders; CIRM, therefore, may continue to fund embryonic stem cell research regardless of the outcome of the Sherley litigation or future federal litigation.**

The sanctuary in California for hESC research is of global importance. In Europe, the European Court of Justice is considering the opinion of its Advocate General that stem cell patents are "contrary to ethics and public policy" because they require "industrial use" of human embryos.[10] It is rare for the court of 13 members to reject the recommendation of its Advocate General. In an open letter opposing the opinion, other leading European stem cell researchers wrote:

> *It is premature to suggest that human embryonic stem cells can be replaced in development of therapies. Although induced pluripotent stem cells offer additional possibilities, particularly for disease modeling, the reprogramming process is still imper-*

fect. Scientists working in stem-cell medicine will not be able to deliver clinical benefits without the involvement of biological industry. But innovative companies must have patent protection as an incentive to become active in Europe. The advocate-general's opinion therefore represents a blow to years of effort to derive biomedical applications from embryonic stem cells in areas such as drug development and cell-replacement therapy. If implemented, European discoveries could be translated into applications elsewhere, at a potential cost to the European citizen.

Peter Andrews (Univ. of Sheffield),
Austin Smith (Wellcome Trust),
Katherine Verfaille (Katholieke Univ., Leuven)

REGARDLESS OF THE FINAL DECISION OF the European Court of Justice, the potential future of instability of European patent protection signaled by these events will further enhance the value of Proposition 71 and the California Constitution's protection of human embryonic stem cell research and its funding.

The importance of preserving access to human embryonic stem cell research has recently been emphasized by the multiple top line journal articles describing the critical differences between iPS derived stem cells and embryonic stem cells. A number of these derivation differences could have major negative impacts on therapeutic applications; at this point, human embryonic stem cells remain the bench mark, the gold standard, for validating the accuracy of cell derivations and the best, existing option for many types of cellular therapies.

THE PRIVILEGE OF SERVICE: A TRIBUTE TO THE GOVERNING BOARD

It has been a great privilege, as Chairman, to serve with each and every member of the distinguished and committed Board. I wish to convey my deepest admiration and gratitude for the service of the Board members during my tenure. Each member of the Board has brought a treasury of talent and experience that has left an indelible impact, improving the quality and outcomes of the Board's contribution to this mission. Many Board members have served on one or more Subcommittees, Task Forces and/or Working Groups, representing hours of their invaluable time spent on additional work toward meeting our mission, with those in leadership roles dedicating yet more effort over the years. We cannot thank them enough.

THE DEDICATION OF STAFF

The External Review Panel found that CIRM had made remarkable progress in less than six years, especially given that the progress has been driven by a board, and a staff that averaged in the low forties in number, further limited to expenditures of approximately 5 percent of the agency's cumulative, annual grant and loan budgets. Each member of the small, highly credentialed staff is a remarkable, dedicated contributor, inspired by the mission, working endless hours with an intense effort, to advance stem cell science and therapies. (For a staff list please see p. 47.)

Motivating most staff members are memories of a family member or friend suffering from chronic disease or injury or one whose life ended with an early, untimely death. Through the commitment and sacrifice of each staff member, we move one step closer to empowering new discoveries, new therapies for a better world with less suffering and greater hope. When the story is told, years later, of the extraordinary medical discoveries and advances funded by the CIRM Board and staff, many may paraphrase Winston Churchill's words, (rarely) "in human history have so many owed so much to so few"; but, all will also remember, this great dedicated experiment—led by the "few"—was made possible by the vision of the voters of California.

MILESTONES OF PROGRESS HONOR OUR PROMISES

As I watched my mother die with Alzheimer's, stripped of every memory of family, friends, children—every hope and dream of her life—I promised her I would do my best to see that others would not suffer her same death while "living" out their last years. Stem cell research for Alzheimer's is in its early stages. Although surprising progress has been made with Proposition 71 funds, "there are [still] miles to go before [we] sleep;" but, our Milestones of Progress honor our promises and provide hope that years of future commitment by all of us, patient advocates and scientists, business and biotech leaders, may deliver on those promises for my mother, your father or brother, and all of our children, to protect them from chronic disease or injury that might otherwise steal their lives and hopes.

A MESSAGE TO CALIFORNIA'S CITIZENS

In 2004, the voters of California gave Proposition 71 the largest vote total for any major funding initiative in California's history. At 7,018,000 votes, Proposition 71 received more votes in 2004 than any US Senator in California's history. The mandate from this visionary vote by California citizens has given birth to a new renaissance in the understanding of the human body and its battles with millennia of suffering from chronic disease.

The future of mankind is in your hands, California. A gateway to medical discoveries and therapies has opened. Let us support and defend this opportunity

LIST OF BOARD LEADERSHIP, SUBCOMMITTEE, TASK FORCE AND WORKING GROUP LEADERS

(See pages 44 – 47 for complete membership lists)

CURRENT AND FORMER BOARD LEADERSHIP

- Robert Klein, Chair
- Sen. Art Torres (Ret.), Vice Chair
- Duane Roth, Vice Chair
- Dr. Ed Penhoet, Former Vice Chair

CURRENT BOARD SUBCOMMITTEE LEADERSHIP

- Sherry Lansing, Chair, Governance Subcommittee
- Dr. Claire Pomeroy, Vice-Chair, Governance Subcommittee
- Michael Goldberg, Chair, Finance Subcommittee
- Marcy Feit, Vice-Chair, Finance Subcommittee
- Jeff Sheehy, Chair, Science Subcommittee
- Dr. Oswald Steward, Vice-Chair, Science Subcommittee
- Dr. Francisco Prieto, Chair, Evaluation Subcommittee
- Dr. Ted Love, Vice-Chair, Evaluation Subcommittee
- Sen. Art Torres (Ret.), Chair, Legislative Subcommittee
- Dr. Francisco Prieto, Vice-Chair, Legislative Subcommittee
- Sen. Art Torres (Ret.), Chair, Communications Subcommittee

PAST BOARD SUBCOMMITTEE LEADERSHIP

- Dr. Ed Holmes, Chair, Grants Working Group Search Subcommittee
- Dr. David Kessler, Chair, Standards Working Group Search Subcommittee
- Dr. Michael Friedman, Chair, Facilities Working Group Search Subcommittee
- Dr. Phillip Pizzo, Vice Chair, Presidential Search Subcommittee
- Dr. Tina Nova, Chair, Legislative Subcommittee
- Dr. Tina Nova, Vice-Chair, Governance Subcommittee
- Dr. Ed Penhoet, Vice-Chair, Science Subcommittee
- Dr. Gerald Levey, Chair, Evaluation Subcommittee
- Robert Klein, Chair, Presidential Search Committee
- Robert Klein, Chair, Legislative Subcommittee
- Robert Klein, Vice-Chair, Legislative Subcommittee

BOARD TASK FORCE LEADERSHIP

- Dr. Ed Penhoet, Chair, IP Task Force
- Duane Roth, Chair, Loan Task Force
- Marcy Feit, Co-Chair, Bridges Program Development Task Force
- David Serrano Sewell, Co-Chair, Bridges Program Development Task Force
- Gayle Wilson, Co-Chair, Task Force on Congressional Policy on Human Embryonic Stem Cell Research
- Robert Klein, Co-Chair, Task Force on Congressional Policy on Human Embryonic Stem Cell Research

for our children's lives. Indeed, our lives may depend on the discoveries born from the sacrifice and commitments of California's scientists and physicians. The Milestones of Progress of Proposition 71 serve as witness to the dawn of the California Stem Cell Renaissance, a new hope for the future of mankind to reduce the suffering of every child, every woman and every man on this planet from chronic disease and injury.

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[1] Robert Frost, "Stopping by Woods on a Snowy Evening," 15-16

[2] See this letter online for links to the External Advisory Panel report including biographies: www.cirm.ca.gov/2010AnnualReport_Chair

[3] See this letter online for links to the presentation to the board by Dr. George Daily, Dr. Rick Klausner, Dr. Nancy Wexler and Dr. Alan Bernstein: www.cirm.ca.gov/2010AnnualReport_Chair

[4] See section 100304 of CIRM's intellectual property regulations: http://www.cirm.ca.gov/reg/pdf/Reg100304_IP_NonProfit_Org.pdf

[5] The general fund of the State of California is not projected to be burdened by the bond debt services for the Stem Cell research funding through 2013, on a net economic basis. It is paying the debt service with new state tax revenues generated by the research funding and the tax revenues created by research facilities construction funded through matching fund contributions from private donors and institutions.

[6] *Clusters and Entrepreneurship; Journal of Economic Geography*; Delgado, Porter and Stern; May 28, 2010

[7] *Sherley v. Sebelius*, 704 F. Supp.2d 63 (D.D.C. 2010)

[8] The family must have completed their family planning and these cells would otherwise be thrown away.

[9] *Sherley v. Sebelius*, ___ F.3d ___, 2011 WL 1599685 (D.C. Cir. 2011).

[10] http://www.independent.co.uk/news/science/ruling-on-stemcell-patents-may-spell-end-of-research-in-europe-2275771.html