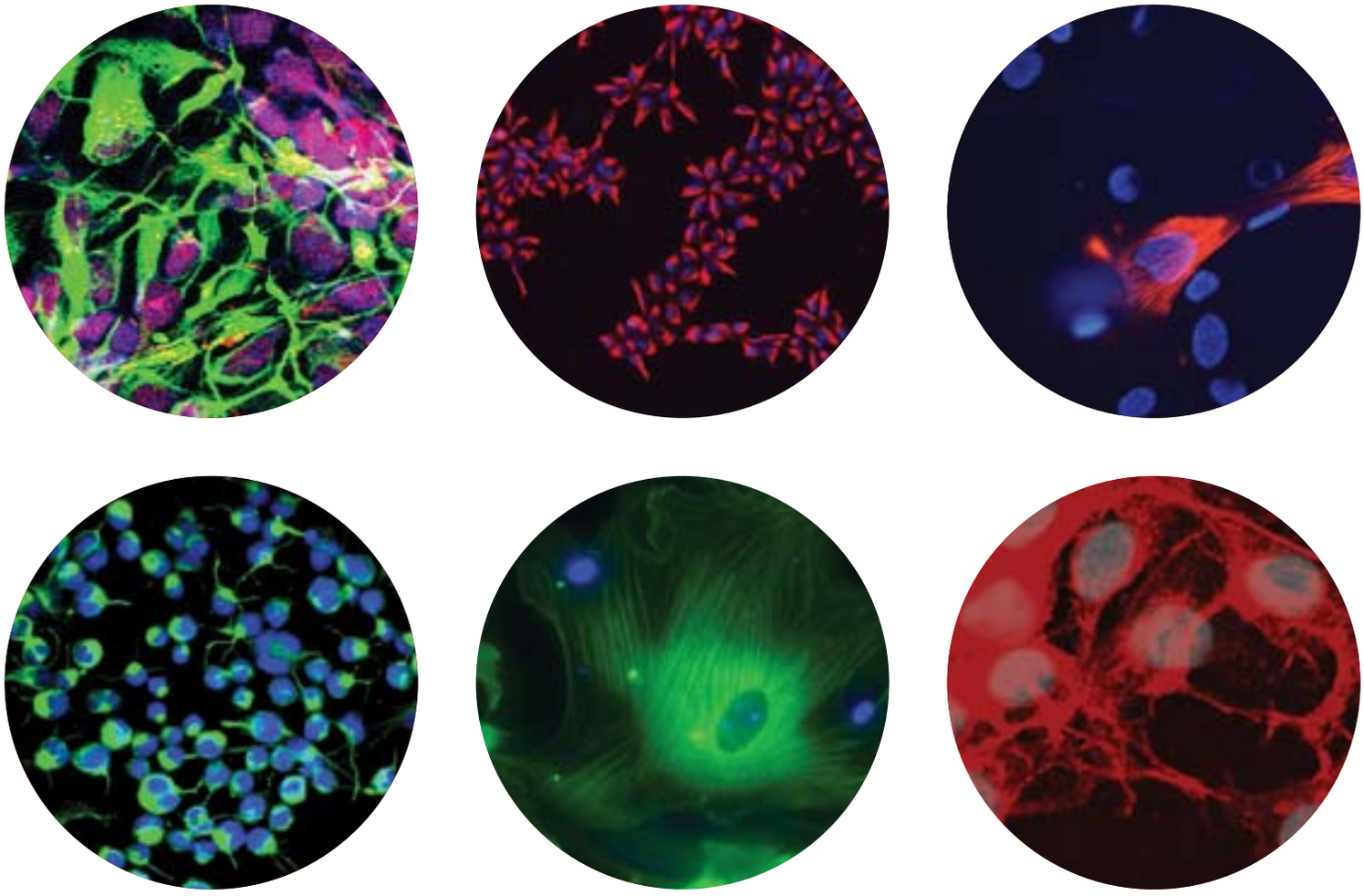
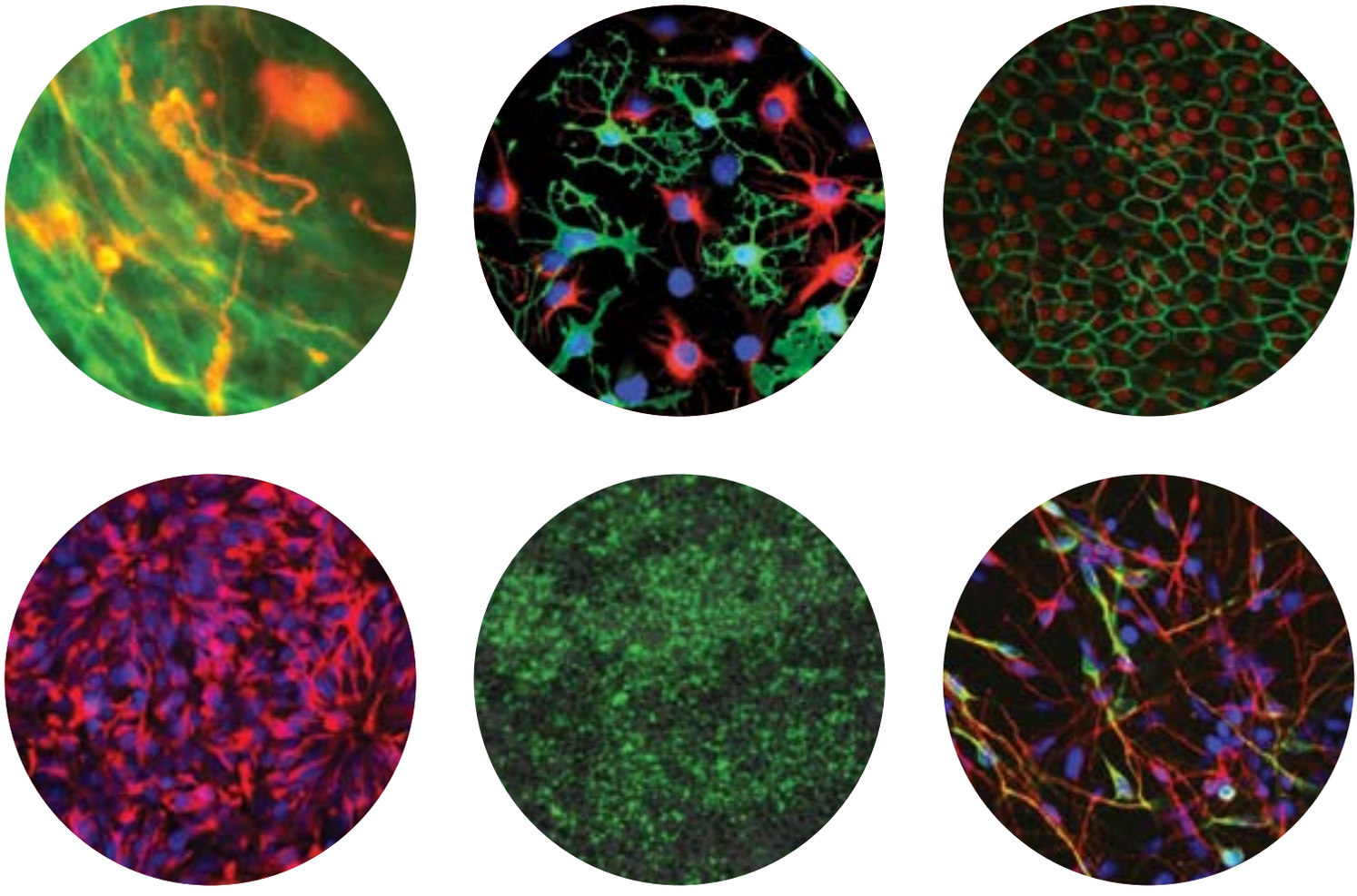
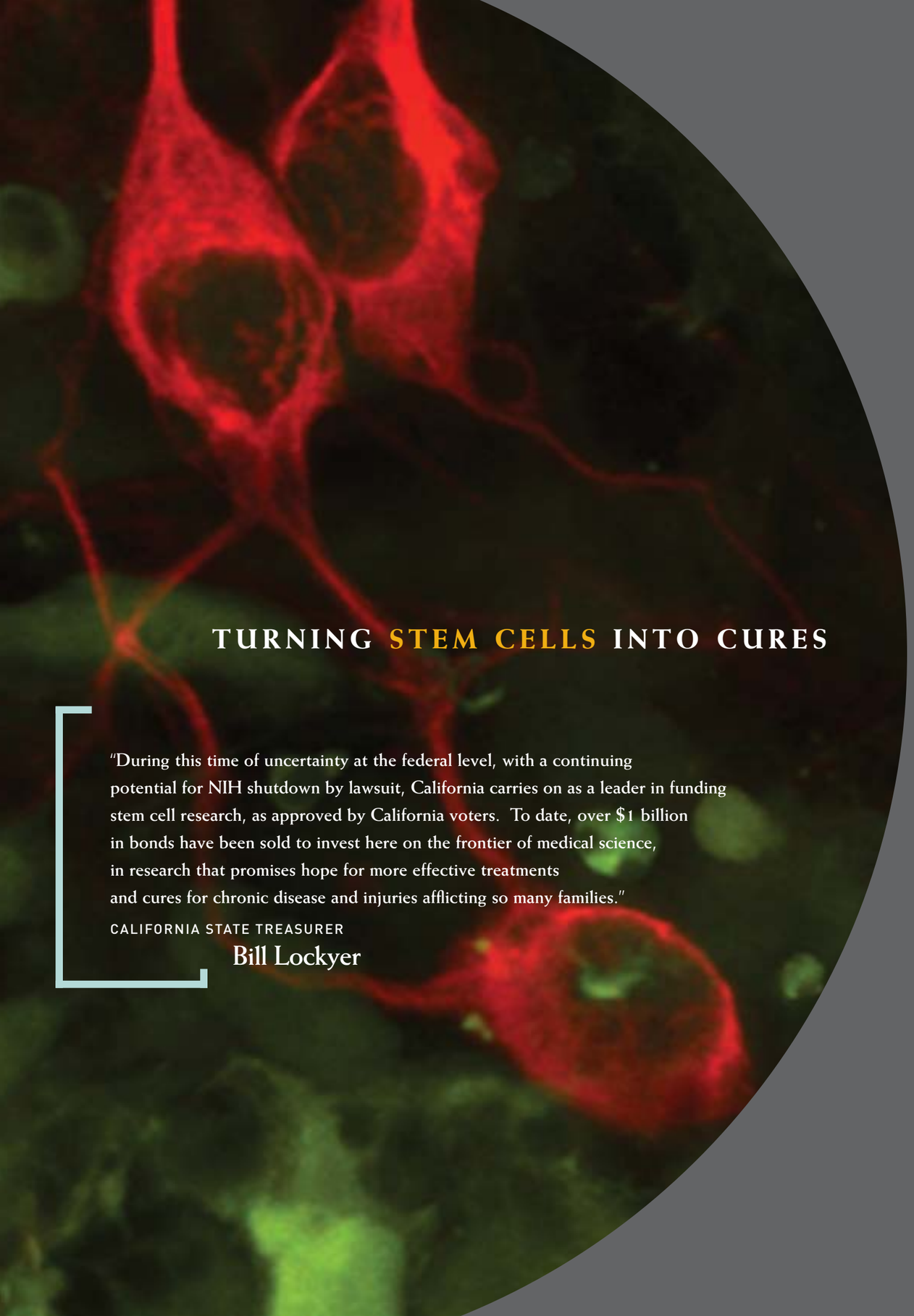


CIRM CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE ANNUAL REPORT 2010





TURNING STEM CELLS INTO CURES

"During this time of uncertainty at the federal level, with a continuing potential for NIH shutdown by lawsuit, California carries on as a leader in funding stem cell research, as approved by California voters. To date, over $1 billion in bonds have been sold to invest here on the frontier of medical science, in research that promises hope for more effective treatments and cures for chronic disease and injuries afflicting so many families."

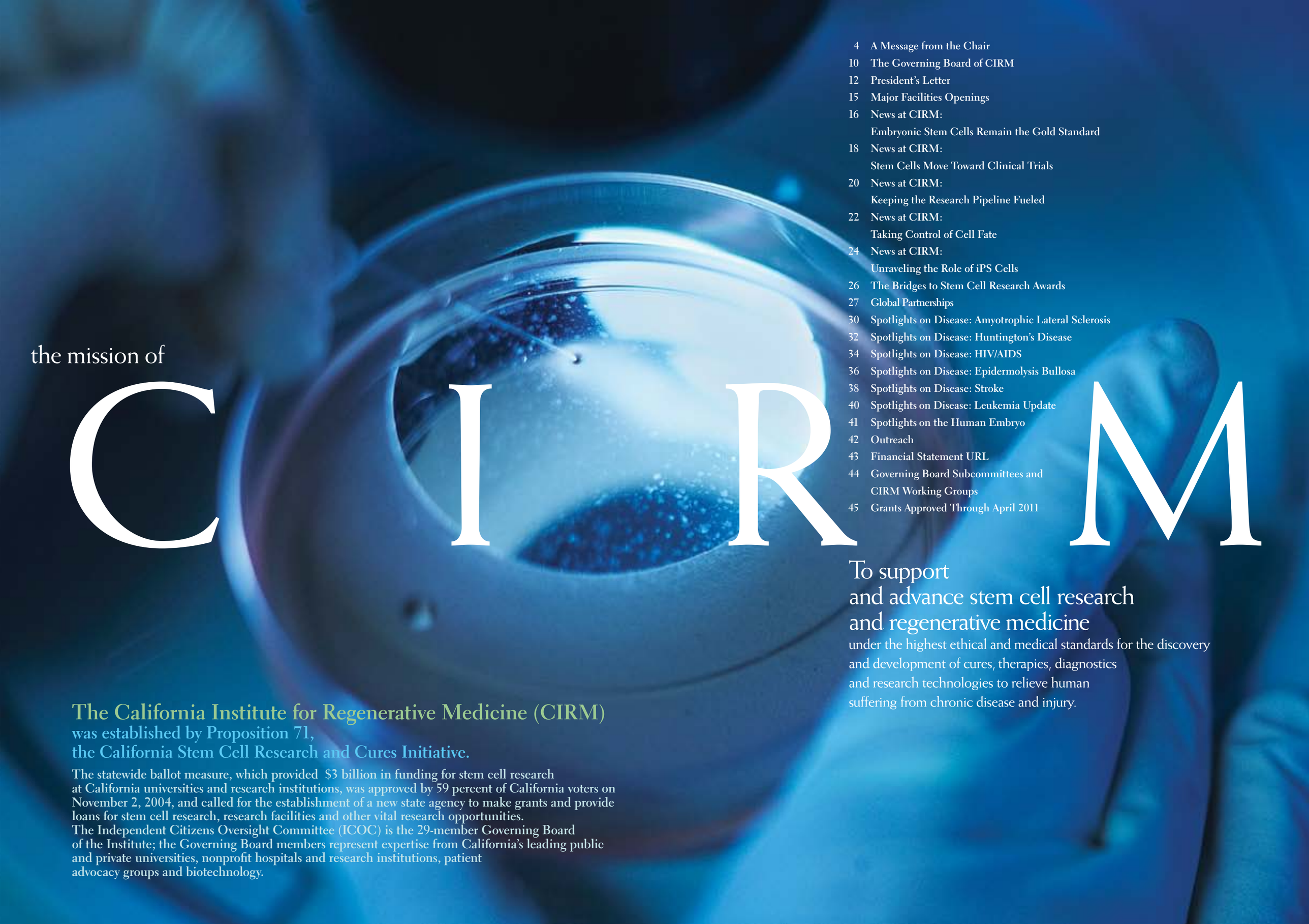
CALIFORNIA STATE TREASURER

Bill Lockyer

Autoimmune Diseases Arthritis Crohn's Disease Devic's Syndrome Multiple Sclerosis Osteoporosis Systemic Lupus Erythematosus (Lupus) Systemic Sclerosis Type 1 Diabetes **Cancers** Bladder Brain/Central Nervous System Breast Colon/Lower Bowel Endometrium/Cervix Ovary Esophagus Kidney Leukemia Liver Lungs/Respiratory System Lymphoma Myeloma Oral Cavity Pancreas Prostate Skin Stomach **Cardiovascular Diseases** Acute Ischemic Heart Disease (angina) Myocardial Infarction (heart attack) Chronic Ischemic Heart Disease (athersclerotic heart disease) Cardiomyopathy Cerebrovascular Disease (stroke) **Circulatory/Respiratory Diseases** Chronic Obstructive Pulmonary Disease Pulmonary Fibrosis **Injuries** Severe Burns Spinal Cord Injury **Eye Disorders** Macular Degeneration Retinitis Pigmentosa **Infectious Diseases** HIV/AIDS **Metabolic Diseases** Adrenoleukodystrophy Aspartylglycosaminuria Canavan's Disease Cystic Fibrosis Fabry Disease Fucosidosis Gaucher Disease Leukodystrophy Mucopolysaccharidoses Niemann-Pick Disease Pompe Disease Porphyria Sickle Cell Disease Tay-Sachs Disease Type 2 Diabetes **Muscular Dystrophies** Becker Duchenne Emery Dreifuss Facioscapulohumeral Fukuyama Limb Girdle Myasthenia Gravis Myotonic Dystrophy **Neurological Diseases of Adulthood** Alzheimer's Disease Huntington's Disease Lou Gehrig's Disease (ALS) Parkinson's Disease **Neurological Diseases of Childhood** Asperger Syndrome Autism Cerebral Palsy Childhood Disintegrative Disorder Down Syndrome Epilepsy Hydrocephalus Rett Syndrome

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Today's Investment • Tomorrow's Therapy • Future Cures



the mission of

CIRM

To support and advance stem cell research and regenerative medicine

under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury.

The California Institute for Regenerative Medicine (CIRM) was established by Proposition 71, the California Stem Cell Research and Cures Initiative.

The statewide ballot measure, which provided $3 billion in funding for stem cell research at California universities and research institutions, was approved by 59 percent of California voters on November 2, 2004, and called for the establishment of a new state agency to make grants and provide loans for stem cell research, research facilities and other vital research opportunities.
The Independent Citizens Oversight Committee (ICOC) is the 29-member Governing Board of the Institute; the Governing Board members represent expertise from California's leading public and private universities, nonprofit hospitals and research institutions, patient advocacy groups and biotechnology.

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

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

[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

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

REPRESENTING PATIENTS, RESEARCHERS, BIOTECHNOLOGY – AND YOU

CIRM is governed by 29 dedicated Californians representing patients, researchers and the biotechnology industry whose knowledge, passion and commitment to CIRM's mission has guided the organization through a successful first six years. These board members serve on six subcommittees and on the three working groups that provide recommendations to the board regarding CIRM funding, ethical standards and facilities.

CIRM PUBLIC MEETINGS:

ICOC meetings: **69**

Subcommittee meetings: **114**

Standards working group meetings: **23**

Grants working group meetings: **28**

Facilities working group meetings: **19**

Leadership

ROBERT KLEIN, J.D.
(CHAIR)
President,
Member, International Advisory Board, JDRF

ART TORRES, J.D.
(VICE CHAIR)
Board of OneLegacy Transplant Donor Network

DUANE J. ROTH
(VICE CHAIR)
CEO and Board Member, CONNECT

Biotechnology representatives

MICHAEL GOLDBERG
General Partner, Mohr, Davidow Ventures

TED W. LOVE, M.D.
Executive Vice President, Head of Research and Development, Onyx Pharmaceuticals

ED PENHOET, PH.D.
Director, Alta Partners; Board Member, Gordon & Betty Moore Foundation

Patient advocates

MARCY FEIT, R.N., M.S.N.
Type II Diabetes
President & CEO, ValleyCare Health Systems

LEEZA GIBBONS
Alzheimer's Disease
Founder & Board Chair, The Leeza Gibbons Memory Foundation

SHERRY LANSING
Cancer
Founder and Chair, Sherry Lansing Foundation

FRANCISCO J. PRIETO, M.D.
Type I Diabetes
President, Sacramento-Sierra Chapter, American Diabetes Association

ROBERT A. QUINT, M.D., F.S.C.A.I.
Heart Disease
Charter Member & Founding Fellow, Society for Cardiac Angiography Interventions

JOAN SAMUELSON, J.D.
Parkinson's Disease
Founder, Parkinson's Action Network

DAVID SERRANO SEWELL, J.D.
MS/ALS
Amyotrophic Lateral Sclerosis Association, National Multiple Sclerosis Society

JEFF SHEEHY
HIV/AIDS
Director for Communications, UCSF AIDS Research Institute

JONATHAN SHESTACK
Mental Health
Founder & Vice President, Cure Autism Now

OSWALD STEWARD, PH.D.
Spinal Cord Injury
Chair and Director, Reeve–Irvine Research Center, University of California, Irvine

Research representatives

RICARDO AZZIZ, M.D., M.P.H. M.B.A.
Chairman, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center

SUSAN V. BRYANT, PH.D.
Vice Chancellor for Research and Professor, School of Biological Sciences, University of California, Irvine

JEANNIE FONTANA. M.D., PH.D.
(Alternate)
Director, Sanford-Burnham Medical Research Institute

ROBERT BIRGENEAU, PH.D.
Chancellor, University of California, Berkeley

KENNETH C. BURTIS, PH.D.
(Alternate)
Professor of Genetics, Dean of the College of Biological Sciences, Molecular and Cellular Biology, University of California, Davis

MICHAEL A. FRIEDMAN, M.D.
President & CEO, City of Hope

FLOYD E. BLOOM, M.D.
Executive Director, Science Communication, The Scripps Research Institute

DONALD C. DAFOE, M.D.
(Alternate)
Director, Pancreas Transplantation, Kidney and Pancreas Transplant Center, Cedars-Sinai Medical Center

GORDON GILL, M.D.
[Alternate]
Professor of Medicine and of Cellular & Molecular Medicine, Dean of Scientific Affairs, University of California, San Diego

DAVID BRENNER, M.D.
Vice Chancellor for Health Sciences and Dean, School of Medicine, University of California, San Diego

JAMES ECONOMOU, M.D., PH.D.
[Alternate]
Vice Chancellor for Research, University of California, Los Angeles

SAM HAWGOOD, M.D.
Dean,
USCF School of Medicine and Chair, Department of Pediatrics

WILLIAM BRODY, M.D., PH.D.
President, Salk Institute for Biological Studies

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ALAN TROUNSON, PH.D.

Few things are more fulfilling than setting goals and seeing them met—and to have a panel of outside reviewers agree that CIRM has been a real success. • In December 2006, our Governing Board adopted a strategic plan with very ambitious five-year and 10-year goals for the agency. These goals were set a year prior to my arrival at CIRM and to be frank, when I looked at the goals the first time I thought several of them might be a stretch in the given time frame, and one or two still may be difficult to achieve. But the progress in the past three years has certainly exceeded my initial expectations. • The 2006 plan called for a review of progress after three years, so during the second half of 2010, agency staff undertook a thorough self-assessment followed by an extensive review by an eight-person external advisory panel (EAP) made up of world leading stem cell researchers, science policy experts, and patient advocates and an ethicist (names of the panelists can be found here: http://www.cirm.ca.gov/Announcement_092810). Staff presented their self-assessment to the EAP in October and the panel presented its findings to our board in December. • We found that half the 10 five-year goals had already been met, including creating new methods of making stem cell lines. The remaining five-year goals are on a plausible track for completion in the next year or two, well within the five-year window. Also, CIRM grantees have published papers advancing progress toward nearly all 10 of the 10-year goals, including the ultimate goal of seeing embryonic stem cell–derived cells in clinical use. They have made sufficient progress to believe that these goals are achievable. This finding was hugely satisfying, as was the assessment of the EAP regarding the agency's early years: • "Progress during this first stage of CIRM's development has been remarkable; CIRM has built significant additional research capacity in the state, has attracted scores of talented young people to stem cell research, and has catalyzed large and important stem cell developments across the state. The EAP was most impressed with this rapid startup, the overall quality of the scientists and projects that have been funded, the development of major buildings and other facilities for stem cell research, the forging of a raft of important international partnerships and the innovative training programs that are in place."

However, the report doesn't leave time for CIRM to rest on these laurels. The panel provided a number of recommendations for CIRM to accelerate the field by making its funding more flexible, opportunistic and able to quickly respond to major discoveries, particularly those that are close to the clinic. The panel made some very thoughtful and helpful recommendations that will enable CIRM to deliver its mandate by becoming an even more effective organization.

The EAP report voiced confidence in CIRM's ability to be nimble and make the adjustments suggested. "The EAP feels confident that CIRM is poised to build on the success of the first stage to drive further growth toward its long-term mission of providing significant health and economic benefits to the people of California."

The panel grouped its findings into 10 key recommendations. Since December, CIRM's management team has been drafting a new operations plan that will spell out the tactics it proposes for carrying out those recommendations. We presented that plan to our board in March and here I would like to walk you through some of the most important recommendations and our preliminary plans for carrying them out.

The first two recommendations simply encourage us to maintain the scientific excellence of what we fund and to continue to sustain fundamental discovery by supporting the most creative basic science. These simply require us to maintain the high standards and effective systems we have in place thanks to the highly dedicated members of our science office team.

In paving a path from fundamental to translational research the panel called for CIRM to develop a more aggressive, proactive approach to identify innovation across the whole therapeutic landscape. We believe we can accomplish this by more aggressively reviewing "hot areas" of breaking science and using the insights of an industry advisory group and of our collaborative funding partners around the globe. Once we find a hot spot of innovation we will need to move quickly to identify suitable California partners and arrange linkages no matter where the hot spot is.

The EAP said CIRM needs to create a process for prioritizing its portfolio, particularly its therapeutic candidates. We need a way to use expert advice to identify which programs deserve continued support and which do not. Our outside grant review panels' consideration of "relevance," along with the milestone/progress committee we are setting up, could go a long way toward setting priorities most likely to result in broadly adopted therapies. Relevance is a term used by industry to measure clinical impact on patients combined with a reasonable business/practice model for delivery.

Creating a "porous pipeline," the EAP said, would allow potential clinical projects to come from either inside or outside of CIRM's current funding, or even from outside of California. We believe we should be able to create more flexible funding processes that add a rolling funding cycle that could capture innovative projects at the time they are most ripe for support rather than only within set Request for Application schedules.

The panel asked that we not ignore social, ethical, regulatory and health care delivery issues, saying we should stimulate the research that is needed to move the field to everyday practice. To this end we are considering creating an advisory group to identify critical issues in these areas and hope to take a leadership role in developing standards for manufacturing and cell integrity for clinical use. We are also studying the possibility of establishing CIRM-sponsored clinical units for the delivery of cell therapies.

The EAP saw enabling more significant engagement with industry as critical to the next phase of CIRM. We were told we needed to be more accommodating to industry timelines and financial restraints. In response we will be looking for ways to streamline our grants award processes and developing mechanisms for industry to more quickly seek grant review. We will be increasing the number of industry reviewers on our grant review panels and we will be developing ways to encourage industry to use the patents and other intellectual property created by CIRM-funded projects.

The EAP also suggested we broaden our collaborative funding partnership program beyond the current nine countries and three U.S. states and foundations. We will be looking for ways to encourage multiple international and interstate partnerships on projects. At the same time we will continue looking for additional hubs of excellence around the world that can be added to the current network. We are also exploring options for partnering with the National Institutes of Health Clinical Center and its newly created National Center for Advancing Translational Sciences.

CIRM's efforts to increase its education and outreach activities with the public were strongly encouraged by the committee, which called for a significant increase in the breadth of this work. We intend to expand a program we began last year using a team of patient advocate outreach coordinators to work directly with the many disease-specific groups in the state. We also hope to enlist more of our grantee researchers in public education projects and expand our work with media outlets of all types.

The last recommendation from the EAP, to re-examine the roles of the Governing Board and CIRM managers, is an ongoing process. Our board is actively engaged in looking at the criteria its members believe are the top credentials for a new chair to succeed our visionary founding chair, Robert Klein.

As we enter CIRM's "phase II," looking for ways to implement these recommendations, it is clear to all of us at the agency that we are taking on these sometimes daunting tasks for one reason: to fulfill the mission of CIRM to accelerate the development of new therapies for patients. That is what we owe the voters of California. Thank you for your support.

We are taking on these sometimes daunting tasks for one reason: to fulfill the mission of CIRM to accelerate the development of new therapies for patients.

"CIRM'S INVESTMENT IN STEM CELL RESEARCH BUILDINGS CREATED JOBS AND REVENUE FOR THE STATE AND SOLIDIFIES CALIFORNIA'S POSITION AS THE LEADER IN DEVELOPING THE STEM CELL THERAPIES OF THE FUTURE. ONE OF THE NEXT GREAT CALIFORNIA INDUSTRIES WILL BE BIOMEDICAL RESEARCH, AND CIRM IS LEADING THE WAY."

– CALIFORNIA ASSEMBLY SPEAKER JOHN PÉREZ

SEVEN CIRM MAJOR FACILITIES OPENED THIS PAST YEAR,

creating state-of-the art space for carrying out stem cell research. CIRM's initial investment of $271 million leveraged private donations and institutional commitments toward 12 buildings and recruitments worth more than a billion dollars. That investment created 13,000 job years and $100 million in tax revenues for the state at a time when they were critically needed.

A. Stanford University
LORRY I. LOKEY STEM CELL RESEARCH BUILDING
Total: $200 M
Lorry Lokey: $75 M
CIRM: $43.6 M

B. University of California, Los Angeles
ELI AND EDYTHE BROAD CENTER OF REGENERATIVE MEDICINE AND STEM CELL RESEARCH
Total: $43 M
The Eli and Edythe Broad Foundation: $20 M
CIRM: $19.8 M

C. University of Southern California
ELI AND EDYTHE BROAD CIRM CENTER FOR REGENERATIVE MEDICINE AND STEM CELL RESEARCH
Total: $80 M
CIRM: $27 M
The Eli and Edythe Broad Foundation: $30 M

D. University of California, Irvine
SUE AND BILL GROSS STEM CELL RESEARCH CENTER
Total: $80 M
CIRM: $27.2 M
Sue & Bill Gross: $10 M

E. University of California, Davis
INSTITUTE FOR REGENERATIVE CURES
Total: $62 M
CIRM: $20 M

F. University of California, San Francisco
RAY AND DAGMAR DOLBY REGENERATION MEDICINE BUILDING
Total: $123 M
CIRM: $34.9 M
Ray and Dagmar Dolby: $36 M
The Eli and Edythe Broad Foundation: $25 M

G. University of California, Merced
STEM CELL INSTRUMENTATION FOUNDRY
Total: $7 M
Ed and Jeanne Kashian: $100,000
CIRM: $4.4 M

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EMBRYONIC STEM CELLS REMAIN THE GOLD STANDARD

On Aug. 23, 2010 federal judge Royce C. Lamberth ruled federal funding of human embryonic stem cell research impermissible under current laws. This decision suspended the ability of the NIH to fund research using human embryonic stem cells, a result that NIH director Francis Collins likened to pouring sand in the engine of discovery.

By September 9 the U.S. Court of Appeals put a hold on that ruling, allowing funding to continue, though the final outcome of the case is still unknown. With this surprising turn of events, one question kept surfacing: Why do we even need embryonic stem cells when the science of adult stem cells and reprogrammed iPS cells is so advanced?

In the Beginning

IN 1988, Irv Weissman of Stanford University isolated the first adult stem cells. These were the blood-forming stem cells from the bone marrow of mice. He soon isolated the same cells in humans, and over the following decade he isolated stem cells in additional tissues and started a series of companies dedicated to developing therapies based on those discoveries.

Given that Weissman's reputation and personal income are invested in the future of adult stem cells you'd think he would be their biggest fan. Instead, Weissman, who is now the director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, is one of the most vocal supporters of funding for embryonic stem cells.

Adult stem cells, or tissue-specific stem cells, reside within the bone marrow, brain, blood, skin, liver or other tissues until disease or injury calls upon them to finish maturing to repair the damage.

"These cells are restricted in what they can do," Weissman said. "No adult stem cell can ever go on to be another cell type, even one that's closely related."

By contrast, embryonic stem cells can form every single cell type in the body. They come from embryos discarded after a couple completes in vitro fertilization treatment, can be frozen or grown indefinitely in the lab and with a bit of coaxing can mature into any desired cell type.

This flexibility is what accounts for much of the therapeutic hope for embryonic stem cells. They've been matured into nervous system precursor cells that are now in clinical trials for spinal cord injury and they can also form structures in the eye that are now being tested as a therapy for two forms of blindness. Other research teams have matured the cells into types that could become therapies for diabetes, skin diseases, heart disease, neuronal diseases or cancer, among others.

By Way of Comparison

A LESS DISCUSSED but equally critical role for embryonic stem cells is as a research tool. Weissman's team has relied on knowledge gained from embryonic stem cells to guide their adult stem cell discoveries. Rather than sifting through mouse tissues looking for adult stem cells, his team matured embryonic stem cells until they reached the adult stem cell stage. They could then use what they'd learned about those stem cells to find the counterparts in actual animal tissues.

James Thomson, one of the first to reprogram skin cells into embryonic-like iPS cells, has said that restrictions on funding for embryonic stem cells set the discovery of reprogrammed iPS cells back by about five years. He wrote in the Dec. 3, 2007 *Washington Post*, "Work by both the U.S. and Japanese teams that reprogrammed skin cells depended entirely on previous embryonic stem cell research."

Creating the initial iPS cells and the newer techniques that followed (See "Making a Better iPS Cell," p. 24) came about, in part, by studying embryonic stem cells to understand what it is that makes a cell able to form all cell types of the body.

Even with improvements in creating iPS cells, there's a lot we still don't know. Paul Knoepfler at the University of California, Davis says there are hints that iPS cells when transplanted are more prone to forming tumors than embryonic stem cells. But then, those studies were done on iPS cells created using an outdated method. How do the newer techniques compare? Nobody will know until they've done the comparisons against embryonic stem cells.

Keeping the Pipeline Full

ADULT STEM CELLS were first successfully used in humans in 1968 in the form of a bone marrow transplant (it's the blood-forming stem cells in the bone marrow that rebuilt the blood system). Those cells are now in clinical trials for a range of diseases, and adult neural stem cells are just starting to be tested for spinal cord injury and ALS, among other conditions.

To some, the fact that adult stem cell clinical trials have started means embryonic stem cells came along too late. By that logic, cancer patients would still be receiving the very first extremely toxic and only somewhat effective chemotherapies.

Instead, scientists continued testing new ideas as they emerged. Through that clinical trial and error process we now have highly targeted antibody-based cancer therapies as well as more effective standard chemotherapies. This range of therapeutic options would never have been developed if scientists were satisfied with their earliest attempts.

Funding restrictions for embryonic stem cells would mean not only fewer embryonic stem cell-based therapies to be tested, but also fewer adult, cancer, or iPS cell therapies as well.

Scientists in the Lurch

Soon after the ban of funding for human embryonic stem cell research went into place, CIRM surveyed our grantees to learn the impact on California scientists. • Twenty-two percent of respondents said they had NIH funding for embryonic stem cell research and only 5 percent of grantees said the ruling would make no difference to their overall research strategy. Also, 65 percent of grantees who had NIH support said that if the NIH freeze holds they'll need to reduce or eliminate positions in their labs. The most telling finding from the CIRM survey was that 76 percent of grantees said the funding freeze would impact their ability to carry out research with adult, cancer or iPS stem cells.

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STEM CELLS MOVE TOWARD CLINICAL TRIALS

In naming Proposition 71 the California Stem Cell Research and Cures Act its authors emphasized the goal of delivering life-saving regenerative medical treatments and cures to the people of California and the world. This past year brought considerable progress toward that goal.

The most significant advancement was the announcement that Geron's therapy for spinal cord injury based on embryonic stem cells would begin enrolling new patients. Soon after, two additional trials based on embryonic stem cells joined Geron with approval to begin trials.

Early Progress Toward the Clinic

THREE OF THE 14 disease teams awarded in October 2009 have already achieved major milestones. At the University of Southern California, Paula Cannon, who is working with the team headed by John Zaia of City of Hope, has published a proof of principle paper on the team's effort to create blood-forming stem cells that can produce HIV-resistant T cells. Her team showed that in mice, genetically modified human blood-forming stem cells were able to form a new blood system that could control HIV infection.

"This hybrid of gene and stem cell therapy shows that it is possible to create HIV-resistant immune cells that can eventually win the battle against HIV," said Cannon in a USC press release.

Karen Aboody, also of City of Hope, received Food and Drug Administration approval in June to begin a clinical trial with neural stem cells that act as carriers for an enzyme that converts a pro-drug to an active cancer chemotherapeutic agent. While the FDA approval came for a different agent and a different protocol than the one she has proposed for the CIRM disease team, the cell type is the same, and this should greatly speed approval of the CIRM-funded clinical trial application. The CIRM regimen uses a more powerful chemotherapeutic agent.

A third team, led by Stanford's Irv Weissman, is developing an antibody-based drug to treat leukemia. The drug binds to a protein that leukemia stem cells use to avoid being ingested and removed by the body's immune system. This protein is found on some other cancer stem cells, including those for non-Hodgkins lymphoma. The team has reported that a test drug could cure non-Hodgkins in mice in 60 percent of cases.

The Disease Team Awards required teams including basic scientists and clinicians from both industry and academia to show a roadmap for getting to clinical trials in four years. These collaborations speed the process of establishing clinical trials by ensuring that clinically relevant issues are considered early and by avoiding safety issues being discovered late in the process.

More Candidates for Cures

AS THE DISEASE team projects grow closer to human clinical trials, CIRM continues to fund new work in the earliest stages of that pathway. CIRM's Early Translation II Awards fund the transition of a basic discovery about a disease into a drug or therapy that could eventually benefit patients.

This year, the awards came in two categories: One funds all the steps needed to produce a drug candidate worthy of costly pre-clinical testing. The other, a Feasibility Award, funds one or two of those steps that move the research further down the pipeline but not to the point of a drug candidate.

Altogether the CIRM Governing Board issued awards for $71 million in grants for 21 Early Translational II Awards making a total of 37 Early Translation Awards to date.

"We are looking for ways to complement our leading edge of stem cell-based treatments for patients and these projects will load our frontline portfolio with promising studies on autism, muscular dystrophy, Canavan disease and liver disease," said CIRM president Alan Trounson. "These projects will enhance the potential medical options available for patients and hopefully in the near future produce cures for such debilitating handicaps and diseases."

The awards cover a broad spectrum of diseases. Some award recipients are looking for alternative paths to the clinic for diseases such as HIV and brain tumors, which are already under investigation by CIRM grantees. Others address conditions and injuries new to CIRM's drug candidate portfolio, including degenerative bone conditions (see sidebar), blindness and autism.

One award went to University of California, San Diego scientist Alysson Muotri, who will be following up on her initial work developing a model for understanding and treating forms of autism (see Understanding Autism p. 22).

Treating Osteoarthritis

Forty million Americans live with constant pain caused by degeneration of the cartilage in the joints or osteoarthritis. Their only hope for pain relief comes from costly surgery to entirely replace the joint. • One of the Early Translation II projects at the Scripps Research Institute aims to provide an alternative to surgery. The plan is to activate a patient's mesenchymal stem cells within the joint to form new cartilage and prevent further damage. • The team has already tested compounds on stem cells in a lab dish to find ones that promote new cartilage and that protect existing cartilage from additional damage. With their CIRM award, they now hope to develop a promising drug candidate to protect and restore cartilage, and give hope to the 1.8 million people predicted to need joint replacements in 2015.

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KEEPING THE RESEARCH PIPELINE FUELED

From its inception, CIRM has been invested in pumping fuel—in the form of new researchers and new research ideas—into the research pipeline that leads to new therapies.

This effort includes recruiting top scientists—young and established—to California and to stem cell science, while also funding the basic studies that lead to new ways of understanding and eventually treating disease.

Recruiting the Brightest

CIRM AIMED its earliest rounds of funding at creating a robust stem cell research community in California to attract new stem cell investigators to the state. This began with its first ever grants for training in 2006 and continued with its Jump Start Program in 2007, which included SEED grants to bring new investigators and innovative ideas to the field, Comprehensive Grants to support mature projects by researchers with a track record in stem cell research and Shared Labs to provide critical infrastructure and training in human embryonic stem cell use.

The strategy clearly worked. CIRM has documented 102 faculty-level stem cell scientists who have moved to California from other states and other nations since 2006. Thirty-nine of those are senior level faculty regarded as leaders in the field.

Joanna Wysocka, a Stanford researcher who won the Outstanding Young Investigator Award at last year's meeting of the International Society for Stem Cell Research, cited the CIRM SEED program for bringing her into stem cell research.

This year CIRM poured more fuel into the pipeline when it launched the Research Leadership Awards, which help recruit established or emerging leaders in stem cell science. The grants provide six years of salary and research support intended to enable these researchers to pursue highly innovative projects. The first Leadership Award went to the Sanford-Burnham Medical Research Institute to aid in recruiting Robert Wechsler-Reya, a thought leader in neural development and cancer stem cells from Duke University.

Fundamentals Foster Cures

THROUGHOUT its existence CIRM has funded research that addresses fundamental questions about what makes a stem cell a stem cell and what pushes some of them to mature into very specific tissues. Last year the agency funded 16 Basic Biology II Grants for a total of $22.4 million, creating fodder for future therapies.

In addition to opening up new avenues of research, this fundamental work can help therapies already well along the pipeline, according to CIRM president Alan Trounson. "We expect many of these outstanding projects to provide answers that remove road blocks to projects that are already close to the clinic."

The Basic Biology II Grants run the gamut of human development. One seeks to turn immature "pre-egg" follicles in the ovaries removed from cancer patients into mature eggs that could be used for nuclear transfer—so-called therapeutic cloning. Obtaining sufficient eggs has held back this line of research. Another grant is looking at aging and the possibility of using systemic proteins, which are found abundantly in young brains but less so in older ones, to try to make older brains more able to regrow neural tissue.

A Foundational Hurdle

"IN WRITING Proposition 71, we anticipated the need to overcome the immune response in order to fulfill one of the ultimate promises of regenerative medicine," said Robert Klein, chair of the CIRM governing board.

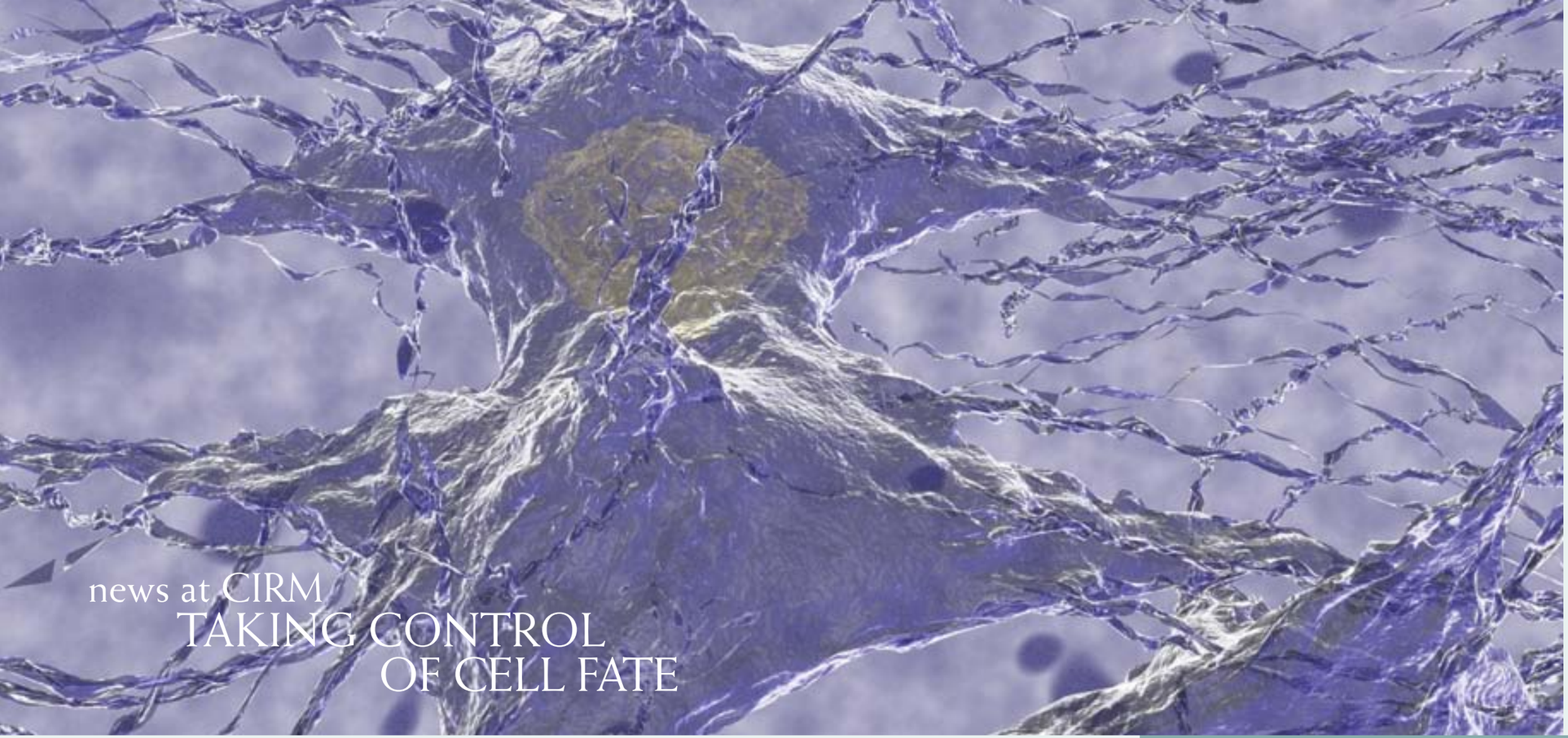
By issuing $25 million for 19 Stem Cell Transplantation and Immunology Awards, the agency made significant strides toward achieving this goal. These unique awards force stem cell scientists to form partnerships with transplant immunologists in order to apply for the awards.

"It has significant value to have some of the world's leading stem cell scientists being part of a team with some of the world's leading immunologists," said CIRM governing board member Jeff Sheehy just prior to the board vote on the grants.

Two California stem cell teams availed themselves of CIRM's international Collaborative Funding Partner Program to find immunologist collaborators at a hotbed of immunology research: Monash University, in the Australian state of Victoria. The Victorian government has committed $1.2 million to fund the work on these projects in Australia.

Full Cycle for Diabetes

Type 1 diabetes occurs after a child's immune system has gone out of control and attacked the child's own insulin producing cells. But the body does have cells capable of stopping this self-attack. These cells could allow the immune system to come full cycle and stop the progression toward diabetes by preserving the insulin producers. • Jeff Bluestone at the University of California, San Francisco, has been granted an early translational award to do just that. He is trying to harness the natural immunosuppressive properties of T regulatory cells to counter autoimmunity against insulin producing beta cells. • The research team also set its sights on using T regulatory cells to promote tolerance of stem cell grafts designed to replace already damaged insulin producing cells. This would ease the path to using stem cells to reverse diabetes.



news at CIRM

TAKING CONTROL OF CELL FATE

Between a dish of stem cells and hope for a cure stands the pesky problem of turning those stem cells into a therapeutic cell type—a retina for eye disease, or a pancreatic cell for diabetes. Research this past year has shown that adult cells may change their identities, cell transplants can be made safer and someday the blind may see, thanks to advances CIRM scientists throughout California have made in controlling stem cell fate.

Career Switch

DOGMA ONCE HELD that if a cell was a doctor it would need to go back to kindergarten before it could grow up to become a lawyer: An adult cell needed to be reprogrammed back to an embryonic-like state and from there, these so-called iPS cells would be shepherded to a new adult fate.

That changed in 2009 when Harvard Stem Cell Institute researchers successfully converted one type of mouse pancreatic cell directly into insulin-pumping pancreatic beta cells. Cellular doctors, it turned out, could become lawyers after all.

2010 brought several additional cellular career switches, including one by Stanford scientist Marius Wernig, a CIRM grantee, who turned skin cells into nerve cells.

Later in the year, CIRM grantee Deepak Srivastava, director of the Gladstone Institute of Cardiovascular Disease at the University of California, San Francisco, coaxed mouse cardiac fibroblasts, the heart's support cells, to turn directly into primitive heart muscle cells. The research appeared in the August issue of *Cell*.

Srivastava's heart cell research could have important implications for the treatment of heart failure.

"Half of the cells in the heart are fibroblasts, so the ability to call upon this reservoir of cells already in the organ to become beating heart cells has tremendous promise for cardiac regeneration," Srivastava said. Nearly 6 million Americans suffer from heart failure because the heart is unable to repair itself after a heart attack, but only 2,000 hearts become available for transplanting each year.

Understanding Autism

IN MAY 2009, CIRM held a workshop in which leading scientists discussed ways in which stem cell research could benefit people with autism. A key recommendation came to pass this year when CIRM grantees at the Salk Institute for Biological Studies were able to study neurons predisposed to autism spectrum disorders.

The team took skin cells from people with a genetic form of autism called Rett's syndrome, reprogrammed those back to iPS cells, and matured those embryonic-like cells into neurons. The unusual neurons that resulted provided scientists with a first glimpse of what makes an autistic neuron different. They had smaller cell bodies and fewer connections between neurons.

"Being able to study Rett neurons in a dish allows us to identify subtle alterations in the functionality of the neuronal circuitry that we never had access to before," said lead author Fred Gage, a professor in the Salk's Laboratory of Genetics.

The team took the work an additional step, exposing those scrappy neurons to an experimental drug and thereby reversing some abnormalities. Now they hope to study neurons developed from people with other forms of autism to start understanding the full spectrum of symptoms.

Scene of the Crime

ADULT NEURAL stem cells take advantage of the body's 911 system when they rush to the scene of damage in mouse models of multiple sclerosis. Once in place, the cells take on a mature fate.

Tom Lane, an investigator at the Sue & Bill Gross Stem Cell Research Center at the University of California, Irvine, discovered the interactions that help stem cells home in on damage in research published in the *Proceedings of the National Academy of Science*. Lane, a CIRM grantee, earlier showed that adult neural stem cells improved motor function in mice with multiple sclerosis.

MS destroys myelin, the insulating sheath that covers nerves. Intact, myelin allows signals to propagate along the nerve; when damaged, signaling is interrupted.

When myelin corrodes, Lane discovered, inflammatory cells activate receptors on neural stem cells. Those stem cell receptors recruit protein guides called chemokines, which lead them to the accident and guide the stem cell's eventual fate. As the stem cells travel through the central nervous system, they begin to differentiate.

They reach the repair site in the form of oligodendrocyte precursor cells and finish maturing onsite. Three weeks after a stem cell treatment initiates, the cells are mature.

"In this study, we've taken an important step by showing the navigational cues in an inflammatory environment like MS that guide stem cells," said Lane. "Hopefully, these cues can be incorporated into stem cell–based treatments to enhance their ability to repair injury."

Blocking Tumors

Stem cells have an inherent disposition to form tumors called teratomas which raises concerns for transplantation therapies. • CIRM grant recipient Yang Xu, a biology professor at the University of California, San Diego, has uncovered a way to reduce the growth of teratomas, suggesting a hope for their complete eradication. • In a paper appearing in the *Proceedings of the National Academy of Science*, Xu reported he was able to reduce the mass of teratomas formed in mice by inhibiting a gene that regulates their ability to form all cell types, called pluripotency. • Xu speculates that teratoma formation may be eliminated entirely by targeting several pluripotency factors simultaneously. • Calling the approach a "proof of concept," Xu said, "At this point, we only see a significant but partial effect because we are targeting only one pathway." • The experiment stopped teratoma growth after transplantation of pure, undifferentiated stem cells, reducing their mass by 70 percent. • "Once we identify more pathways required for teratoma formation by embryonic stem cells, we might be able to completely suppress the formation," Xu said.

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UNRAVELING THE ROLE OF IPS CELLS

In the three years since scientists successfully turned back the clock on human adult skin cells, CIRM researchers have been devising more efficient ways of making these reprogrammed cells and harnessing them to study disease. As CIRM scientists improve techniques for creating the flexible cells, they are also discovering that iPS cells do not behave—for better or for worse—exactly like their embryonic counterparts.

Making a Better iPS Cell

SINCE 2006, when Shinya Yamanaka of the Gladstone Institutes and Kyoto University first reprogrammed mouse skin back to an embryonic-like state, stem cell scientists have been scurrying to improve on the technique in humans.

The problem was that despite the cells' obvious usefulness in understanding and possibly treating disease, creating them involved permanently inserting cancer-causing genes. Plus, techniques to generate the cells were extremely inefficient.

Papers quickly began appearing demonstrating that the number of genes needed has been whittled down and that the efficiency has improved, with 2010 bringing significant advances by CIRM grantees.

In February, CIRM grantees at Stanford University discovered a way to transform fat cells into iPS cells without requiring viruses.

"This technique is not only safer, it's relatively simple," Michael Longaker, Stanford University professor of surgery, said in a press release. Longaker is a co-author of the study that appeared in *Nature Methods* in February, 2010.

The team used so-called minicircles of DNA to reprogram the cells into pluripotency. These minicircles contain just the four genes needed to transform the cells, along with a fluorescence gene that allows the cells to be tracked. The minicircles are about half the size of naturally occurring DNA rings called plasmids that have been used in other iPS transformations, and unlike integrating viruses, the minicircles are lost over time along with the potentially dangerous reprogramming genes, making the cells safer for therapy.

The idea, said Stanford cardiologist Joseph Wu, is to one day take a fat or skin biopsy from a member of a family with heart problems, reprogram the cells and make cardiac cells to study in a lab dish. Wu, the senior author of the study, notes: "This would be much easier and less invasive than taking cell samples from a patient's heart."

Later in the year a team at Harvard University developed another method for virus-free creation of iPS cells. In that work, the scientists used transient RNA in a technique that also appears to be much more efficient than previous techniques.

Modeling Diseases in a Dish

DESPITE CONCERNS about genetic anomalies in iPS cells, (see sidebar) they are proving valuable in understanding the origin of diseases. CIRM grantees have taken skin samples from people with genetic forms of autism, premature aging, Parkinson's disease and schizophrenia, reprogrammed them into iPS cells and matured those into the affected cell type. The resulting cells have provided a first glimpse of what might be happening at the cellular level in those conditions.

Take Parkinson's disease, for example. Work by CIRM grantees at Stanford University and The Parkinson's Institute has led to neurons in a lab dish that exhibit signs of the disease. The cells, matured from iPS cells created from a woman with a genetic form of Parkinson's disease, produce excess protein that is a hallmark of the disease and also show signs of a form of cellular stress associated with Parkinson's disease.

In addition to providing insights into a disease, these models can be used for the first time to screen for drugs that halt or reverse disease symptoms in human cells.

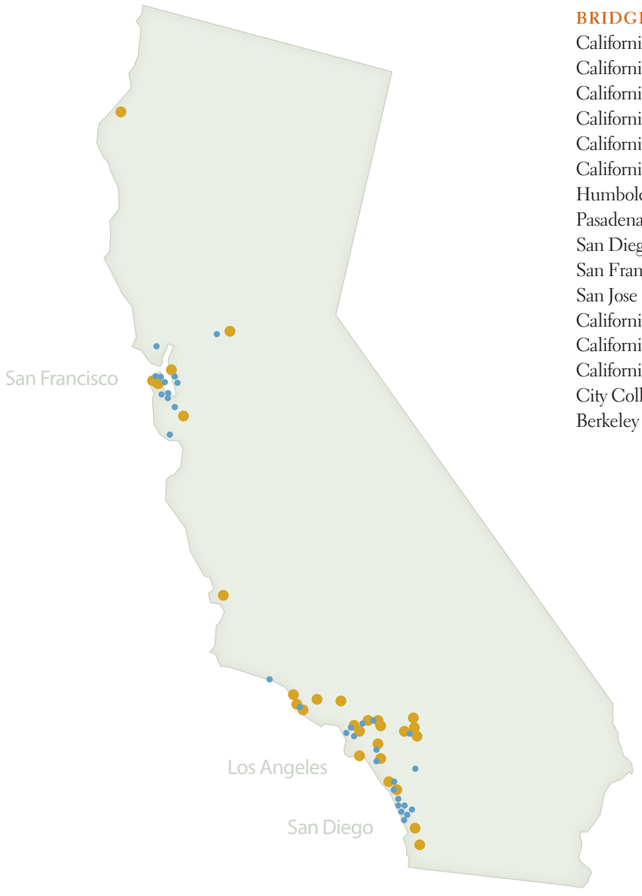
Assessing Reprogrammed Cells

Recent studies have shown that some iPS cells are not as pluripotent as scientists had hoped, and they contain anomalies compared with embryonic stem cells. • A team working at Harvard, which included one CIRM trainee at Stanford, found that iPS cells derived from blood and bone favored making their tissue of origin. Researchers linked the inflexibility to differences in the chemical adornments called methylation that decorate the DNA. This methylation affects which genes are active and are characteristic of particular cell types. • A second Harvard team confirmed the findings of the first and showed it could reduce the differences between the iPS cells and embryonic stem cells by culturing the reprogrammed cells for a longer period of time. • Related work led by CIRM grantee Jeanne Loring of The Scripps Research Institute shows that iPS cells have significant genetic differences compared with embryonic stem cells. They found that iPS cells tended to have gene duplications or deletions that could cause those cells to become cancerous—a concern for those hoping to use the cells therapeutically.

The Bridges to Stem Cell Research Awards

CIRM's 16 Bridges to Stem Cell Research Awards to undergraduate and masters-level programs train the next generation of stem cell scientists to fill jobs in California's growing stem cell research sector — filling a void predicted by BayBio and the California Public Policy Institute. As the first participants graduate, students are already being hired into technician jobs, and being accepted into medical and graduate schools in large numbers.

● Internship Hosts ● Bridges Participants



BRIDGES PROGRAMS

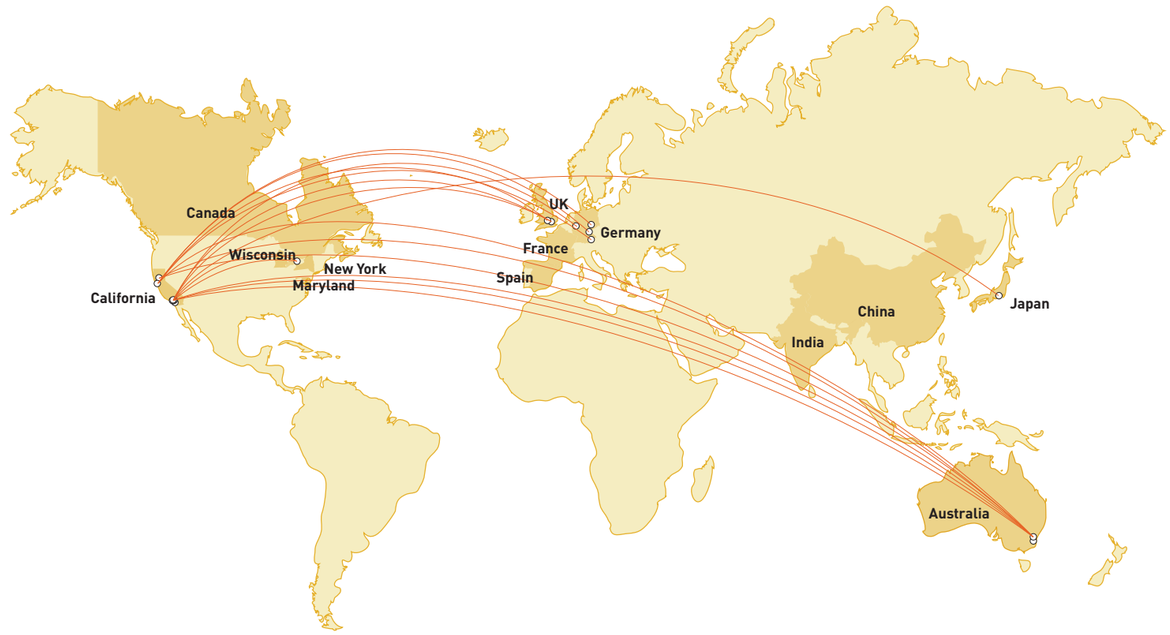
California Polytechnic State University, San Luis Obispo
California State Polytechnic University, Pomona
California State University, Channel Islands
California State University, Long Beach
California State University, Sacramento
California State University, San Marcos
Humboldt State University
Pasadena City College
San Diego State University
San Francisco State University
San Jose State University
California State University, Fullerton
California State University, Northridge
California State University, San Bernardino
City College of San Francisco
Berkeley City College

EDUCATIONAL PARTNERS

Irvine Valley College
Oxnard Community College
Moorpark Community College
Ventura Community College
East Los Angeles College
Citrus College
Mira Costa College
San Diego Miramar College
Cal State Los Angeles
San Bernardino Valley College
Riverside Community College
Moreno Valley College

"CIRM's $24 million Bridges to Stem Cells Program continues to be a great success within our portfolio of programs. It provides broad access to state universities and community college undergraduates and master's-level students to receive high level training needed to build a strong foundation for the stem cell biomedical industry. Particularly during this time of state funding cuts, the Governing Board's commitment to ensure that a diverse array of Californians have these opportunities makes me especially proud of my seven years of service."

—DAVID SERRANO SEWELL, CIRM GOVERNING BOARD MEMBER



CIRM has formed partnerships with international funding agencies in nine nations and two international states to create collaborations connecting the best scientists from around the world. To date, 16 California stem cell scientists have partnered with colleagues in five different countries in an effort to develop new disease therapies.

SPOTLIGHT ON DISEASES

At each board meeting, a Spotlight on Disease presentation features patients, clinicians and researchers speaking about the hope of stem cell research.

THESE ARE THEIR STORIES...

Videos of these presentations are available on the annual report website: www.cirm.ca.gov/2010AnnualReport

AMYOTROPHIC LATERAL SCLEROSIS

THE NEIGHBORHOOD IS BAD. SOME NEIGHBORS ARE DOWNRIGHT TOXIC, AND EVERYBODY ELSE SUFFERS FOR IT.

That's the situation with the degenerative disease amyotrophic lateral sclerosis, where cells in the neighborhood of motor neurons damage those neurons and cause a slow bodily degeneration. And it's leading researchers to focus on a community improvement campaign, said Don Cleveland, Ph.D., chair of cellular and molecular medicine at the University of California, San Diego School of Medicine. • The symptoms of ALS appear when motor neurons detach from the muscles they control. Once disconnected, the neurons die and the muscles waste. ALS patients lose the ability to do things for themselves: to walk, to speak and even to swallow. Eventually, the muscles that control breathing fail—the cause of most ALS deaths.

Although the roots of ALS are uncertain, three genetic mutations have been linked to it. But researchers had to determine just where the mutations did their dirty work. Were motor neurons damaged by their own genes, or was the damage caused by gene expression in neighboring cells?

Using rodents genetically engineered to develop ALS, researchers first shut off the ALS gene in the motor neurons, but kept it running everywhere else. As expected, the onset of disease was delayed, Cleveland said. But there was little meaningful improvement. "The speed by which the disease progresses is unchanged."

Then they reversed the experiment, keeping the gene going in the motor neurons, but shutting down its operation in its "intimate partner," the starburst-shaped astrocytes. In this case, symptom onset was unchanged, but the disease's progression slowed dramatically. It turns out astrocytes with the ALS mutation release a toxin that damages the motor neurons.

"In fact, the animals live more than twice as long," Cleveland said. The team hopes to replace mutant-expressing astrocytes with normal ones in ALS patients.

Life Technologies Corp. of Carlsbad, Calif., is growing embryonic stem cells and coaxing them to become astrocyte precursor cells that will then be injected into the spinal cords of ALS patients. That trial will begin within four years if animal trials succeed.

Researchers will inject the cells in either the lumbar or lower spine, where the leg muscles are innervated, or in the cervical spine (the neck), where motor neurons control breathing.

In preliminary animal studies, the astrocytic precursor cells survived and traveled along the spinal column, becoming astrocytes. Later trials will see if they spruce up the vicinity.

"What we learned is neighborhood really matters," Cleveland said.

"What kind of quality of life do you want, and what can you do to impact the quality? That's how I look at life."
DAN DESMOND

WHAT IS IT LIKE TO LIVE WITH ALS?

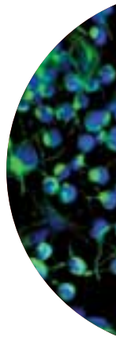
Dan Desmond caught himself using a hoe as a crutch as he walked his 6-acre property east of San Diego. It was one of the little hints he ignored until the day four years ago when he couldn't finish a hike. "My legs just weren't working," he said.

He had amyotrophic lateral sclerosis, the doctors told him, Lou Gehrig's disease. He went online to learn more and spent two hours at the ALS Association office in San Diego. "I did not like what I was hearing," he said. "I did not like the way things were going." But he found a way to cope.

"I still have a great life with my children, grandchildren and friends," the 64-year-old said. But the disease progresses. He's in a wheelchair. The muscles in his chest, arms and hands are growing weaker.

He subscribes to a philosophical attitude. "Everyone has depression at different times, and everybody's going to die at one time or another. So what we're talking about, from here to death, what kind of quality of life do you want, and what can you do to impact the quality? That's how I look at life."

He says he knows stem cell research underway today is not likely to help him, "but the research is going to help thousands of people down the road, and I think that's wonderful."



HUNTINGTON'S DISEASE

LIKE EMERGENCY RESPONDERS AT AN ACCIDENT SCENE, MESENCHYMAL STEM CELLS

move from brain cell to brain cell, looking for the injured. • Jan Nolta, Ph.D., director of the University of California, Davis Institute for Regenerative Cures, intends to harness the paramedic services of these bone marrow–derived cells and treat Huntington's disease. "They are very social," she says of the cells. "They seem to query other cells and ask them if they need anything." Inserted into the brain, they actually seek out damage. • Some 2,000 people are diagnosed with Huntington's every year in the United States. Unlike many inherited diseases, which require two copies of a disease-causing gene to wreak havoc, Huntington's rears its head with a single mutant gene. That means children of someone with Huntington's have a 50-50 chance of developing the always-fatal disease.

The errant Huntington's gene is a copy machine run amok, repeating the recipe for the same three nucleic acids 38 times or more. The protein created by this wild repetition, called huntingtin or htt, damages a class of brain cells called medium spiny neurons.

When a medium spiny neuron is healthy, it is shaped something like a spider web, with axons extending in all directions, controlling movement, cognition and emotion. But under htt's influence, it pulls in those axons. Cell-to-cell communication stops, and the person develops involuntary dance-like movements. The condition leads to behavior changes; a sweet-tempered person becomes irascible. Cognitive function declines.

To disrupt this destruction, Nolta married the mesenchymal cell's charitable tendencies with an htt-killer. On their own, mesenchymal cells secrete neural growth factors that can restore synaptic connections, though they cannot touch the htt, which continues to plunder. But animal studies showed that strands of RNA can be tailored to chop the htt RNA, decreasing Huntington's symptoms and prolonging survival. Nolta's team of researchers engineered mesenchymal stem cells to manufacture short interfering RNA, or siRNA. Videos of mesenchymal cells engineered to make this siRNA show cells pouring the siRNA into any sick cells they encounter. Her team has a patent pending on this technology.

The first human studies will use the mesenchymal cells without siRNA, to study the effect of the neural growth factors that mesenchymal stem cells produce. The next study will add the siRNA to the mesenchymal cells.

"I'm excited we've now shown that the technology CIRM funded is working, and that mesenchymal stem cells are safe to implant into the brain," Nolta said. "There are so many people in the Huntington's community whom we care about deeply, and we are hoping to have a real impact in treating this disease."

WHAT IS IT LIKE TO LIVE WITH HUNTINGTON'S DISEASE?

Sherry lives balanced on the odds of a coin toss. • Since she was 9, when her father was diagnosed with Huntington's disease, she's known that she has a 50-50 chance of receiving the same diagnosis. During the next 11 years, as she watched her father fail tragically, his personality changing, his body growing weaker, she coped by staying busy, swimming and playing water polo.

Just knowing she might develop Huntington's is a burden. So many things worry her. "If I trip or fall or mess up at work, I think, 'Oh, I might have HD.' If I'm moody or something, I wonder, 'Is this like the first sign?'"

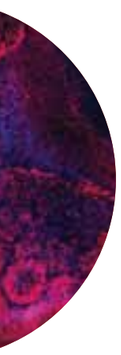
That's one reason the 27-year-old hasn't taken the genetic test to learn her status. "If I tested positive, I would symptom search even more than I do now."

Another complication: She doesn't give her last name because she fears the discrimination that could follow if her risk status were revealed.

She worries even more about losing the abilities that matter to her. "I love outdoor activities. I love traveling, reading, talking, walking, eating—I'm very good at eating. I just don't want to give up those things I love most in life: my relationships, my independence."

Still she is optimistic about stem cell research. "Whenever I'm having a rough day, I think about it. It just gives me hope."

"I just don't want to give up those things I love most in life: my relationships, my independence."
SHERRY



HIV/AIDS

CALL IT MOLECULAR JUJIT-SU. THE HUMAN IMMUNODEFICIENCY VIRUS THAT CAUSES AIDS

is a wily adversary, evolving around opponents enlisted to defeat it. But researchers at City of Hope in Duarte, Calif., led by John Zaia, M.D., intend to employ the strength of the virus against itself, the way jujitsu practitioners leverage an enemy's force to shape his downfall. • The lynchpin in this strategy is the protein CCR5, which makes a doorway HIV uses to enter an immune cell. Individuals resistant to HIV have a mutation in the CCR5 gene. German researchers "reinvigorated the field," Zaia said, with a paper in the *New England Journal of Medicine* in 2009 about a stem cell transplant using cells from an HIV-resistant donor. The transplant not only successfully treated the patient's myeloid leukemia, but cleared his HIV as well. Since the treatment, doctors have been unable to detect any HIV in the patient using even the most sensitive tests.

Because of the odds against finding a matching donor with the CCR5 mutation for every person with HIV, the paper didn't show the way to a cure. But it did highlight the hope of stem cell transplants. Zaia will use stem cells to create HIV resistance with the help of molecular scissors—an engineered molecule called a zinc-finger nuclease, a technology developed by Richmond, Calif., company Sangamo BioSciences Inc.

Zinc "fingers" are peptides selected to bind to a specific area of DNA. The fingers grab a targeted sequence and sever it. Normally, the CCR5 protein snakes through the cell membrane in a series of hairpin curves. But cut the CCR5 gene, and the protein no longer appears on the cell surface; HIV's entryway disappears like a vanishing door in a Harry Potter novel.

To make the door fade forever, the gene must be disabled in a patient's stem cells, which will hand the mutation down to future cell generations. Animal studies show that only a fraction of the stem cells need the CCR5 mutation to create disease resistance. Whereas other genetic engineering approaches must alter great numbers of cells to create lasting change, and must keep those new cells running for a lifetime, the jujitsu nature of the zinc-finger approach means the zinc fingers must operate only briefly, mutating only a small percentage of all the stem cells.

Animal studies show HIV's killing efficiency becomes its undoing, jujitsu style. The disease attacks the unmutated cells. The survivors all carry the mutation, and the virus has no one to plunder. Viral levels fall.

Zaia says the first patients to try mutated cell transplants will be those with AIDS lymphoma who need a complete stem cell transplant to combat that cancer.

"There is a need for improved treatment of HIV/AIDS," Zaia says. "The zinc-finger technology offers real promise."

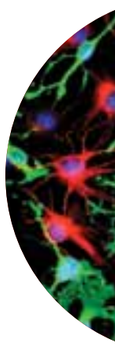
> "I truly believe our best hope for better treatment, and ultimately a cure, will come from the hands and hearts and minds of these astonishing people."
> LORING LEEDS

WHAT IS IT LIKE TO LIVE WITH HIV?

It was perhaps the biggest moment of Loring Leeds' life, but as he lay waiting for doctors to return his stem cells to his body, Leeds realized it was a signature moment for the crowd in the room as well. • It was 1998, and surrounding him were the doctors and scientists who had developed a treatment for non-Hodgkin lymphoma in AIDS patients—something most of the medical community at the time considered pointless and hopeless. But Leeds' stem cell treatment was even more dramatic, because some of his cells were genetically modified to express an enzyme researchers hoped would short-circuit AIDS.

"There was this deafening silence, and I realized that moment was the culmination of their life's work," Leeds said. Today, Leeds, an artist, is cancer free, and though the AIDS enzyme treatment did not work, his HIV is undetectable. The treatment he received was a precursor to the HIV work now being carried out by two CIRM disease teams.

"These people are the most dedicated, the most compassionate, the most passionate people I've ever met," Leeds said. "They are visionaries. They are the best humanity has to offer. I truly believe our best hope for better treatment, and ultimately a cure, will come from the hands and hearts and minds of these astonishing people."



EPIDERMOLYSIS BULLOSA

AN INFANT'S SKIN PEELS OFF IN SHEETS, REVEALING ANGRY RED FLESH BELOW.

In the disease called dystrophic epidermolysis bullosa, there is something wrong with the collagen tethers that anchor the top layer of skin to the dermis beneath. The skin sloughs off or blisters at the slightest insult—the rub of a shirt collar, the touch of a hand, the movement of the eye during dreams. Even birth. • The skin's impermanence results from a misstep in a gene that forms the collagen tethers. • EB comes in a less severe dominant form or a more devastating recessive form. Four to eight babies in the United States are born each year with this latter form. Forty percent will die before age 35, said Alfred Lane, M.D., chair of dermatology and pediatrics at the Stanford University School of Medicine. But even the 24 to 28 children born annually with the dominant form of EB suffer from fragile skin, painful wounds, frequent blisters and scarring. • A team of Stanford University researchers hopes to grow new, genetically corrected skin for these children. Skin that stays where it belongs.

Key to the strategy are induced pluripotent stem cells, grown-up cells that are convinced to return to their embryonic youth. Cells of the embryo may mature into any cell type; that is, they're pluripotent. With induced pluripotency, investigators will take a patient's fully differentiated skin cells and coax them back to pluripotence, says Marius Wernig, M.D., an assistant professor at the Institute for Stem Cell Biology and Regenerative Medicine at Stanford.

While the cells are in their pluripotent state, researchers will repair the gene using homologous recombination. The correction takes advantage of DNA's willingness to swap genetic material with complementary—that is, homologous—DNA strands. The complementary strands introduced to the pluripotent cells will carry a correction for the error that causes EB. Although as few as 1 percent of the cells may adopt the correction, that's enough. Cells identified with properly correct genomes will be grown into skin cells for transplant to patients.

"If you look at this entire project, every step is, in principle, established. In principle we know how we can do it," Wernig said. "The challenge is to pull all the pieces together in a way that works reliably."

WHAT IS IT LIKE TO LIVE WITH EB?

Chuck and Christine Anderson were butterfly children. • Born with an inherited condition that made their skin as fragile as a butterfly wing, Chuck died at 27 of skin cancer. His sister, Christine, died of heart failure at 14. • "These children taught me an incredible lesson in resilience, determination and good cheer," says their mother, Lynn Anderson. She is the president and founder of the Epidermolysis Bullosa Research Foundation.

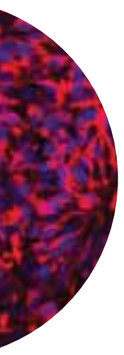
They were born with the recessive form of dystrophic epidermolysis bullosa. "The glue that holds the skin together is missing," Anderson explains. "The skin tears or blisters at the slightest provocation."

Things as simple as putting on a shoe can cause chronic wounds. "Stiff pants make blisters. Pull on the arm, and the skin comes off," she says.

"Imagine not being able to swallow because you have scarring in your esophagus. You have difficulty eating because you have sores in your mouth," she says. The disease brings chronic anemia, malnutrition and growth retardation because most nutrition goes toward skin repair. When Chuck Anderson was 27, he weighed 59 pounds.

Anderson says she has great hopes for EB research. She is grateful for the researchers "who have helped my children's suffering come to something good, who have helped me believe that EB is not forever."

> "These children taught me an incredible lesson in resilience, determination and good cheer."
> LYNN ANDERSON



STROKE

STEM CELLS AT FIRST SEEMED IDEAL REPLACEMENT PARTS, LIVING LEGOS FOR STROKE-DAMAGED BRAINS.

But when Gary Steinberg, director of neurosurgery at Stanford University's School of Medicine, put human stem cells into the brains of rats with induced stroke, he saw the cells didn't just turn into new neurons to swap for the damaged ones. While about half of the cells became functioning neurons, the benefits went beyond their contribution. The stem cells seemed to respond to a suite of signals the damaged brain sent in its attempt to quell the stroke-triggered chaos. The result: reduced inflammation, increased blood supply, new growth on existing neurons and new neuronal connections. In addition, rats treated with stem cells recovered function in limbs affected by stroke. • Normally, the brain's stroke distress calls rarely summon sufficient repair. Fifteen percent of people with ischemic stroke – that is, stroke caused by blockage in an artery – die from it, and stroke caused by a burst blood vessel kills half its victims. Among the survivors of both kinds of stroke, damage can be devastating. A third can no longer care for themselves, and three-quarters lose the ability to complete some tasks of daily living. • Steinberg hopes that cells derived from embryonic stem cells, with their ability to travel directly to damaged areas in the brain, could bring dramatic change. Stem cells implanted in rodents with stroke worked to repair damaged areas, summoned there, apparently, by signaling chemicals called chemokines. Further research showed that the stem cells emit a signaling protein called vascular endothelial growth factor. When Steinberg blocked VEGF using the cancer drug Avastin, many of the stem cell's positive effects disappeared.

Stem cells act as an efficient delivery device for VEGF and other growth factors, Steinberg said, integrating into the environment, responding to nearby signals, and releasing the growth factor only where and when needed.

Although his goal is to begin a phase 1 stroke trial with human embryonic stem cells by 2014, his group recently opened enrollment in a Phase 1 trial sponsored by the Mountain View company, SanBio, using bone-marrow derived stem cells. In this safety study, surgeons will implant cells in patients whose stroke occurred six months to a year earlier. In a previous small trial using these cells, there were no adverse effects, and some participants saw improvements in movement, memory and spatial processing.

"I believe that stem cells transplantation for stroke holds great promise," Steinberg said. "Over the next probably two decades we will see remarkable advances."

"There are so many things doctors can do with stem cells that will really help. Oh yes, I'm very hopeful."
K. MICHAEL COOPER

WHAT IS IT LIKE TO LIVE WITH STROKE?

If K. Michael Cooper ever thought about giving up after his stroke Thanksgiving morning 2003, his wife, Annemieke Wiegman, wouldn't let him. • He was 56 years old when the sudden loss of circulation in his brain changed the Redwood City man's life. He couldn't speak. He couldn't swallow. He couldn't move his right side. But almost from the start, Annemieke treated her husband like a man with a very important deadline.

"She kept telling me, I only had six months to get better," he said. While other patients were wheeled to lunch, Annemieke insisted Cooper use a walker. While other families helped loved ones eat, "My wife let me struggle and make a mess." Annemieke launched a rehabilitation program, lifting her husband's unresponsive arm and leg 12 times every day.

"She did not give up on me, and I did not want to give up, "he said.

Released from rehab on Christmas Eve, Cooper continues to work on his recovery, especially his speech, still peppered with small hesitations and stutters.

While Cooper believes in working on recovery, he relishes the promise of stem cells.

"There are so many things doctors can do with stem cells that will really help," he said. "Oh yes, I'm very hopeful."

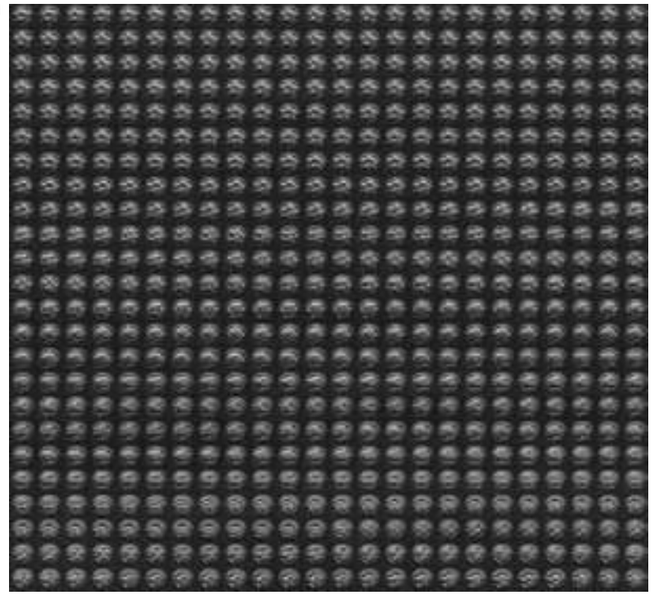
DRUG BASED ON STEM CELL STUDIES BRINGS HEALTH

Three years ago Theresa Blanda was too sick to work. Her blood disease forced her to use a walker to move around. A bone marrow transplant was her only hope for a cure.

Bone marrow transplants are risky and expensive—the procedure costs roughly $250,000.

Today, she's back at work. Blanda participated in a trial for a drug initially discovered through work by CIRM grantee Catriona Jamieson at the University of California, San Diego. The drug, co-developed by the San Diego-based company TargeGen, Inc, treated her pre-leukemic disease and took her off the bone marrow transplant list.

Studying the earliest stages of embryo development has helped improve the success rate of in vitro fertilization. Events in the first few days of development might also underlie common diseases.



SPOTLIGHT ON THE HUMAN EMBRYO AND HUMAN EMBRYONIC STEM CELL RESEARCH

"I can't believe the progress we've made in the past years with human embryonic stem cells and embryology. We have unprecedented tools to understand human development and we can begin to understand basic questions like where does sporadic disease come from in the population."

RENEE REIJO PERA
DIRECTOR, STANFORD CENTER FOR HUMAN EMBRYONIC STEM CELL RESEARCH AND EDUCATION

Inside California and abroad, CIRM has worked to broaden understanding of stem cell research—the science and the hope—and to strengthen communities of researchers themselves.

CALIFORNIA AND BEYOND

Within California, people had three opportunities this year to learn more about work funded by CIRM in their neighborhoods. Town Hall Forums in San Diego, Los Angeles and San Francisco brought CIRM scientists together with community members to discuss ongoing science and the progress toward cures. • The San Francisco Town Hall Forum, co-sponsored by the International Society for Stem Cell Research, which was holding its annual meeting in the city, focused on the growing trend of stem cell tourism. • Unregulated clinics throughout the world have been offering unproven therapies at great cost to desperate patients. Not only might those treatments not help, Jeanne Loring, Ph.D., a CIRM grantee at Scripps Resarch Institute who spoke at the forum, warned that they could be dangerous.

"Stem cell tourism is an exploitation of the promise of stem cells," she said. The forum was recorded and is available on the CIRM web page.

The ISSCR has offered to investigate clinics at no cost through its new web page: A Closer Look at Stem Cell Treatments, www.closerlookatstemcells.org.

CIRM's educational mission expands beyond once-per-year forums. A new education portal on the website now provides a series of five modular curricula available to high school teachers. Each can fit within existing California teaching requirements, and provides lesson plans and hands-on activities.

The extensive set of course materials and activity resources will help high school and other educators prepare the youth of California to join the fast-growing biotech economy and help that sector find the workers its leaders say are already in short supply.

"Collaborations between our Canadian scientists and California-based scientists and institutions have been among the most remarkable international endeavors in science that I have witnessed. Although no money from CIRM was invested in Canada, intellectual capital was, and in a two-way fashion the whole greatly exceeded the sum of the parts. The pace of development in the cancer stem cell area, for example, has been nothing short of outstanding and our understanding of that disease process has been turned on its head all because CIRM, and its Chair Robert Klein, saw the multiplier effect that could be had through global collaboration."

CAL STILLER, FORMER CHAIR, GENOME CANADA; CHAIR, ONTARIÃO INSTITUTE FOR CANCER RESEARCH; 2010 CANADA GAIRDNER AWARD RECIPIENT

REACHNG ACROSS BORDERS

CIRM ONLY FUNDS RESEARCH CARRIED OUT IN CALIFORNIA. However, excellent stem cell science is taking place worldwide. In order to connect the leading minds in stem cell science, CIRM has formed partnerships with 11 international funding agencies and one U.S. state, and one state-based foundation.

These partnerships connect outstanding scientists without regard to geographic location. When an award that includes an international collaborator is approved for funding, CIRM funds the scientists in California and the funding partner is responsible for the international portion of the research.

This past year the CIRM Governing Board approved four Early Translational Awards and one Basic Biology III Award that include German collaborators, one Basic Biology II award that includes a Japanese collaborator, and two Stem Cell Transplantation Awards with Australian collaborators, bringing the total to 16 international teams.

BRIDGING THE DIVIDE

Outreach within the stem cell community keeps those scientists connected and the research pushing forward. • Our CIRM Bridges trainees, who are undergraduate and master's students doing work in California stem cell labs, rubbed elbows at a meeting in the summer. Students from around the state presented their internship projects and discussed their plans for the future. • The students, many of whom are from lower economic level homes, have plans for graduate school, medical school, or careers in California's flourishing stem cell industry.

"I love it and I think that I'll never turn my back on biology now," said Nicole Haste, a Bridges student at San Francisco State University.

Even established stem cell scientists benefit from a bit of face time. The CIRM grantee meeting in spring 2010 brought together grantees and their lab members to present results, talk about obstacles and form collaborations.

In June, 2010, many of these same scientists met some 4,000 of their international colleagues at the yearly meeting of the International Society for Stem Cell Research, co-sponsored by CIRM and held in San Francisco.

Events like these bring scientists together to overcome barriers in translating stem cell science into cures.

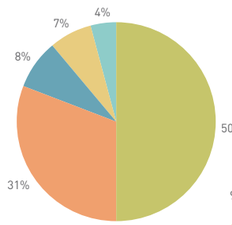
A DAY TO REMEMBER

THE THIRD ANNUAL STEM CELL AWARENESS DAY expanded CIRM's stem cell outreach to 20 schools within California, eight educational events in the state, six events in other U.S. states, and activities in four countries.

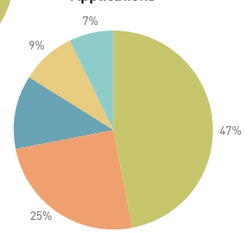
The day, held October 6, was proclaimed state-wide by the governor of California. Scientists within California visited 20 schools with lectures and school-wide assemblies about stem cell science. In addition, 20 events world wide included tours or public lectures to educate their local community about this important field of research and the work that's going on at institutions near them.

Internationally, Monash University in Victoria, Australia held a day-long event with talks and activities, and events in Ireland, England, Australia and Canada educated people about stem cell science in those countries

Awarded grants



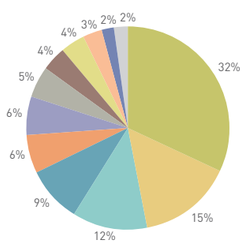
Applications



Science Category
By award number

- Basic research
- Translational research
- Pre-clinical research
- Facilities
- Training

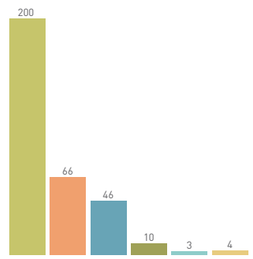
Disease Category
By award number



- Neurological disorders
- Cancer
- Heart disease
- Blood/immune disorders
- Sensory organs
- Multiple disorders
- Diabetes
- Bone/cartilage disorders
- Muscular disorders
- GI/liver disease
- Reproductive disorders
- Other disorders

Human Cell Type Usage
By award number
(some awards use multiple cell types)

- Embryonic
- iPS cell
- Adult
- Cancer
- SCNT
- Other



For a full report on the CIRM finances see the annual report online at www.cirm.ca.gov/2010AnnualReport

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Type II Diabetes

SHERRY LANSING
Cancer

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Type 1 Diabetes

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GRACE PAVLATH, PH.D.
Emory University

JOHN RASKO, PH.D., FRCPA, FRACP
University of Sydney

THEODORE RASMUSSEN, PH.D.
University of Connecticut

Total grants approved for funding THROUGH APRIL 2011

Institution	Total Grants	Total Funds
STANFORD UNIVERSITY	56	$186,489,478
UNIVERSITY OF CALIFORNIA, LOS ANGELES	43	$140,596,577
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	36	$112,364,241
UNIVERSITY OF CALIFORNIA, SAN DIEGO	35	$82,819,851
UNIVERSITY OF SOUTHERN CALIFORNIA	19	$71,933,514
UNIVERSITY OF CALIFORNIA, IRVINE	27	$71,878,458
UNIVERSITY OF CALIFORNIA, DAVIS	19	$61,187,635
SANFORD CONSORTIUM FOR REGENERATIVE MEDICINE	1	$43,000,000
CITY OF HOPE NATIONAL MEDICAL CENTER	9	$41,586,199
THE SCRIPPS RESEARCH INSTITUTE	14	$37,377,357
UNIVERSITY OF CALIFORNIA, BERKELEY	14	$39,692,934
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES	15	$39,154,585
BUCK INSTITUTE FOR AGE RESEARCH	6	$33,017,217
BURNHAM INSTITUTE FOR MEDICAL RESEARCH	17	$30,982,832
VIACYTE, INC.	4	$26,281,356
THE J. DAVID GLADSTONE INSTITUTES	13	$22,633,004
UNIVERSITY OF CALIFORNIA, SANTA CRUZ	9	$19,468,564
CHILDREN'S HOSPITAL OF LOS ANGELES	8	$18,040,423
UNIVERSITY OF CALIFORNIA, SANTA BARBARA	6	$13,496,575
CEDARS-SINAI MEDICAL CENTER	5	$10,940,472
UNIVERSITY OF CALIFORNIA, MERCED	5	$8,494,301
IPIERIAN, INC.	2	$7,123,887
UNIVERSITY OF CALIFORNIA, RIVERSIDE	4	$6,055,762
THE PARKINSON'S INSTITUTE	2	$5,029,749
BIOTIME, INC.	1	$4,721,706
THE JACKSON LABORATORY WEST	1	$3,841,240
SAN DIEGO STATE UNIVERSITY	2	$3,464,360
SCRIPPS HEALTH	1	$3,118,431
FLUIDIGM CORPORATION	2	$2,693,424
GAMMA MEDICA-IDEAS, INC.	2	$2,478,347
LUDWIG INSTITUTE FOR CANCER RESEARCH	3	$2,473,053
PALO ALTO INSTITUTE FOR RESEARCH AND EDUCATION, INC.	2	$2,408,275
CALIFORNIA INSTITUTE OF TECHNOLOGY	1	$2,318,580
SAN JOSE STATE UNIVERSITY	1	$1,756,260
CALIFORNIA STATE UNIVERSITY, CHANNEL ISLANDS	1	$1,755,906
CALIFORNIA STATE UNIVERSITY, SAN MARCOS	1	$1,754,664
PASADENA CITY COLLEGE	1	$1,750,491
SAN FRANCISCO STATE UNIVERSITY	1	$1,736,058
HUMBOLDT STATE UNIVERSITY	1	$1,638,863
CALIFORNIA STATE UNIVERSITY, NORTHRIDGE	1	$1,627,220
LA JOLLA INSTITUTE FOR ALLERGY AND IMMUNOLOGY	1	$1,503,998
CALIFORNIA STATE POLYTECHNIC UNIVERSITY, POMONA	1	$1,459,297
ESCAPE THERAPEUTICS, INC	1	$1,453,040
GMR EPIGENETICS	1	$1,452,693
CALIFORNIA POLYTECHNIC STATE UNIVERSITY, SAN LUIS OBISPO	1	$1,419,009
CALIFORNIA STATE UNIVERSITY, LONG BEACH	1	$1,355,700
CALIFORNIA STATE UNIVERSITY, SACRAMENTO	1	$1,343,940
CALIFORNIA STATE UNIVERSITY, FULLERTON	1	$1,281,180
CALIFORNIA STATE UNIVERSITY, SAN BERNARDINO	1	$1,161,017
CITY COLLEGE OF SAN FRANCISCO	1	$1,110,608
BERKELEY CITY COLLEGE	1	$1,086,819
VISTAGEN THERAPEUTICS, INC.	1	$971,558
VALA SCIENCES, INC.	1	$906,629
HUMAN BIOMOLECULAR RESEARCH INSTITUTE	1	$714,654
CHILDRENS HOSPITAL OAKLAND RESEARCH INSTITUTE	1	$55,000
GRAND TOTAL	**406**	**$1,186.456,991**

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University of California, San Francisco
Biomedical ethics related to oocyte, embryo and stem cell research

TED PETERS, PH.D.
Pacific Lutheran Theological Seminary, Graduate Theological Union
Biomedical ethics of stem cell research; genetics

DOROTHY ROBERTS, J.D.
Northwestern University School of Law
Bioethics and the interplay of gender, race, and class in legal issues concerning reproduction and bioethics

PATRICK TAYLOR, J.D.
Children's Hospital Boston,
Legal, ethical, compliance and policy issues

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Epigenetics, SCNT

TIMOTHY KAMP, M.D., PH.D.
University of Wisconsin
Cardiac stem cell therapy

ANN KIESSLING, PH.D.
Harvard University School of Medicine
SCNT & oocyte derivation, IVF and egg donation

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Neurodegenerative diseases

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Schools of Health Professions, City University of New York, Hunter College
Cellular biology/biochemistry, hematopoietic stem cells

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Oncology, molecular genetics, and cell biology, hematopoietic stem cells

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Reproductive biology; IVF and egg donation

JOHN WAGNER, M.D.
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JAMES WILLERSON, M.D.
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STEM CELL PHOTOGRAPHY

Cover, from upper left:
Motor neuron progenitors derived from human embryonic stem cells (SHARYN ROSSI at the University of California, Irvine)

Neural precursors generated from human embryonic stem cells (XIANMIN ZENG at the Buck Institute for Age Research)

Smooth muscle cells derived from mouse neural crest stem cells (DEEPAK SRIVASTAVA at the Gladstone Institutes)

Adult neural stem cells (DAVID SCHAFFER at the University of California, Berkeley)

Smooth muscles cells derived from human embryonic stem cells (ALEXEY TERSKIKH at the Sanford-Burnham Medical Research Institute)

Dopaminergic neurons derived from human embryonic stem cells (ANDREI KOCHEGAROV at the University of California, Riverside)

Human embryonic stem cells differentiating into neurons (GUOPING FAN at the University of California, Los Angeles)

Adult neural stem cells (DAVID SCHAFFER at the University of California, Berkeley)

Retinal pigment epithelium derived from human embryonic stem cells (DAVID BUCHHOLZ AND SHERRY HIKITA at the University of California, Santa Barbara)

Neurons derived from human embryonic stem cells (XIANMIN ZENG at the Buck Institute for Age Research)

Retinal pigment epithelium derived from human embryonic stem cells (DAVID BUCHHOLZ at the University of California, Santa Barbara)

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