The California Institute for Regenerative Medicine

Science, Governance, and the Pursuit of Cures

Committee on a Review of the California Institute for Regenerative Medicine

Board on Health Sciences Policy

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

PREPUBLICATION COPY: UNCORRECTED PROOFS

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by Contract No. 2267 between the National Academy of Sciences and the California Institute for Regenerative Medicine. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the organizations or agencies that provided support for the project.

International Standard Book Number 0-309-0XXXX-X

Additional copies of this report are available for sale from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at: w**ww.iom.edu.**

Printed in the United States of America

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Suggested citation: IOM (Institute of Medicine). 2013. *The California Institute for Regenerative Medicine: Science, governance, and the pursuit of cures.* Washington, DC: The National Academies Press.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the Nation. Improving Health.

PREPUBLICATION COPY: UNCORRECTED PROOFS

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Charles M. Vest is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON A REVIEW OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

HAROLD T. SHAPIRO (*Chair*), President Emeritus, Professor of Economics and Public Affairs, the Woodrow Wilson School of Public and International Affairs, Princeton University, New Jersey
TERRY MAGNUSON (*Vice Chair*), Vice Dean for Research, School of Medicine, S.G. Kenan Professor and Chair, Department of Genetics, University of North Carolina at Chapel Hill
RICHARD R. BEHRINGER, Professor, Department of Genetics, the University of Texas MD Anderson Cancer Center, Houston
REBECCA S. EISENBERG, Robert and Barbara Luciano Professor, School of Law, University of Michigan, Ann Arbor
INSOO HYUN, Associate Professor, Department of Bioethics, School of Medicine, Case Western Reserve University, Cleveland, Ohio
GARY A. KORETZKY, Francis C. Wood Professor, Perelman School of Medicine at the University of Pennsylvania, Philadelphia
CATO T. LAURENCIN, Albert and Wilda Van Dusen Distinguished Professor of Orthopaedic Surgery; Professor of Chemical, Materials and Biomolecular Engineering; Chief Executive Officer, Connecticut Institute for Clinical and Translational Science; and Director, Institute for Regenerative Engineering, the University of Connecticut, Farmington
AARON D. LEVINE, Assistant Professor, School of Public Policy, Georgia Institute of Technology, Atlanta
MICHAEL H. MAY, Chief Executive Officer, Center for Commercialization of Regenerative Medicine, Toronto, Canada
CHERYL A. MOORE, Executive Vice President and Chief Operating Officer, Howard Hughes Medical Institute, Chevy Chase, Maryland
STUART H. ORKIN, David G. Nathan Professor of Pediatrics; Chair, Department of Pediatric Oncology, Dana-Farber Cancer Institute; and Investigator, Howard Hughes Medical Institute, Harvard Medical School, Boston, Massachusetts
ALLEN M. SPIEGEL, Marilyn and Stanley M. Katz Dean, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York
SHARON TERRY, President and Chief Executive Officer, Genetic Alliance, Washington, DC

Consultant

RALPH SNYDERMAN, Chancellor Emeritus for Health Affairs; and James B. Duke Professor, School of Medicine, Duke University, Durham, North Carolina

IOM Staff

ADRIENNE STITH BUTLER, Senior Program Officer
JING XI, Research Associate
THELMA L. COX, Senior Program Assistant
DONNA RANDALL, Administrative Assistant
LORA K. TAYLOR, Financial Associate
ANDREW M. POPE, Director, Board on Health Sciences Policy

REVIEWERS

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Laurence Baker, Stanford University
Christopher H. Colecchi, Broadview Ventures, Inc
James Fossett, University of Albany
Joseph G. Hacia, University of Southern California
Zach Hall, Retired
Mark S. Humayun, University of Southern California
Edison Liu, The Jackson Laboratory
Mary Majumder, Baylor College of Medicine
Robert M. Nerem, Georgia Institute of Technology
Mahendra Rao, The National Institutes of Health
David Resnick, Nixon Peabody
Janet Rossant, University of Toronto
William A. Sahlman, Harvard Business School
Bernard Siegel, Genetics Policy Institute
Nancy S. Wexler, Columbia University

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the report's conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Ellen Wright Clayton,** Vanderbilt University and **Huda Akil,** University of Michigan. Appointed by the National Research Council and the Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

The energetic, imaginative, and committed coalition of California citizens and others responsible for the passage of Proposition 71 in the 2004 general election produced a social innovation. While state initiatives in research and development are not new, this initiative, in both scope and design, broke new ground. In essence, the voters of California expressed a strong desire to move ahead in the field of regenerative medicine, including research using human embryonic stem cells, despite the ongoing near paralysis of the federal government in aspects of this arena. In the globalized world of biomedical research, they grasped the possibility that by building on California's already strong and deep biomedical research and biotechnology community and by structuring a distinctive model of finance, they could not only dramatically advance the field of regenerative medicine, but also establish California as one of the worldwide hubs in this promising area of biomedical research and development. At the time, this was also a courageous initiative given that certain aspects of regenerative medicine, especially work using embryonic stem cells derived from human embryos, were highly controversial in ethical terms. It is worth remembering that in 2004, there had been little demonstration of the potential for reprogramming somatic cells to bring them to a pluripotent state.

The California Institute for Regenerative Medicine (CIRM) was the organization charged with responsibility for thoughtfully expending the $3 billion set aside by voters through the passage of Proposition 71 to advance critical aspects of the field of regenerative medicine in California. Indeed, one of the Institute's principal aims was to help create in California an international hub of research and development in regenerative medicine. It is the committee's judgment that overall, CIRM has done a very good job of initially establishing and then updating the strategic plans that have set priorities for and guided its programs, and of taking advantage of its guaranteed flow of $300 million a year for 10 years to establish a sustainable position in regenerative medicine for California. The challenge of moving its research programs closer to the clinic and California's large biotechnology sector is certainly on CIRM's agenda, but substantial achievements in this arena remain to be made.

Despite its demonstrable achievements to date, as well as the largely positive independent reports covering various aspects of its operations, no one would claim that CIRM is a perfect organization or that it should adhere slavishly to its initial form of organization, set of regulations, or pattern of priorities. The field of regenerative medicine has advanced rapidly since November 2004, and CIRM itself has seen the need to alter its activities and approaches in some areas. The committee believes the same should be true of its governance structure, some of its administrative practices, and its use of external perspectives on strategic scientific priorities

and on the evaluation of other key policies, such as Intellectual Property, to ensure that they continue to encourage the development and deployment of new treatments. Experience has shown that Proposition 71 can, in partnership with the California Legislature and the governor, be amended in a manner that would optimize CIRM's functionality and best serve the interests of the citizens of California.

In this report, the committee has endeavored to evaluate various aspects of CIRM's programs and experiences with the aim of acknowledging both its successes and remaining challenges. The committee also has considered the lessons of CIRM's experience for other states, or even the federal government, that might wish to use CIRM's experience to inform some of their initiatives.

Finally, we wish to thank our colleagues on the committee for their tireless devotion to this task. We also wish to express our appreciation to CIRM for its openness and responsiveness to the committee's many requests for information during the course of this study.

Harold T. Shapiro, Chair
Terry Magnuson, Vice Chair
Committee on a Review of the California
Institute for Regenerative Medicine

Acknowledgments

Several individuals and organizations made important contributions to the study committee's process and to this report. The committee wishes to thank these individuals, but recognizes that attempts to identify all and acknowledge their contributions would require more space than is available in this brief section.

To begin, the committee would like to thank the sponsor of this study. Funds for the committee's work were provided by the California Institute for Regenerative Medicine (CIRM). The committee thanks Lynn Harwell, who served as project officer, and CIRM staff for their assistance during the study process.

The committee gratefully acknowledges the contributions of the many individuals who assisted in the conduct of this study. The perspectives of many individuals and organizations were valuable in understanding CIRM and its work. The committee thanks those who provided important oral testimony at its open workshops. Appendix A lists each of these individuals and their affiliations. As part of its review, the committee also visited three sites that receive CIRM funding to gather information about the role of that support in their work. In addition, many individuals with knowledge of CIRM, as well as analogous programs in other states, participated in interviews with committee members (see Appendix A). The committee also received written testimony through several questionnaires targeting various stakeholder groups. The committee greatly appreciates the time, effort, and information provided by all of these knowledgeable and dedicated individuals.

Contents

Acronyms

CCR5	C-C chemokine receptor type 5
CEO	chief executive officer
CFO	chief financial officer
CIRM	California Institute for Regenerative Medicine
CPRIT	Cancer Prevention Research Institute of Texas
CRADA	cooperative research and development agreement
CTRC	clinical translational research center
CTSA	Clinical and Translational Science Award
EAP	External Advisory Panel
FDA	Food and Drug Administration
FTE	full-time equivalent
GSP	gross state domestic product
GWG	Grants Working Group
hES	human embryonic stem (cell)
HHS	Department of Health and Human Services
ICOC	Independent Citizens Oversight Committee
IND	Investigational New Drug
IOM	Institute of Medicine
iPS	induced pluripotent stem (cell)
IRB	institutional review board
ISSCR	International Society for Stem Cell Research
MSCRF	Maryland Stem Cell Research Fund
NACD	National Association of Corporate Directors
NAS	National Academy of Sciences
NCSL	National Conference of State Legislatures
NGA	National Governors Association

NIH	National Institutes of Health
NRC	National Research Council
NYSTEM	New York State Stem Cell Science Research Fund
OTA	Office of Technology Assessment
R&D	research and development
RFA	request for applications
RNAi	ribonucleic acid interference
SAB	Scientific Advisory Board
SVP	senior vice president
SWG	Standards Working Group
TGR	The Guttmacher Report
UCLA	University of California, Los Angeles
UCSD	University of California, San Diego
UCSF	University of California, San Francisco

Summary[1]

ABSTRACT

The California Institute for Regenerative Medicine (CIRM) was created in 2005 by The California Stem Cell Research and Cures Act (Proposition 71) to distribute $3 billion in state funds for stem cell research. The passage of Proposition 71 by the voters of California occurred at a time when federal funding for research involving human embryonic stem cells was uncertain, given the ethical questions raised by such research. During its initial period of operations, CIRM has successfully and thoughtfully provided more than $1.3 billion in awards to 59 California institutions, consistent with its stated mission. As it transitions to a broadened portfolio of grants to stimulate progress toward its translational goals, the Institute should obtain cohesive, longitudinal, and integrated advice; restructure its grant application review process; and enhance industry representation in aspects of its operations. CIRM's unique governance structure, while useful in its initial stages, might diminish its effectiveness moving forward. The committee recommends specific steps to enhance CIRM's organization and management, as well as its scientific policies and processes, as it transitions to the critical next stages of its research and development program.

Proposition 71 (The California Stem Cell Research and Cures Act) was adopted by the voters of California on November 2, 2004, to provide substantial state support for a comprehensive in-state stem cell research program. The California Institute for Regenerative Medicine (CIRM) was created in 2005 to carry out this program. The act established a distinctive model of both finance and governance for CIRM. The Institute itself was to be governed by an Independent Citizens Oversight Committee (ICOC) and was to be financed through the issuance of long-term general obligation bonds of the State of California. CIRM was charged by Proposition 71 with determining the most effective means of distributing $3 billion in state funds for stem cell research and research on regenerative medicine more broadly over at least 10 years. Its principal aims are to accelerate certain critical aspects of the science of regenerative medicine and its translation into treatments for a spectrum of currently intractable human diseases.

[1]This summary does not include references. Citations for the findings presented in the summary appear in the subsequent report chapters.

Research on stem cells is an important area of biomedical research because of the promise it holds for developing new and more effective treatments for a wide variety of diseases. However, the last decade and a half has seen continuing uncertainty regarding the federal government's willingness to fund research using human embryonic stem (hES) cells. Given that the federal government has traditionally been the largest source of funding for biomedical research outside of industry and the largest funder of basic research, some believed that the United States was forgoing an important opportunity to be a pioneer in developing the basic research necessary to produce critical new clinical applications. It was in this context that a broad group of California-based scientists, leaders in higher education in the state, disease advocates, and others mounted the Proposition 71 initiative. The aim of this initiative was to fill the gap created by fluctuating and uncertain federal policies, thereby helping both to develop new clinical modalities and to create a leadership position for California in this critical area of biomedicine. It is worth remembering that in 2004, there had been little demonstration of the potential for reprogramming somatic cells to bring them to a pluripotent state.

CHARGE TO THE COMMITTEE AND STUDY APPROACH

At the request of CIRM, the Institute of Medicine (IOM) convened the Committee on a Review of the California Institute for Regenerative Medicine in 2011 to critically review the Institute and produce a report including recommendations for how CIRM could improve its performance. The committee's statement of task is presented in Box S-1.

The committee was not asked to assess the wisdom of the California voters in passing Proposition 71. However, many of the detailed provisions of Proposition 71 directly impact aspects of CIRM's operations that the committee was asked to evaluate in its charge. The committee was also not asked to rigorously evaluate the details of CIRM's scientific contributions, specific grant awards, or its impact on the field of regenerative medicine. This report evaluates some of the unique aspects of CIRM's origins, its governance structure, and its scientific and intellectual property policies. The report is intended to help CIRM consider the best path forward for achieving its mission.

CIRM'S ORIGINS AND TRANSITION

CIRM is in many ways a bold social innovation. CIRM's existence is the result of the work, initiative, commitment, and imagination of a broad, diverse, and evolving group of dedicated citizens, scientists, university leadership, disease advocacy organizations, and some members of the California Legislature. CIRM differs from many other competitive scientific research programs in its innovative funding model, which provides for a stable source of funding for research in regenerative medicine over 10 years, financed by the issuance of general obligation bonds of the State of California. This approach transfers the financing burden of current research funding from current to future tax revenues. In these respects CIRM is both a creative supplement to the more traditional sources of biomedical research funding in the United States and an innovative initiative designed to further strengthen California's biotechnology efforts.

BOX S-1
Statement of Task

The California Institute for Regenerative Medicine (CIRM) asked the Institute of Medicine (IOM) to convene a committee to produce a report providing an independent assessment of CIRM's programs, operations, strategies, and performance since 2005. Specifically, the committee was charged with addressing the following questions:

- **CIRM's initial processes**—What can be learned from the history and process of building consensus in the public and scientific communities to support the inception and work of CIRM?
- **CIRM's programmatic and scientific scope**—Does CIRM have the portfolio of projects and grant opportunities necessary to meet its scientific goals? How can CIRM improve upon its existing array of programs? What additional programs and initiatives are recommended to meet its goals? What impacts have been seen from international agreements? Does CIRM's scientific strategic plan address the range of relevant issues in regenerative medicine within CIRM's mandated scope of work?
- **CIRM's organizational and management systems**—Are the internal organizational and management systems (in particular the board and working group structures and operations, the peer review system, the conflict of interest guidelines, and the grants management system) effective in working toward the institute's scientific goals? Are the systems that are in place scientifically and ethically valid and rigorous? Do they achieve the level of transparency and the level of stakeholder and scientific community involvement needed to meet the institute's public responsibilities and scientific goals?
- **CIRM's funding model**—Has the funding model for CIRM had an impact on the work of the institute? What are the advantages of CIRM's model for covering long-term costs of medical research? Could aspects of this funding model serve as a paradigm for other states or countries? What has been the economic impact of CIRM's research and facilities awards and grants?
- **CIRM's intellectual property policies**—What are the strengths and weaknesses of CIRM's policy for sharing revenue generated by intellectual property? How does this model compare to the model governing federally-supported research?

The principal objective of this review was to ensure that all aspects of CIRM's operations are functioning at peak performance. The committee was asked to provide recommendations regarding short-, medium-, and long-term actions that could improve the performance of CIRM.

Estimating the long-term economic impact of investments in a particular set of biomedical research activities is a complex task that requires at the very least considerable time and experience with various treatments and/or cures that result from those investments. In the short term, CIRM's expenditures are supporting approximately 3,400 jobs and their innovative efforts have also attracted substantial additional private and institutional resources to this research arena in California CIRM's long-term impact on such critical aspects of the California economy as state tax revenues and health care costs beyond the shorter-term and temporary impact of its direct expenditures cannot be reliably estimated at this point in CIRM's history.

Because the funding provided by Proposition 71 is limited to the $3 billion initially authorized, it is now critical for CIRM to continue to develop its plans for taking fullest advantage of its achievements in order to help support a sustainable future in which its funding circumstances could be quite different. The committee believes that in this process, it will be important for CIRM to increase industry inputs and share with the public any plans to obtain private-sector support for its ongoing activities and how any such arrangements might affect its continuing public obligations, including those related to CIRM-funded intellectual property, as well as its obligations as laid out in its access plans.

> ***Recommendation 2-1.***[2] ***Develop a Sustainability Platform.*** **CIRM should work with its current and future partners and those who have been substantial recipients of CIRM support to develop and present to the public its plans for sustaining the momentum of its achievements as it moves beyond its first decade of operations.**
>
> **Any such plan should address such key strategic areas as how CIRM intends to obtain funding after bond proceeds have been spent, how the venture philanthropy fund proposed in the 2012 Strategic Plan will interface with CIRM, and impacts of any new funding models on the role and structure of the ICOC.**[3]

GOVERNANCE OF CIRM

Assembling the broad coalition of citizens and institutions that were united in their enthusiasm for stem cell research, but had somewhat different perspectives, had implications not only for the design of Proposition 71 but also for the ongoing programs and operations of CIRM. While the restrictions on amending the administrative structure of CIRM established in Proposition 71 had the advantage of protecting the Institute's ongoing operations from outside interference in an ethically controversial arena, they also made it difficult to modify the organization's structure in response to experience and/or changing circumstances. Moreover, these protections, whatever their benefits, appear to some to shield CIRM from the normal accountability mechanisms in place for state agencies. In assessing the governance of CIRM, the committee considered issues of operations versus oversight, the ICOC and working group structure, and conflict of interest definitions and policies.

Operations Versus Oversight

Proposition 71 established the 29-member ICOC as the governing board of CIRM and created three large working groups—a 19-member Scientific and Medical Accountability Standards Working Group, a 23-member Scientific and Medical Research Funding Working Group (Grants Working Group), and an 11-member Scientific and Medical Facilities Working Group—to provide guidance to the ICOC. The CIRM president serves as the Institute's chief executive officer, but the ICOC board chair has significant operational responsibilities in

[2]The committee's recommendations are numbered according to the chapter of the main text in which they appear.
[3]See main body of the report for full text of this recommendation.

addition to managing the ICOC itself. In some cases, the allocation of responsibility for important management functions is split between the president and the board chair.

The committee recognizes that CIRM's current governance structure, as designed under Proposition 71, may have been appropriate at the start of the endeavor and contributed to its early success. Now that CIRM is a more mature organization, however, it would benefit from a clear and appropriate separation of duties, with the board being responsible primarily for independent oversight and strategy and staff for the implementation of the board's policies. The current structure of the ICOC impedes independent oversight because it relies on the ICOC to function as both overseer and executer.

The committee believes good governance requires that the board delegate more authority and responsibility for day-to-day affairs to the president and senior management. The Little Hoover Commission recommended that CIRM and the legislature eliminate overlapping authority between the chair and president and improve the clarity and accountability of each. This recommendation was echoed by the External Advisory Panel, which called for clarity in the division of roles and responsibilities between these two positions, particularly with respect to strategic direction, policies, international partnerships, funding decisions, public communications, and oversight.

> ***Recommendation 3-1. Separate Operations from Oversight.*** **The board should focus on strategic planning, oversee financial performance and legal compliance, assess the performance of the president and the board, and develop a plan for transitioning CIRM to sustainability. The board should oversee senior management but should not be involved in day-to-day management. The chair and the board should delegate day-to-day management responsibilities to the president. Each of the three working groups should report to management rather than to the ICOC.**

Board and Working Group Structure

The predominance of direct stakeholders—defined as individuals with a direct stake in the process and outcomes of CIRM's activities that arises outside of their service to the Institute—in the composition of the ICOC compromises its independence beyond the entanglement of operations and oversight. Board members who have personal and professional interests in the activities of CIRM that go beyond the interests of the general public undoubtedly bring considerable energy and commitment to the tasks before them, but they may also introduce bias into the board's decisions that compromises its stewardship over CIRM as a public institution. The board's composition should be modified to include a majority of members who are independent in the sense of having no direct personal or professional interest that might compete or conflict with the interests of CIRM and the people of California in ways that might bias their decisions (see also the discussion of conflict of interest below).

The working groups currently report to the chair. The committee believes they should report to CIRM senior management, with the ICOC being reserved to perform its responsibilities for high-level and independent strategic oversight. Thus, it is important that the chair and other ICOC members not serve on the working groups. As board members on the working groups are replaced, the working groups should not lose the fundamental and critical perspective of disease advocates; instead, any board members of the working groups who are disease advocates should be replaced by an equal number of other disease advocates who are not board members. The

committee's recommendation is intended to both redefine and expand the role of disease advocates.

> ***Recommendation 3-2. Change the Composition and Structure of the Board and Working Groups.*** **CIRM should put systems in place to restructure the board to have a majority of independent members, without increasing the size of the board. It should include representatives of the diverse constituencies with interests in stem cell research, but no institution or organization should be guaranteed a seat on the board. Consideration should be given to adding members from the business community. The terms of board members should be staggered to balance fresh perspectives with continuity.**
>
> **The chair and other ICOC members should be prohibited from serving on the working groups. During the reconstitution of the working groups, the current level of representation of disease advocates should be maintained, such board members being replaced with other disease advocates who are not board members.**

Conflict of Interest Definitions and Policies

The built-in allocation of ICOC board seats to university leadership, patient advocates, and members of the biotechnology industry, for example, ensured that a high percentage of those seats would be permanently occupied by persons with almost unavoidable, conflicts of interest, whether actual or perceived, between their roles as ICOC board members and their other, non-CIRM responsibilities. At very least the perceived conflicts are one factor that has led some observers, perhaps unfairly, to continue to question the integrity and independence of some of CIRM's decisions. Such conflicts, real or perceived, are inevitable given the provisions of Proposition 71 and were not addressed by Senate Bill 1064.[4] Conflict of interest is not misconduct, but bias that potentially skews the judgment of a board member in favor of interests that may be different from or narrower than the broader interests of the institution. Inherent conflicts arise from the interests of board members as employees of grantees and as representatives of disease advocacy organizations. The committee did not uncover or search for evidence of any inappropriate behavior by any ICOC board members. The point is that the board suffers from a wide range of perceived conflicts generated directly by the particular and unique governance requirements of Proposition 71. This threatens to undermine respect for ICOC decisions.

California law focuses primarily on financial conflicts of interest, but the committee believes that personal conflicts of interest arising from one's own or a family member's affliction with a particular disease or advocacy on behalf of a particular disease also can create bias for board members. Studies in psychology and behavioral economics show that conflict of interest leads to unconscious and unintentional "self-serving bias" and to a "bias blind spot" that prevents recognition of one's own bias. Bias distorts evaluation of evidence and assessment of what is fair.

[4]California Legislature (Sen. Bill No. 1064), approved by Governor September 30, 2010. Filed with Secretary of State September 30, 2010.

The presence of conflicts of interest for individual board members would be less cause for concern if the board had more non-conflicted members. CIRM should address real and apparent conflicts of interest, including and beyond financial interests, built into its governance structure regardless of whether these conflicts have in theory been waived by the voters or excused under California law.

> ***Recommendation 3-3. Revise Conflict of Interest Definitions and Policies.*** **CIRM should revise its definitions of conflict of interest to recognize conflicts arising from nonfinancial interests, such as the potential for conflict arising from an individual's interest in a specific disease, and should reassess its policies for managing conflict of interest in light of this broader definition.**

An important theme of the committee's governance recommendations is for CIRM to transition from the governance structure initially outlined in Proposition 71 to one the committee believes would better serve the interests of the citizens of California and the field of regenerative medicine. In assessing CIRM's current governance structure and proposals for reform, the committee did not limit considerations and recommendations to the boundaries imposed by Proposition 71. Instead, the committee worked to develop recommendations that would best serve CIRM and the California taxpayers from this point forward. The committee fully appreciates the fact that even in the best of circumstances, such a transition, if carried out thoughtfully, must take place over time.

THE SCIENTIFIC PROGRAM

The ICOC adopted its first scientific strategic plan in December 2006. The goals during this initial phase were to develop appropriate laboratory facilities for stem cell research, to fund basic research in stem cell biology, to invest in programs focused directly on research on a broad range of diseases, and to establish a long-term foundation for California's leadership in stem cell research and development**.** In this first crucial period of operations, CIRM provided—in a remarkably expeditious and thoughtful manner—more than $1.3 billion in awards to 59 institutions. The focus of these awards was fully consistent with CIRM's stated mission and was important for building the infrastructure for stem cell research in California. Collaborations with funding partners and stem cell researchers in the United States and around the world have attracted tens of millions of dollars in matching funds for CIRM projects, and resulted in new levels of cooperation and funding in the field. It is clear that in this initial period, CIRM substantially enhanced California's position as one of the key international hubs of activity in regenerative medicine.

Two years after developing its initial strategic plan, CIRM moved to broaden its portfolio of grants to stimulate progress toward its translational goals. Over time fourteen disease team awards totaling $210 million were made. A subsequent evaluation of the progress of these teams in 2011 led to the termination of one of these grants. It is not possible to say at this stage whether the net cast by CIRM's disease teams is too wide or too narrow. What is clear is that the resources ultimately required to bring any one of these initiatives to the bedside far exceed those available from CIRM.

Evolution Past the Initial Phase

In 2012, CIRM developed a new strategic plan outlining 10 goals that build on and extend those efforts articulated in the 2006 plan. The new plan increases the priority of projects clearly focused on moving toward clinical trials for evidence of therapeutic benefit and the development of partnerships with both industry and other centers for research in regenerative medicine. These are the key objectives that, in part, reflect CIRM's response to the 2010 External Advisory Panel review. This shift is illustrated further by the July 26, 2012, announcement of an additional eight disease team awards totaling approximately $151 million. These teams are expected either to have filed a request to begin clinical trials or to have completed a Phase 1/2 clinical trial within 4 years. The latest round of awards brings the number of disease teams to 22 and the total funding for this program to approximately $360 million. CIRM-supported late-stage research projects now address 37 different disease areas.

Given the pressure for CIRM to show progress in therapeutic applications within its limited time frame, the rapid transition to the disease teams and the stated goals of the 2012 strategic plan are understandable. Nonetheless, based on the consensus of both academic and industrial stem cell experts who provided comments to the committee, and given both the lengthy time frame generally required for development of new therapies and the high failure rate of clinical trials at Phase 1 or 2, the committee believes the translational goals enumerated in the 2012 strategic plan are unrealistic. Instead of focusing purely on quantitative measures, such as numbers of trials and disease areas, the CIRM should also focus on fundamental biological mechanisms that ultimately determine the success or failure of a specific disease intervention and on the careful design of translational studies to make them maximally informative even in the absence of any demonstrable clinical benefit.

To guide its ongoing implementation of the 2012 strategic plan, CIRM proposes to create a Clinical Advisory Panel and Industry Advisory Board. Although the committee supports CIRM's intent to establish advisory boards, it recommends that one Scientific Advisory Board be established. Striking the proper balance in research across the portfolio of basic, translational, and clinical studies will require that CIRM solicit broad input in executing its strategic plan. The committee believes the proposed Scientific Advisory Board could serve an invaluable role in this process.

> ***Recommendation 4-1. Establish a Scientific Advisory Board.*** **CIRM should establish a single Scientific Advisory Board comprising individuals with expertise in the scientific, clinical, ethical, industry, and regulatory aspects of stem cell biology and cell-based therapies. A single Scientific Advisory Board, as opposed to multiple advisory boards as proposed in the 2012 strategic plan, would provide cohesive, longitudinal, and integrated advice to the president regarding strategic priorities, which is lacking in the current CIRM organizational structure. The majority of the members of the Scientific Advisory Board should be external to California, appointed by and reporting to the CIRM president. Such an external board would be invaluable in vetting ideas for new RFAs, suggesting RFAs that otherwise would not have been considered, and helping CIRM maintain an appropriate balance in its research portfolio. Input from this board would help CIRM make fundamental decisions about dealing with challenges that cut across particular diseases, decide which discoveries should progress toward the**

clinic, and determine how best to engage industry partners in developing new therapies. The board's reports and the president's response to those reports should be delivered to the ICOC and discussed in sessions open to the public.

Omitted Areas of Emphasis

CIRM made strategic decisions that resulted in the omission of some important areas of emphasis during its initial phase, areas that fall squarely within the CIRM mandate. For example, there is a lack of RFAs addressing the novel ethical and regulatory aspects of clinical applications of potential stem cell therapies Most of CIRM's ethics and public policy spending has focused on intramural funding for public outreach and education and the internal development of technical, instrumental, and procedural policy frameworks for basic stem cell research.

Also lacking are proposals that would prepare academic institutions in California for collaboration with the private biotechnology or large pharmaceutical sectors. CIRM has engaged industry in a number of ways. However, CIRM's relatively small investment in industry projects (roughly 6 percent of its total budget) and the notable absence of industry representatives on most disease teams demonstrate the inadequate emphasis of CIRM's translational/development RFAs on what is needed to enable regulatory approval for cell-based therapies.

Recommendation 4-3. Fund Research and Training on Ethical and Regulatory Issues. **CIRM should sponsor training programs and workshops and offer new grant opportunities aimed specifically at identifying and addressing ethical and regulatory issues surrounding stem cell-based clinical trials research. CIRM should use the information resulting from these initiatives, together with current knowledge, to strengthen its ethical standards for CIRM-funded human subjects research based on sound empirical and theoretical grounds.**

Recommendation 4-4. Enhance Industry Representation in Key Aspects of CIRM Organization. **Industry representation on the ICOC, the Scientific Advisory Board, the Standards Working Group, and the Grants Working Group should be enhanced to leverage industry's expertise and resources in product development, manufacturing, and regulatory approval in support of the ultimate goal of bringing therapies to patients.**

Grant Review and Funding Process

The committee recognizes the magnitude of CIRM's successful effort to develop a grant management infrastructure within a remarkably short period of time following passage of Proposition 71. Given the complexity of this endeavor and the legislated limitation on staff size (initially no greater than 50 full-time equivalents), the overall success of this grant management infrastructure is impressive.

At the same time, CIRM's credibility requires that the grant review process be expert, transparent, and fair. The committee has considerable concern about the role of the ICOC with regard to management versus oversight of CIRM activities, particularly for the grant-making process. The ICOC may move applications from one tier to another before taking a final vote.

Examination of ICOC records indicates that the shifting of applications from one tier to another does occur, including some for major programs with large budgets. As of October 22, 2012, 62 extraordinary petitions were heard by the ICOC, of which 20 (32 percent) were successfully funded. The committee is troubled by the extraordinary petition mechanism and suggests that this practice be eliminated.

Given that membership of the ICOC includes individuals who have vested interests in which diseases are supported by grants and who represent institutions that stand to benefit greatly from grant-making decisions, it is not surprising that, even if no actions have been taken as a result of these interests, many in the community feel that irreconcilable conflicts exist. The committee believes these inherent and perceived conflicts diminish the credibility of the ICOC and therefore decrease its potential to be effective as a transparent, impartial body.

> ***Recommendation 4-2. Restructure the Grant Review and Funding Process.*** **CIRM should restructure the grant review and funding process to separate oversight and strategic planning from day-to-day operations. The ICOC should remain responsible for oversight and articulation of an overall strategic plan. However, grant management, funding recommendations, and grant administration should be the responsibility of the CIRM scientific staff, reporting to the president. This restructuring would help mitigate concerns related to conflicts of interest and would also put the review and funding process in the hands of those best equipped to make those decisions.**
>
> **The committee recommends several changes pertaining to the development and approval of RFAs, composition of the Grants Working Group, reordering of rankings by CIRM staff, notification of applicants, and process for making final decisions.[5]**

INTELLECTUAL PROPERTY POLICIES

Intellectual property is a policy tool for motivating investments in innovation. CIRM has devoted considerable attention to the development of its intellectual property policies, repeatedly drafting and revising them in response to wide-ranging feedback from various stakeholders.

The argument for intellectual property rights differs for inventions developed with public funds and those funded privately. When the public bears the cost and risk of the research and development that yields an invention, it is arguable whether the public should not have to pay again for the same invention through higher prices as a result of the exclusionary rights conferred by patents. Often, however, substantial further private investment is necessary after government funding ceases, especially when the recipient of the latter funding is a research institution that is not in the business of translating new scientific discoveries into commercial products.

The Bayh-Dole Act of 1980 has been particularly influential in setting the ground rules for patenting of inventions by universities. While the intellectual property policies of CIRM follow the broad contours of the Bayh-Dole regime, there are some differences.

Consistent with the approach of the Bayh-Dole Act,[6] Proposition 71 appears to assign a significant role to contracts as a mechanism for implementing CIRM's intellectual property

[5]See main body of the report for full text of this recommendation.
[6]35 U.S.C. § 202(c).

policies by binding grantees to its terms.[7] In practice, however, CIRM has instead used regulations to govern intellectual property for CIRM-funded research results. By their terms, these regulations bind not only CIRM grantees and loan recipients but also their collaborators and licensees, and even third parties who subsequently acquire rights from them.[8] Some flexibility is built into the regulations, but this flexibility also creates uncertainty as to how the regulations will be applied in the future. In addition, CIRM's intellectual property policies apply to a broader range of research outcomes than is covered by the Bayh-Dole Act.

Moreover, CIRM's intellectual property regulations, unlike Bayh-Dole, call for revenue sharing, with provisions designed to generate direct financial returns to the state treasury. Perhaps the most controversial aspect of CIRM's intellectual property provisions is the requirement that grantees and their exclusive licensees submit to CIRM "access plans" that will afford access to any drug resulting from CIRM-funded research to "Californians who have no other means to purchase the drug."[9] Federal law and other state-funded stem cell programs have no comparable provisions. Uncertainty about how the system will work could make industry cautious about licensing and investing in CIRM-funded inventions, especially if they have the option of turning to other sponsors that do not impose similar requirements.

CIRM holds "march-in rights" that allow it to enter into license agreements on behalf of a grantee or its exclusive licensee with respect to a CIRM-funded invention under three circumstances: (1) the grantee, collaborator, or exclusive licensee is failing to exercise reasonable efforts to achieve practical application of the invention; (2) the grantee, collaborator, or exclusive licensee has failed to submit or comply with an access plan; or (3) the grantee, collaborator, or exclusive licensee has unreasonably failed to use a CIRM-funded invention to alleviate a public health emergency declared by the governor.[10]

Overall, CIRM's intellectual property policies reflect a reasonable effort to balance conflicting interests of different constituencies, each with a legitimate stake in these policies. The actual impact of the policies may not be clear for many years, but the concerns of stakeholders are already apparent. Some of the more contested provisions attempt to address competing views by giving CIRM discretion over implementation, but this flexibility cuts two ways: it allows for adaptation to particular circumstances, but it also creates uncertainty and risk for potential developers of commercial products. CIRM might reduce some of the uncertainty arising from the unfamiliarity of its policies by modifying those policies to conform more closely to the more familiar Bayh-Dole approach. Departures from the Bayh-Dole approach may put CIRM-funded invention at a growing disadvantage in the future as funding from other states and the federal government yield competing candidates for commercial development that are available for licensing on more favorable terms.

---

[7]Proposition 71 divides responsibility for CIRM's intellectual property policies among the ICOC, which is assigned to "establish policies regarding intellectual property rights arising from research funded by the institute"; the chairperson, whose responsibilities include "to lead negotiations for intellectual property agreements, policies, and contract terms"; and the president, whose responsibilities include "to manage and execute all intellectual property agreements and any other contracts pertaining to the institute or research it funds." Codified at California Health and Safety Code § 125290.40.

[8]California Health and Safety Code § 125290.40(j); interview with Scott Tocher and Elona Baum, January 24, 2012.

[9]California Health and Safety Code § 125290.80; 17 California Code of Regulations § 100607.

[10]17 California Code of Regulations § 100610(b).

Recommendation 5-1. Incorporate Future Enforcement of Intellectual Property Policies in the Sustainability Platform. **As part of the plan maximizing the continued impact of CIRM's many achievements (see Recommendation 2-1), CIRM should propose regulations that specify who will have the power and authority to assert and enforce in the future rights retained by the state in CIRM-funded intellectual property. CIRM should seek to clarify which state agencies and actors will be responsible for the exercise of discretion currently allocated to CIRM and the ICOC over future determinations on issues regarding march-in rights, access plans, and revenue-sharing rights that might arise years after CIRM's initial funding period has passed. As it has done in the past, CIRM should provide ample opportunity for public comment on proposed changes to its intellectual property policies that pertain to transition planning.**

Recommendation 5-2. Consider Harmonizing Intellectual Property Policies with Policies of Bayh-Dole Act. **As other sources of funding for stem cell research become available and as the field of regenerative medicine advances from the laboratory to the clinic, the ICOC should reconsider whether its goal of developing cures would be better served by harmonizing CIRM's IP policies wherever possible with the more familiar policies of the Bayh-Dole Act.**

CONCLUSION

The creation of CIRM resulted from the initiative, imagination, and hard work of a broad group of stakeholders in California. In its initial years, CIRM has been highly effective in building an impressive research portfolio. The Institute's governance structure is, however, unusual in important respects that the committee believes could diminish its effectiveness going forward. While the profile of the ICOC was understandably designed to include representatives from a broad range of those most concerned and most knowledgeable regarding the future of regenerative medicine, its members were also the constituencies expected to benefit most directly and immediately from CIRM's grants. The committee believes that CIRM and the taxpayers of California would be better served going forward by a structure and processes whereby the role of the ICOC would remain focused on broad oversight and strategic planning rather than involvement in day-to-day management issues.

The committee has offered several recommendations for CIRM and the transition to its next stage of operations. As discussed above, the committee did not limit its recommendations to the boundaries imposed by Proposition 71. In the committee's view, some recommendations (2-1, 4-1, 4-3, and 5-1) can be carried out by CIRM without legislative action. For others (3-1, 3-2, 3-3, 4-2, 4-4, and 5-2), CIRM may be able to make modest moves in line with the recommendations, but may need to work with the state legislature in order to fully implement them. The committee is aware that its recommendations come at a time when CIRM may well be faced with pressing challenges resulting from the expiration of Proposition 71 funding and/or dynamic changes in the field of regenerative medicine. The committee hopes its recommendations will be considered not only now, but in the future as decisions are made.