



**LITTLE HOOVER COMMISSION
November 20, 2008**

**Written Testimony of CIRM Governing Board Chair Robert N. Klein
and President Alan Trounson**

On behalf of the Governing Board of the California Institute for Regenerative Medicine (“Board”) and the agency, the California Institute for Regenerative Medicine (“CIRM”), we are pleased to have the opportunity to testify before you today in connection with the Little Hoover Commission’s review of Proposition 71’s governance structure.

A Personal Preamble

Proposition 71 Was Written to Serve Patients

Proposition 71 was written from a patient’s perspective; its goal is to bring therapies to patients and benefit patient families in California and throughout the world. To provide a context for understanding Robert Klein’s motivation for writing Proposition 71, and to provide a framework for evaluating the purpose and effectiveness of the Board and agency structure, it is important to describe Robert Klein’s perspective and motivations as a patient advocate, and to understand the general organizing principle behind the design of the patient advocate, scientific and industry roles on the governing Board.

The Patient Advocate Perspective

Fundamentally, after my (Robert Klein’s) youngest son was diagnosed with Juvenile Diabetes I worked with the International Board of the Juvenile Diabetes Research Foundation to obtain supplemental National Institutes of Health funding for diabetes research. It soon became clear that the leadership of the National Institute of Diabetes and Digestive and Kidney Diseases believed that stem cell research – including embryonic stem cell research – appeared to be essential to curing diabetes. Other researchers have identified 70 other areas of chronic disease and injury for which stem cell research holds promise of major advances in therapy.

It was clear that the Bush administration's restrictions on embryonic stem cell would effectively prevent the federal government from advancing this essential research. California was the state best positioned with its biotech research capacity, in its non-profit and commercial sectors, to launch a substitute national program. California represents 50% of the nation's biotech research capacity and, if evaluated as a nation, it has more biotech research capacity than any other nation in the world.

The Disease Breakthrough Cannot Be Predicted

From the history of the National Institutes of Health, it was clear that for a new field of medical research, one cannot predict the disease area where a breakthrough will occur. Although Robert Klein's son has Juvenile Diabetes and his mother is dying with Alzheimer's and Alan Trounson's brother nearly died of AIDS before a new therapy could be introduced, both realize that these may not be the diseases that are mitigated or cured, first, by stem cell research. For their families, and for every family, our best opportunity to successfully discover therapies is to focus our resources into objective, scientific peer reviewed, medical research that seeks a breakthrough that will guide the entire field towards successful therapy solutions. Blindly focusing resources behind a specific disease target, without competitive peer review comparing the funding decision with every other disease, might set back finding a solution for one's own family by a decade or more.

The History of Recombinant DNA

The history of Recombinant DNA is instructive. Like embryonic stem cell research, the opponents to this vital potential field of medical research protested the ability to do the research and claimed that there would never be any human benefit for our children or our children's children. In 1977, the protesters shut down Harvard's labs in Cambridge, Massachusetts. To protect the research, patient advocates joined with physicians, scientists, and business leaders to plead with Congress throughout 1977 not to shut down this research, but rather to broadly extend and increase the funding for Recombinant DNA research across the entire field of medical inquiry. In the spring of 1978, the first human product to treat disease was announced by the University of California at San Francisco and the City of Hope. The product, artificial human insulin, keeps Robert Klein's son alive every day. The discovery unleashed a medical revolution that, in the next decade, led to 100 critical drugs, and in the most recent decade, gave us the knowledge that helped us decode the human genome. This history is our legacy; the lesson instructs us for the future.

The Patient Advocate Perspective – In Summary

Whether viewed, therefore, from the patient advocate perspective, or from the perspective of the physician or scientist, all of our interests in the stem cell field have a common, controlling drive: find the breakthrough or breakthroughs that will inform and guide the entire field in its search for therapies across 70 different areas of chronic disease and injury. No preconceived or biased focus will serve anyone's interests, because the best science must be followed to search out quickly, safely, and accountably those rare but vital insights that – like artificial human insulin – will give birth to a broad array of therapies which will reduce human suffering. We must – particularly in the early years – sustain a broad and diverse portfolio, if we are to prevail.

Officers of the State: The Controlling Principle

In the pursuit of medical discovery and insights, the patient advocates, the medical school deans, the scientists, and industry veterans with therapeutic development experience are all united in our role as “officers of the state of California.”

Each of us, as a Board member, understands, that the disease and/or medical tragedy originally motivating us has the best chance of a cure or therapy, if all of our efforts are thrust in common behind an objectively determined, broad-based portfolio of medical research. It is this goal and objective that controls the design of the Board and the inclusion of each of the five contributing resource groups that represent treasuries of knowledge and experience essential to guiding the mission.*

Their role also assumes a continuing portfolio examination to sustain a breadth of inquiry covering particularly promising research proposals with the potential to examine disease field specific problems that are important to maintain minimum, critical portfolio balance. All programmatic inquiries from any member must meet the standard of proof on objective scientific quality with the full voting board.

* Resource groups are: 1) patient advocates; 2) medical schools; 3) research hospitals; 4) academic and independent research institutions; and 5) industry veterans with proven therapy development experience.

Proposition 71 Structure

In order to properly address the specific issues identified by the Commission's staff, we would like to describe briefly the structure of CIRM and the actions we have taken since CIRM's inception in 2005 to ensure transparency and accountability.

California voters overwhelmingly approved Proposition 71, the California Stem Cell Research and Cures Act, in November 2004, with 59 percent voting in favor of filling a gap in federal funding for human embryonic stem cell research specifically, and stem cell research generally, in order to develop life-saving regenerative medicine therapies and cures. (Text of Prop. 71, App. 1.) The measure was also designed to engage the biotechnology industry in California to speed the development and delivery of therapies to Californians who suffer from chronic disease and injury while ensuring that Californians have an opportunity to benefit from their investment.

a. The Governing Board

CIRM is governed by a 29-member Board comprised of Californians with expertise in: (1) managing large research grants and complex institutions and conducting cutting edge medical research; (2) understanding the critical path for the development of successful experimental medical treatments and directing the approval process through the Food and Drug Administration and other regulatory bodies and ethical committees; and (3) advocating on behalf of Californians who suffer from a variety of chronic diseases and injuries, including participating in the review of applications for medical research grants. Among other responsibilities, the Board is charged with: (1) adopting scientific, medical, ethical, and intellectual property policies; (2) making final decisions on all grant awards; and (3) overseeing the operations of CIRM. (Board Bylaws, App. 2.)

b. The Grants, Standards, and Facilities Working Groups

To assist the Board in carrying out its duties, Proposition 71 established three expert advisory groups: (1) the Scientific and Medical Research Funding Working Group ("Grants Working Group"), which makes recommendations regarding research standards and awards; (2) the Scientific and Medical Research Facilities Working Group ("Facilities Working Group"), which makes recommendations regarding facilities standards and awards; and (3) the Scientific and Medical Accountability Standards Working Group ("Standards Working Group"), which makes recommendations regarding scientific, medical, and ethical standards. These working groups, which are comprised of experts in their respective fields and patient advocate members of the Board, provide critical information to the Board to inform its decisions regarding standards and grant and loan awards. (See Grants Working Group Bylaws, App. 3; Standards Working Group Bylaws, App. 4; and Facilities Working Group Bylaws, App. 5.)

c. The Institute

CIRM, led by the President, provides scientific expertise and leadership, implements the policies and programs adopted by the Board, and manages the standards and grant-making processes, including overseeing grant and loan recipients. (CIRM Internal Governance Policy and Organizational Chart, App. 6.) As a result of the highly specialized and urgent nature of CIRM's mission, substantial differences exist between CIRM and other state agencies.

For example, CIRM is limited to no more than 50 employees, while comparable funding organizations often have staffs that are more than twice as large. As a result, CIRM staff perform a variety of specialized functions that would ordinarily be handled by a much larger number of employees at other agencies and that are unique to running an Institute dedicated to scientific discovery and the delivery of therapies. Because of their need for specialized expertise and flexibility, CIRM staff are exempt from civil service and are compensated based on the salary levels for comparable positions at California medical schools and research institutions. The compensation of CIRM employees reflects not only the heavy demands placed upon them, but also the limitations on employment with CIRM; employees serve at the will of the President and CIRM's anticipated life-span is 10-14 years, which rules out the possibility of the long-term career track available for many civil service positions.

In addition, CIRM enjoys a continuous appropriation to ensure that it has sufficient resources to fulfill its mission. CIRM is authorized to spend no more in taxpayer funds than six percent (6%) of the three billion dollars (\$3,000,000,000) in bonds approved by the voters for administrative purposes. The cap on administrative spending is significantly more restrictive than the administrative budgets of most comparable funding organizations, and for that reason, CIRM has carefully husbanded its resources to ensure that the agency has sufficient funding for administration and grant oversight to last for the duration of the program.

All of CIRM's operations are subject to three levels of oversight, which include the legislative and executive branches of government and also an annual review by the Citizens' Financial Accountability Oversight Committee, which is chaired by the Controller. This Committee is tasked with reviewing CIRM's annual, independent audit and the agency's financial practices and performance. (*See* <http://www.sco.ca.gov/eo/cfaoc/>.) CIRM is therefore subject to a unique review annually.

d. Application of State Law

Notwithstanding these differences, CIRM must comply with many of the same state rules and regulations that apply to other state agencies. For example, CIRM employees and Board members must comply with state conflict of interest and financial disclosure laws. The Board is subject to the Bagley-Keene Open Meeting Act and the Public Records Act, and it must adopt regulations pursuant to the Administrative Procedure Act. Indeed, in its short history, the Board has held more than 110 public Board and subcommittee meetings in addition to dozens of public advisory group meetings, offering an unprecedented opportunity for public participation.

Because of CIRM's specialized mission, Proposition 71 established several important exceptions to these rules. For example, in order to accommodate a Board comprised in part of individuals with expertise in managing large research grants and institutions, Proposition 71 created an exception to Government Code section 1090, which prohibits a Board from voting on a contract in which one of its members has an interest. The exception in Proposition 71, which was modeled on exceptions for members of county Children and Families Commissions and local workforce investment boards (*see* Gov. Code, §§ 1091.2, 1091.3), permits the Board to vote on a grant award to an institution in which a member has an interest as long as the member refrains from participating in the decision in any way.

Likewise, Proposition 71 requires the Board to adopt conflict of interest rules modeled on the conflict rules of the National Institutes of Health (NIH) for members of CIRM's three working groups. (Working Group Conflict of Interest Regs., App. 7.) Because the working groups are advisory only, and decisions are made by the Board, the members of the working groups are not

subject to state conflict of interest laws; however, in order to ensure accountability and to prevent conflicts of interest, Proposition 71 mandated that the Board adopt specialized conflict of interest rules for members of the working groups.¹

Additionally, Proposition 71 created exceptions from open meeting laws and the Public Records Act for confidential or proprietary scientific data and information. It expressly authorized the Working Groups to meet in closed session to protect the confidentiality of peer review, which is standard practice of all funding agencies, including NIH, that depend on peer review to ensure scientific quality. Notwithstanding these express provisions, the Board has adopted policies, in a formal, documented collaboration with the Legislature, to ensure appropriate transparency and public participation in all working group activities, again, with the limited exception of confidential scientific peer review.

Efforts to Ensure Transparency and Accountability

a. Conflict of Interest Policies

From its inception, the Board and the agency have taken significant steps to ensure transparency and accountability. For example, in addition to a conflict of interest code and a statement of incompatible activities, which are required by state law, the Board has adopted conflict of interest policies for the Board and for CIRM staff that go beyond the requirements of state law. The Board's conflict of interest policy prohibits members of the Board from receiving any financial benefit through a CIRM grant or loan, and the policy for employees prohibits employees from holding an interest in a company that devotes more than five percent of its research budget to stem cell research. (Board Conflict of Interest Policy, App. 8; CIRM Conflict of Interest Policy, App. 9.)

b. Policy Enhancements

In 2005, as CIRM was being established, the Board's leadership worked with legislative leaders, including the President *Pro Tem* of the Senate and three senior members of the Senate, to devise policies that ensure public participation and accountability in the grant review process. Thus, CIRM strengthened the conflict of interest policies for working group members and required disclosure of the members' personal, professional and financial interests. These policies go well beyond state conflict of interest laws, which are limited to financial conflicts, and exceed the standards set by the NIH. The Board also agreed to make available for audit the working group members' conflict of interest forms to ensure that CIRM's processes were strong and effective. In addition, the Board agreed to open the meetings of CIRM's working groups to the public, with the exception of sessions involving confidential peer review. The Board also agreed that the records of the working groups would be subject to the Public Records Act, with the limited exceptions of scientific and medical applications for grants and loans and their peer-reviewed evaluations. To ensure that members of the public have access to the information in all funded applications, the Board requires that every funding recommendation include a public summary of

¹ Under California law, members of an advisory group are not subject to state conflict of interest laws unless the body or Board to which they report routinely adopts their recommendations, without significant changes, over an extended period of time. (Cal. Code Regs., tit. 2, § 18701(a)(1)(A)(iii).) As is evident from a review of Board meeting transcripts, the Board thoroughly reviews and frequently makes changes in the recommendations of the working groups.

the proposal, the evaluation, and the potential benefit to the State of California. Finally, the Board agreed not to amend specific policies adopted in collaboration with the Legislature without a supermajority vote (70% of a quorum to amend policies) and without first providing notice to the Legislature.

Proposition 71 Has Been Subject to Exhaustive Litigation, Reviews, and Audit

a. Litigation

The Board was formed in December of 2004, and the agency has only been in existence since January 2005, but in that time it has been subject to an extraordinary level of judicial, legislative, and executive branch oversight. In February 2005, opponents of Proposition 71 filed original writ petitions in the California Supreme Court to challenge the constitutionality of Proposition 71. The California Supreme Court declined to hear the petitions, but the opponents re-filed their claims in Superior Court and expanded the scope of their action to encompass allegations regarding CIRM's performance and compliance with the law. The cases involved extensive discovery, including hundreds of interrogatories and requests for admission, the production of tens of thousands of pages of documents, and more than 25 depositions. In February 2006, the cases proceeded to trial before Alameda County Superior Court Judge Bonnie Lewman Sabraw who, after considering the documentary evidence and trial testimony, rejected each and every claim advanced by the plaintiffs, including claims that challenged CIRM's compliance with California law.

The Court of Appeal agreed with the trial court, rejecting each of the plaintiffs' claims, including their conflict of interest allegations:

In this case, by approving Proposition 71 the voters have determined that the advantages of permitting particularly knowledgeable persons to decide which research projects to fund outweigh any concerns that these decisions may be influenced by the personal or professional interests of those members, so long as the members do not participate in any decision to award grants to themselves or their employer.

(California Family Bioethics Council v. California Institute for Regenerative Medicine (2007) 147 Cal.App.4th 1319, 1368, App. 10.)

The Court of Appeal concluded:

After careful consideration of all of appellants' legal objections, we have no hesitation in concluding, in the exercise of "our solemn duty to jealously guard the precious initiative power" (*CART, supra*, 109 Cal.App.4th at p. 808), that Proposition 71 suffers from no constitutional or other legal infirmity. Accordingly, we shall affirm the well-reasoned decision of the trial court upholding the validity of the initiative.

(Id. at 1373, App. 10.)

The California Supreme Court declined to review the Court of Appeal's well-reasoned and thorough opinion.

b. Bureau of State Audits

CIRM has also been subject to an extensive performance review conducted by the Bureau of State Audits ("BSA"). BSA staff spent hundreds of hours reviewing CIRM's policies and records and meeting with CIRM staff. BSA staff examined CIRM's strategic plan and policies governing grants management, conflicts of interest, travel, compensation, contracting, and intellectual property. CIRM worked closely with BSA to address each of the issues raised in the review and adopted many of BSA's recommendations before the report was released. (BSA Audit, App. 11.) As CIRM's one-year response to the audit demonstrates, CIRM has now implemented each of the recommendations made by the BSA, with one exception.² (CIRM One-Year Response, App. 12.)

c. Controller's Review

More recently, the Controller conducted a thorough review of CIRM's conflict of interest policies, grant administration, administrative expenses, and expenditures. Significantly, the Controller found that CIRM has "extensive conflict of interest policies that are modeled after and, in some cases, go beyond the National Institute of Health requirements." (SCO Audit, App. 13.) The Controller also found that CIRM's grant administration policies were based on "best practices." Finally, the Controller confirmed that CIRM's expenditures were in compliance with Proposition 71 and CIRM's policies and procedures.

d. Citizens' Financial Accountability Oversight Committee

These reviews occurred in addition to an annual independent financial audit of CIRM and the annual review conducted by the Citizens' Financial Accountability Oversight Committee. The CFAOC has conducted three oversight hearings, supported by reports from the outside auditors and documentation on CIRM's programs, policies, and practices. (See <http://www.sco.ca.gov/eo/cfaoc/>.)

² CIRM declined to seek an opinion from the Attorney General regarding the application of California's conflict of interest laws to the members of the working groups based on subsequent events, including the decision of the Court of Appeal affirming the trial court's decision that the Working Groups are advisory only. (See *California Family Bioethics Council v. California Institute for Regenerative Medicine* (2007, 147 Cal.App.4th 1319, 1364 ["The evidence at trial established that while the ICOC has generally followed the recommendations of the working groups, it has often made changes to the recommendations before awarding grants."], App. 10.)

e. **Legislative and Executive Branch Oversight**

Members of the Board and CIRM staff have testified before numerous legislative committees and have worked closely with the Governor's Office, the Controller's Office, the Treasurer's Office, and the California Stem Cell Research and Cures Finance Committee, which is responsible for approving the issuance of bonds to fund CIRM's programs. For example, working with the Treasurer's Office, CIRM issued bond anticipation notes to fund training grants during the time litigation prevented CIRM from issuing bonds. In a testament to their support for CIRM, California philanthropists purchased \$45 million of these notes with the knowledge that the notes would convert to gifts if Proposition 71 were to be invalidated by the courts. Similarly, CIRM worked with the Governor's Office and the Department of Finance to secure a \$150 million loan from the General Fund to ensure CIRM's ability to fund stem cell research prior to the resolution of the litigation. Thus, CIRM is keenly aware of the importance of maintaining strong relationships with the legislative and executive branches in order to carry out its mission.

In short, CIRM has been subject to a virtually unprecedented level of scrutiny over the course of its brief existence. Although CIRM has benefitted from these reviews, they have imposed a significant strain on CIRM's resources and diverted staff attention from the mission of the agency. We trust that the prior reviews, as well as the materials included in the appendix we have provided, will be useful to you as you embark on your examination of CIRM's governance structure.

ISSUES OF PARTICULAR INTEREST

You have asked us to address the following specific issues:

Question 1

The appropriateness of the CIRM and ICOC organizational structure, membership and roles both to current conditions and if California's stem cell program continues beyond 10 years.

Proposition 71 was designed to establish a mission-driven agency that is insulated from the day-to-day ebb and flow of politics. It is essential that the Board and the agency have a stable environment to objectively evaluate scientific and medical innovations and discoveries, while maintaining a strategic focus and a balanced, thoughtful strategic plan that is not merely reactive to each new scientific discovery, or **apparent discovery**. Five years ago, one group of scientists suggested that adult stem cells could be transdifferentiated into every type of tissue in the body; this research later proved to be incorrect and flawed. (International Society for Stem Cell Research Statement, App. 21.) Years would have been lost if medical science had been diverted to follow this singular approach rather than a broad and thoughtful research strategy – pursuing all types of stem cells. This history illustrates the importance of a design for scientific objectivity and stability. Insulation of science from political issues is designed, into the governance structure of the agency, is critical to ensure long-term and stable funding for a young, controversial, and fast-moving area of medical research. Indeed, Proposition 71 arose out of Californians' frustration with the unwillingness of the federal government to provide timely and sufficient funding for human embryonic stem cell research. This lack of funding starved the nascent field of human embryonic stem cell research and deterred young investigators from entering the field. Proposition 71 was intended to fill the gap left by federal restrictions and also to provide a stable funding stream for investigators in California.

Proposition 71 was also designed to fund the best scientific proposals by imposing high scientific, medical, and ethical standards, by requiring vigorous peer review by experts from outside the state, and by placing the final decisions for funding in the hands of the Board, a group of experts with complementary skills.

a. The Governing Board

Consistent with these goals. Proposition 71 established a 29-member independent oversight board. To prevent a single elected official from exercising undue influence, the appointments to the Board are divided among four constitutional officers (the Governor, the Lieutenant Governor, the Controller, and the Treasurer), each of whom appoints five members of the Board and each of whom has the right to nominate candidates for Chair and Vice Chair. In addition, the President *Pro Tem* of the Senate and the Speaker of the Assembly each appoint one member. The Chancellors of the University of California at San Francisco, Davis, San Diego, Los Angeles, and Irvine each appoint an executive officer from his or her campus. (See Board Bylaws, Exh. A, App. 2.) A majority of a quorum of the Board, defined as 65 percent of eligible members, is required to take action on an issue. Although this threshold presents a challenge, it also ensures full participation and a diversity of perspectives.³

³ To facilitate participation, the Governance Subcommittee of the Board recently recommended a policy to permit a limited number of members to participate by teleconference in regular Board meetings.

The members of the Board must be appointed from among Californians with expertise in managing and conducting research, commercializing medical therapies, and advocating for Californians who suffer from chronic disease and injury. As the Court of Appeal recognized, “[t]here are stringent qualifications for appointment designed to ensure that all members possess appropriate experience and expertise and the persons knowledgeable in the various disease groups that may benefit from the research are represented.” (*California Family Bioethics Council v. California Institute for Regenerative Medicine* (2007) 147 Cal.App.4th 1319, 1332-1333.)

To provide stability to the Board and CIRM, the members serve fixed terms of six or eight years. Aside from the Chair and Vice-Chair of the Board, who are treated as employees for the purposes of receiving compensation, the members of the Board volunteer their time, with some electing to receive only a modest *per diem* of approximately \$100 per day. A sizeable number of Board members have participated in more than 100 meetings since the voters’ approval of Proposition 71, many without compensation.

b. Board Subcommittees

Subcommittees permit the Board to use members’ time and expertise efficiently, and the Board has also created several to assist the Board in its work: (1) the Governance Subcommittee, (2) the Legislative Subcommittee, (3) the Intellectual Property Task Force, (4) the Finance Subcommittee, and (5) the Loan Task Force. These subcommittees have conducted numerous public meetings to focus attention on important subjects, and each makes recommendations to the full Board in its particular area of expertise. For example, the Intellectual Property Task Force has conducted 18 public meetings and hearings to explore complex issues relating to intellectual property generated by CIRM-funded research. Based on the recommendations of the IP Task Force, the Board has adopted regulations governing both non-profit and for-profit grantees. These regulations are now a model for other states that are investing public funds in scientific and medical research.

c. CIRM

The structure of CIRM also reflects the goals of Proposition 71. For example, the agency’s continuous appropriation prevents the funds designated for research from being diverted to other state programs. Research projects require stable funding for a three-to-five-year period – at a minimum -- in order: to retain highly qualified scientists; to develop new academic departments and therapeutic development companies; to develop and refine cutting-edge new technologies; and to ensure that research results are reproducible.

If the Board is to recruit highly skilled employees to fill the agency’s demanding positions, it must have the authority to compensate CIRM employees based on the compensation paid to employees in similar positions at other California research institutions. It also needs to be exempt from civil service employment restrictions so as to terminate those employees who cannot meet the rigorous demands required of an agency funding cutting-edge, ever-changing scientific research.

d. The Grants, Standards, and Facilities Working Groups

The establishment of three advisory working groups ensures that CIRM benefits from the expertise and advice of the leading scientists, clinicians, and ethicists in the United States and the world. The Grants Working Group, comprised of 15 scientists and clinicians drawn from outside

California, seven Board patient-advocate members, and the Chair of the Board, engages in a rigorous peer review of each application. To ensure that the Grants Working Group has the expertise required to review a wide variety of proposals, from basic research to clinical research, CIRM has recruited a variety of experts as alternate and specialist members of the Grants Working Group. For example, more than 60 alternate members are available to assure appropriate expertise in any grant cycle. Likewise, the Standards Working Group and the Facilities Working Groups are comprised of experts in their respective fields. The advice of the Working Groups is invaluable, but as the Court of Appeal recognized, the Board makes the ultimate decisions on research standards and grant awards.

e. CIRM's Success

This structure has served CIRM well. With the advice of the Working Groups and the scientific guidance and leadership of CIRM staff, the Board has: (1) approved scientific, medical, and ethical policies that have become widely recognized as the gold standard; (2) awarded \$614 million through 229 grants to 27 different institutions across California; and (3) awarded \$321 million of that total in facilities and research equipment grants, matched by more than \$880 million in donor and institutional matching funds, to create new research facilities and shared labs throughout the state. CIRM has accomplished these goals notwithstanding significant obstacles, including litigation that froze bond funding until 2007 and the challenges inherent in establishing the first-ever major state medical research funding agency in the United States, with policies and procedures to ensure transparency, accountability, and excellence. Given the rapidly evolving nature of the field of stem cell research and the financial challenges we face, we believe this structure will continue to serve California well as we pursue CIRM's mission.

Question 2

CIRM's adherence to conflict of interest and open-government procedures.

CIRM is committed to remaining transparent and to abiding by the highest ethical standards.

a. Conflicts of Interest

As discussed above, the Board has adopted rigorous conflict of interest standards for Board members (App. 8), for CIRM staff (App. 9), and for members of the working groups (App. 7). CIRM policies exceed the requirements of state law. For example, the scientific members of the Grants Working Group all come from outside California to ensure they cannot personally benefit from CIRM funding, which is restricted to research conducted in the state. In addition, conflict-of-interest policies for working group members cover financial conflicts of interest as well as professional and personal conflicts of interest. (Working Group Conflict of Interest Regulations, App. 7.) State law, by contrast, is limited to financial conflicts of interest.

The Board and CIRM take extraordinary steps to ensure that conflict of interest policies are enforced, as outlined in CIRM's RFA Review Task List and Timeline (App. 14). For example, to ensure the grant-making process is free of conflicts of interest, members of the Grants Working Group are required to file annual disclosure forms identifying their financial interests. In addition, Working Group members certify, prior to the grant review, those applicant institutions and investigators in which they have a financial, professional, or personal conflict of interest. When an application in which a member has an interest is discussed in a working group session, the member leaves the room. At the end of the session, each member certifies, under penalty of perjury, that he/she has not participated in the review of an application in which the member has a financial, professional, or personal conflict of interest. CIRM staff are also screened for conflicts prior to grant review.

The Board also has an extensive process to avoid conflicts. In advance of each meeting at which the Board will be considering applications for funding, CIRM staff provides each Board member with a list of all applicant institutions, principal investigators, and collaborating organizations and investigators that would receive funding pursuant to the application. Along with this list, counsel provides a memorandum to the members describing the Board's conflict of interest rules and state conflict of interest laws and asking members to identify those institutions and investigators in which the member has a financial interest. Board members then submit to CIRM staff certified list identifying their conflicts prior to the scheduled meeting. Staff also review each member's statement of economic interests (Form 700) to screen for additional conflicts that a member may have overlooked. With this information in hand, staff compiles: (1) a master list identifying by application those members who have financial interest in the application, and (2) a list for each member identifying the member's conflicts by application number. Each member receives a copy of his/her conflict list prior to the meeting.

At the Board meeting, the Board considers the rankings and recommendations of the Grants Working Group in three categories: (1) recommended for funding (Tier 1); (2) recommended for funding if funds are available (Tier 2); and (3) not recommended for funding (Tier 3). The Board can and has funded and denied the funding of grants from all three categories; by utilizing the combined expertise of all 29 members, the Board – at times – perceives opportunities or obstacles to specific grants, that the members of the peer review committee may not have fully appreciated. Generally, the Board first considers motions to move individual applications from one tier to another (e.g., from Tier 3 to Tier 1). Before a particular application is discussed, the Chair of the Board asks counsel to screen for members who are ineligible to participate in the discussion. For

the record, counsel identifies those members who have a financial interest in the application and reminds them that they may not participate in the Board's discussion of the application or the Board's vote. Staff then monitor the discussion and the vote to ensure that disqualified Board members abstain, and when a roll call vote is taken on a specific application, conflicted Board members are not called.

Nothing, including these stringent rules and procedures can completely eliminate the possibility of an unintended conflict of interest, but they represent CIRM's best efforts to ensure that decisions are made solely on the merits of an application and to eliminate even the appearance of impropriety.

b. Open Government Procedures

The Board complies with the Bagley-Keene Open Meeting Act and the Public Records Act. Indeed, for a young agency, CIRM has offered a virtually unprecedented opportunity for public participation in its processes. The Board, for example, has met more than 40 times since it first convened in December 2004. At each meeting, members of the public are invited to comment on every action item on the agenda, and at the end of the meeting the Chair invites general public comment.

CIRM has also involved the public in the conduct of its business. For example, in developing the agency's first scientific strategic plan, CIRM held six public hearings and, prior to adopting each of its regulations, conducted public hearings over and beyond the opportunities for public comment provided at Board and subcommittee meetings where the proposed regulations were discussed. CIRM has also invited the public to participate in meetings on important scientific and ethical subjects, such as oocyte donation.

The Board's subcommittees also offer an important opportunity for the public to participate in the development of CIRM's policies on matters ranging from intellectual property to CIRM's loan program. Indeed, one consumer advocate referred to the Intellectual Property Task Force's work as "an excellent example of how public policy should work." (John Simpson, Consumer Watchdog, December 12, 2007 Board Meeting [<http://www.cirm.ca.gov/transcripts/pdf/2007/12-12-07.pdf>].)

The public also has an opportunity to participate in the meetings of CIRM's Working Groups. Although the Working Groups are not bound by the Bagley-Keene Open Meeting Act, the Board made a policy decision to open these meetings to the public, with the exception of scientific peer review. As the National Academy of Sciences has recognized,

Scientific peer review has long been a feature of decision making at key government funding agencies, such as the National Science Foundation and the National Institutes of Health, as well as at other government agencies and private foundations that support research. In virtually all cases, including the leading federal agencies just mentioned, evaluations of the strengths and weaknesses of specific proposals are carried out in sessions that are closed to the public.

(January 2, 2008 Letter from Ralph J. Cicerone, Ph.D., President, National Academy of Sciences, and Harvey

V. Fineberg, M.D., PH.D., President, Institute of
Medicine, App. 15.)

With the exception of scientific peer review, the Working Groups have conducted more than 40 public meetings involving matters ranging from the criteria for the evaluation and award of grants to the standards for informed consent for embryo donors. Indeed, all of the meetings of the Standards Working Group and the Facilities Working Group have been conducted in public.

CIRM has also complied with the Public Records Act, responding to dozens of Public Records Act requests. In addition, CIRM responded to two Administrative Procedure Act petitions. Most recently, the Board approved a petition requesting that the agency adopt a regulation defining the term "California Supplier." After several public hearings and meetings, the Board adopted a policy that was widely supported by consumer groups, grant recipients, and the commercial sector. CIRM also maintains a robust website that offers members of the public a wealth of materials relating to CIRM's grant awards, policies, and upcoming programs and meetings.

Question 3

CIRM's performance in distributing grants in a manner that will achieve the greatest likelihood of medical breakthroughs.

a. CIRM's Grant Awards

Consistent with its 2006 Scientific Strategic Plan, discussed below, CIRM has, to date, committed more than \$614 million to 27 California institutions, including:

- \$37.5 million to train 169 pre-doctoral, post-doctoral and clinical fellows at 16 non-profit and academic research institutions.
- \$46 million to fund 73 Leon J. Thal SEED Grants to bring new ideas and new investigators into the field of human embryonic stem cell (hESC) research.
- \$72 million for 28 Comprehensive Research Grants to support mature, ongoing studies on human embryonic stem cells (hESCs) by scientists with a record of accomplishment in the field.
- \$50 million for 17 Shared Research Laboratory Grants (including 6 Stem Cell Techniques Courses) to fund for the design and renovation of laboratory space, equipment for the new research facilities, and operating expenses for three years.
- \$54 million for 22 New Faculty Awards to encourage and support the next generation clinical and scientific leaders in stem cell research.
- \$271 million to 12 institutions for the construction stem cell research facilities..
- \$1 million to fund the planning stages of an innovative model for disease team research.
- \$59 million for 23 New Faculty II Awards to encourage and support the next generation of clinical and scientific leaders in stem cell research. (CIRM Grant Awards Chart, App. 16.)

In the course of its \$614 million of grant approvals, the Board and the agency have obtained approximately \$900 million in matching fund commitments from donors and institutions (Major Facilities Chart, App._22) and contributions to the agency, for its mission, that exceed \$23 million in value.

b. Proposition 71's Leadership Role

Globally, California's performance under Proposition 71 has earned the state agency a world-class leadership position, with California serving as a full member of the International Stem Cell Forum, along with 19 member nations. Within the United States, California's grant approvals in 2007 alone are approximately seven times the funding by the National Institutes of Health for embryonic stem cell research. CIRM funding has proved a strong magnet for researchers from across the country. Indeed, when a Georgia Tech researcher asked scientists in the U.S. to rank the top states in their discipline, nearly 90 percent of stem cell scientists ranked California in the top three, compared with about half the non-stem cell scientists. A similar percent of stem cell scientists were aware of California's commitment to fund stem cell research on a large scale. As

a result of CIRM funding, twenty-four national and international leaders in stem cell research have moved to California from 10 U.S. universities and six foreign countries.

CIRM's research funding has contributed to significant developments in the field and has been credited in more than 60 research journal articles, most in high-impact publications.

CIRM expects that the research it has funded will lead to clinical trials. Indeed, Catriona Jamieson (UC San Diego), a CIRM grantee, identified a novel drug therapy for *polycythemia vera* (a red blood cell disease that can lead to strokes and leukemia) through her stem cell assay research. This work resulted in a clinical trial less than two years after the assays were initiated, showing the importance of stem cell-based methodologies to developing clinical therapies in complex diseases.

As discussed below, CIRM intends to continue building on its initial successes by stimulating the pipeline for cures through funding for basic research, preclinical development, and clinical research.

Question 4**The agency's appeals process for projects that were not awarded funding.**

Under CIRM's Grant Administration Policy, applicants may file a formal appeal of a recommendation made by the Grants Working Group if there is credible evidence of a conflict of interest. If the President determines that the appeal is meritorious, the application will be subject to a new review. Copies of the current appeals process and proposed amendments to the process are included in the appendix at tabs 17 and 18.

In addition, the Board recently adopted a policy governing extraordinary petitions for Board review of an application. (App. 19.) Pursuant to this policy, an applicant may submit a written petition for extraordinary consideration by the Board at least five business days before the meeting at which the Board is scheduled to consider the application. The petition, which must set forth the basis for the request, is then distributed to Board members and the public. The policy also requires CIRM staff to review the petition and to make a recommendation to the Board, upon the request of a member of the Board. Thus, the policy provides a formal process for applicants to identify what they perceive are errors in the review of their applications and to bring them to the attention of the Board. Applicants, of course, also have the opportunity to participate in Board meetings and to make public comments to the Board.

Question 5

The agency's ability to adapt to changing political and scientific environments.

As discussed above, Proposition 71 was designed to create a mission-driven funding agency that is protected from shifting political winds. CIRM is aware, however, that changes in the political environment can offer new opportunities for collaboration. Indeed, CIRM's leaders have met with the leaders of the NIH and the National Academies of Sciences as well as political leaders in Washington, D.C., including Speaker of the House Nancy Pelosi and Harry Reid, Senate Majority Leader, who have both made stem cell research funding one of their priorities. CIRM will pursue collaborations with the NIH that may accelerate research capacity in a wide spectrum of areas, including basic cell biology, molecular biology, translational medicine, and clinical trials. The agency is also exploring joint research and clinical trial programs with international agencies representing regional medical interests in Europe, Canada, Australia, the Middle East, and Asia. In these discussions we seek a wide array of unique expertise, medical programs, and specific patient groups, with the intent of improving the health of California patients, and those who suffer in common from the same diseases worldwide.

CIRM is keenly aware of the need for the agency to be flexible and responsive to changes in the scientific environment. CIRM's development of a "living" scientific strategic plan illustrates its approach to funding in this fast-evolving area of medical research.

a. The 2006 Strategic Plan

With the background benefit of the National Academies of Science's workshop in December 2004 and a number of public meetings held by the agency and its Board, the scientific staff of the agency led the effort to develop the CIRM's initial scientific strategic plan in December, 2006. (App. 20.) The 2006 strategic plan resulted from months of hard work and public input. Planning began at a scientific meeting held on October 1-2, 2005, "Stem Cell Research: Charting New Directions for California.", in which an international group of stem cell scientists advised CIRM on developing scientific priorities. Data-gathering continued through: interviews with over 70 leading scientists, clinicians, patient advocates and others; three scientific conferences on specific topics; and two public hearings focused on patients and diversity. In addition, the Board devoted two meetings to develop a mission statement, values and strategic principles for the plan.

The 2006 strategic plan defined as the agency's goals "to address the continuum of stem cell research . . . to support not only basic, translational, and clinical research, but also to ensure a secure infrastructure that will serve as a foundation for future advances." (CIRM 2006 Strategic Plan, App. 20.) The plan has served as a blueprint for CIRM's scientific programs. The plan envisions stem cell research funding as a pipeline that includes: (1) research training grants and basic research grants, which provide the foundation for therapy development; (2) preclinical research, where strategies for disease treatment are explored; (3) preclinical development, where studies necessary to meet the regulatory requirements of the Food and Drug Administration (FDA) for an Investigational New Drug (IND) prior to testing in humans are conducted; and (4) clinical research, where the efficacy and safety of treatments are tested in humans. Each aspect of the pipeline is critical to the development and delivery of therapies to patients. CIRM's research funding to date, described above, reflects these priorities.

In addition, CIRM has issued requests for applications for:

- Early Translational Awards, which are designed to move promising basic research in stem cell discoveries toward the clinic.

- Bridges to Stem Cell Research Awards, which will fund undergraduate and Master's level students from the campuses of the California State University and the California Community College system in stem cell research via internships and associated scientific training activities designed to culminate in biotech certifications or advanced degree studies.
- Tools and Technologies Awards, which will support the development and evaluation of innovative tools and technologies for stem cell research to overcome any roadblocks to progress in basic, translational, and/or clinical stem cell research.

CIRM's 2006 strategic plan also recognized that, for two main reasons, adequate research space and equipment for human embryonic stem cell research were essential components of the infrastructure required to achieve CIRM's goals: First, as stem cell investigators were recruited to research institutions in California and new investigators were trained, additional facilities would be required to house them. Our universities were running out of available space. Second, because of NIH rules research on human embryonic stem cells could not be carried out in the same research space used for NIH-funded research. Consequently, CIRM issued two requests for applications (RFAs), one for shared labs and the other for major research facilities.

The initial capital program, the Shared Research Laboratory and Stem Cell Techniques Course, provided over \$50 million for renovating and equipping 17 shared laboratories, six of which received additional funding to conduct Stem Cell Techniques courses. The second program provided \$271 million to 12 academic and not-for-profit institutions for: (1) basic and discovery research. (2) preclinical (translational) research. and (3) preclinical development and clinical research. CIRM's funds were matched by approximately \$870 million in donor and institutional funds. The bulk of these facilities are expected to be operational by July 2010.

b. 2008 Strategic Plan Update

Although the 2006 strategic plan has served the Board and the agency well, the Board and the leadership of the scientific staff recognizes that it is a "living" plan that must be revised, with CIRM periodically reviewing its performance and updating its objectives as new scientific opportunities and challenges arise. CIRM is in the midst of such a review. The purpose of the 2008 strategic plan update, "*Accelerating the Move toward Cures: An Update to the Strategic Plan of the California Institute for Regenerative Medicine*," is to build upon the solid foundation of the 2006 plan by identifying new research directions for CIRM that reflect the rapidly changing scientific landscape of stem cell science as well as the evolving thinking of the Board and of CIRM's staff and many stakeholders. This document also reflects the vision, priorities, and scientific guidance of Dr. Alan Trounson, who became CIRM's President on December 31, 2007, and who initiated the planning process. The draft update will be submitted to the Board for an initial public discussion at the December 2008 Board meeting.

The 2008 strategic plan update reflects the high value that CIRM places on interdisciplinary approaches. Biological scientists, working with physicians, chemists, mathematicians, and others to solve complex problems, can progress faster and further than can scientists working alone. For this reason CIRM awarded "Disease Team Planning Grants" to support up to six months of planning and proposal development for novel, team-based research efforts aimed at reaching FDA approval for human trials within 48 to 60 months. The goal is to safely fast-track research from the laboratory to the bedside, with the ultimate aim of submitting an Investigational New Drug (IND) application to the FDA based on stem cell technology. CIRM's current leadership

considers this approach so critical to the agency's goals that it is recommending a five-to-tenfold increase over the 2006 Plan in funds allotted to the Disease Team research grant program.

CIRM understands that the 2008 revisions to the strategic plan are simply an update to an ever-moving target, for CIRM will always need to closely monitor developments in stem cell technology to be able to rapidly respond to new opportunities and ultimately develop and deliver therapies and cures to Californians suffering from chronic disease and injury. The last few years have been marked by major new directions in stem cell biology – some of which were impossible to predict -- and the next few years will likely yield similar, sudden advances. CIRM's flexibility in responding to the changing scientific landscape will be of the essence if discovery is to pay off in improved patient care.

Question 6

The tradeoffs involved in awarding funding for drug development versus basic research and the impact of each on achieving Proposition 71's goals.

CIRM appreciates the tradeoffs involved in awarding funding for **therapy** development versus basic research and the impact of each on achieving CIRM's mission. Fortunately, CIRM has not been presented with a binary choice. CIRM has the capacity to fund both basic research and therapy development. As CIRM's 2006 and 2008 scientific strategic plans make clear, CIRM recognizes that it must fund both basic research and preclinical and clinical research in order to meet the goals established by Proposition 71. Indeed, CIRM's funding priority is to create a "scientific pipeline to cures" stretching from early discoveries to clinical applications. The draft 2008 update to the strategic plan thus calls for dramatic increases beyond the 2006 plan in the types of research targeted to elicit therapeutic applications, and it envisions significantly more investment in focused "disease team" awards, translational research awards, and linkages to industry—the final conduit for getting research advances to the patient.

It is difficult to separate basic research from therapy development because in the stem cell field the same technologies are often used for both. For example, screening cell responses to libraries of small molecules can be used to identify cell differentiation pathways as well as candidate drugs. The identification of embryonic stem cell lines or induced pluripotent stem cell lines from embryos or patients with Huntington's Disease may identify the cause of the disease but also identify drugs that can prevent the cellular changes that are responsible for death of neurons

In addition, the use of pluripotent stem cells and their derivatives for identifying environmental toxins and for the discovery of new traditional drug candidates may be early clinical developments in stem cell science. In addition, the identification of the dangerous stem cells responsible for the spread or metastasis of cancer is likely to be an early outcome of stem cell research.

The Operational Side of Making a Balanced Portfolio

Building upon the values and foundation expressed in the 2006 strategic plan, the specific goals of the 2008 update of the strategic plan include:

- Measure CIRM's successes and shortcomings in achieving the goals set in the 2006 Strategic Plan and learn from both.
- Outline a system for updating CIRM's future research programs in light of the rapid evolution and new developments in stem cell science and regenerative medicine over the past two years.
- Map a plan for accelerating progress through the "pipeline to cures" by focusing research and organizing CIRM's portfolio to facilitate the connections between CIRM-funded basic stem cell research and translational, pre-clinical, and clinical research.
- Lay out an option for developing robust systems for capturing and evaluating the results of CIRM-funded programs and for sharing these data in ways that accelerate the field.
- Reassess and enhance CIRM's relationships with the biotechnology and pharmaceutical business communities, relationships essential to our goal of lifesaving therapies based on stem cell research.

- Propose new ways for CIRM to lead stem cell science and regenerative medicine by sharing expertise and collaborating with partners in the scientific community, both nationally and around the world.

Keeping CIRM Medical Research on the Cutting Edge

To accomplish this goal, members of the science team rely on multiple sources of information to guide them in monitoring progress in the stem cell field, in framing questions, and in identifying specific areas of opportunity or roadblocks to research progress, all of which form the basis of new RFAs.

To be successful in generating RFAs of high interest and relevance, CIRM's Science Officers must remain on the cutting edges of stem cell biology and regenerative medicine. Toward this end they read and debate the scientific literature, attend national and international scientific meetings, host scientific speakers at research seminars held in CIRM's headquarters, visit and speak with investigators at their home institutions, and participate in frequent scientific discussions with their CIRM peers.

Other sources of information used in framing CIRM's science portfolio include:

CIRM workshops. Workshops provide a useful venue for learning about various scientific fields and for bringing together large and small groups of experts to advise on the best ways for advancing research agendas.

Progress reports. The Grants Administration Policy (GAP) requires that CIRM grantees submit progress reports detailing the research carried out during each funding year. To manage the flow of information, CIRM is developing and implementing the categorization systems and database that will store information according to disease relevance, cell types and technologies employed, research results, questions raised and answered, and possible next steps. Analysis of progress reports may suggest the need to launch entirely new programs, or it may reveal opportunities to make adjustments in current programs, for instance, by encouraging collaborations among investigators pursuing similar or related work in different organizations

CIRM Annual Conference. CIRM has hosted its first grantees conference, with over four hundred CIRM-funded scientists attending. The meeting featured lectures, posters, and interactive science activities. Leading U.S. and international scientists attended by invitation to stimulate discussions on chosen subjects of high priority.

Investigator-initiated Conferences. Also extremely valuable for information sharing are conferences initiated by CIRM investigators, which can now be funded through applications to CIRM.

Patient Advocacy. Patient advocates are incorporated into CIRM's decision-making at many levels. They are members of the Grants Working Group and have a formal role, with scientists and physicians in the Working Group, in formulating recommendations to the Board for project funding.

Stakeholder Guidance. To achieve a balanced portfolio, the Science Office responds to guidance from various stakeholders, including research institutes, companies, clinical centers, patient groups, research foundations, government, and the general community.

A Final Summary: To Drive the Translation of Basic Discoveries to Therapies for Patients

Proposition 71's central goal is to drive the translation and application of basic research discoveries to patients in the clinic, to reduce human suffering. CIRM strategies are to boost innovation in basic science and then ensure that new discoveries are integrated into the clinical pipeline, to benefit California's families and patients worldwide. CIRM therefore intends to fund both basic research and pre-clinical and clinical development to deliver therapies and cures to patients who suffer from chronic disease and injury.