CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

May 14, 2012

From: Ellen G. Feigal, M.D., Senior Vice President, Research and Development

To: Independent Citizens Oversight Committee (ICOC)

Re: Pre-read for 2012 Strategic Plan discussion at ICOC on May 24, 2012

This pre-read for the ICOC is providing context for the May ICOC discussion on the 2012 update of the Strategic Plan. This 2012 Strategic Plan builds on the solid foundation of the 2006 plan and on the 2009/10 update and reassessment. It addresses the recommendations of the external advisory panel, recognizes the rapidly changing scientific landscape of stem cell science and reflects the views of numerous stakeholders who were asked to provide their perspectives on the current and future direction of CIRM. We look forward to a productive discussion.

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CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

2012 Strategic Plan

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INTRODUCTION AND CONTEXT

In November 2004 the voters of California adopted Proposition 71 (the California Stem Cell Research and Cures Act), authorizing the issuance of $3 billion in state bonds to support stem cell research in California. The act created the California Institute for Regenerative Medicine (CIRM) and charged the institute with determining the most effective means of distributing state funds to accelerate the entire field of stem cell biology and regenerative medicine.

In December 2006 CIRM's governing board, the Independent Citizens Oversight Committee, adopted its first scientific strategic plan, which has served as the blueprint for CIRM's scientific programs and procedures. CIRM relied on that plan as the foundation upon which an update to the plan was developed in 2009/2010 and that document is the starting point for the current revision.

As a responsible steward of public funds, CIRM must periodically reevaluate both its funding priorities and operations to stay sharply focused on those research opportunities most likely to achieve therapies and cures. The 2006 scientific strategic plan was intended to be a "living plan" with formal assessment by an outside panel and revision as necessary recommended at years three and seven. Year 1 for the plan was designated to start July 1, 2007, making the first formal assessment due around July 2010.

Accordingly, CIRM's governing board adopted an update to the 2006 plan in the spring of 2010. That document was then provided to an External Advisory Panel (EAP) that was selected in July. The EAP, an eight-member blue ribbon panel was composed of individuals fitting the categories outlined in the 2006 Plan: " . . . scientists, clinicians, ethicists and patient advocates both from within and from outside of California." The Governing Board accepted the report from the EAP in December 2010 (see Appendix A), and senior leadership submitted a response to the report in February (Appendix A).

This 2012 strategic plan update builds on the solid foundation of the 2006 plan and on the 2009-2010 update and re-assessment. It addresses the recommendations of the EAP, recognizes the rapidly changing scientific landscape of stem cell science and reflects the views of numerous stakeholders who were asked to provide their perspectives on the current and future direction of the agency. (see Appendix B)

EXECUTIVE SUMMARY

This document aims to set the expectations for the accomplishments of CIRM as it enters a second, more mature phase. The clock on the agency's first Strategic Plan began in July 2007 and by the time the clock runs out on the five-year goals set at that time those goals will be nearly fully achieved, often in ways that were not imaginable when the goals were set. The accomplishments of those first five years have shown that the field of stem cell science and regenerative medicine can be truly transformative for science, and shows the potential for even greater transformative capacity in clinical medicine.

The ten-year goals set in the initial strategic plan became the basis for setting five-year goals for the current document. CIRM leadership modified those goals to reflect scientific advances in the field, consideration of what is feasible today and to reflect the four new "objectives" and four "key outcomes" developed during the current strategic planning cycle. Those objectives were chosen to reflect CIRM's response to the External Advisory Panel review that was conducted during 2010. The four objectives cover scientific, clinical, economic and community issues. The latter two were not raised to the level of top objectives in the original plan, but reflect the EAP's view that those issues are key to the agency's work becoming sustainable over time.

The current strategic plan lays out three to five principal strategies to accomplish the set objectives and outcomes. It also details a few potential tactics for executing each of the strategies.

Throughout, the current plan shifts CIRM's focus so that the agency will expend a greater portion of its staff intellectual capacity and its available funding toward projects that will move potential therapies toward and into the clinic. For example, the new five-year goals explicitly call for funding at least 10 therapies in early phase clinical trials that collectively impact at least five diseases. This emphasis on translation is fundamental for achieving the primary mission of CIRM, namely accelerating the research and development of break-through therapies that will significantly improve the lives of patients.

The new plan's elevation of an economic objective has been driven by the twin goals of delivering economic benefit to the state of California, and the desire to make California's investment sustainable. The latter requires a greater level of partnership and collaboration with industry and with funders from around the U.S. and around the world. One of the new five-year goals reflects this by overtly setting the target of having 20 CIRM funded programs having outside capital commitments for product development work. The related goal in the prior plan merely said that some CIRM projects should have achieved this milestone.

The strategies developed to accomplish the objectives reflect the field as a whole as well as the research funding strategy projections developed by CIRM leadership to reflect the finite level of investment currently committed to the agency. Those various projections are summarized in the final section of this document and discussed in greater detail in Appendix D. They attempt to align CIRM priorities with the current statistics regarding the odds of success in each phase of therapeutic development, which are discussed in Appendix E.

In its entirety, this plan points to a potentially dramatic legacy for CIRM that can be sustained with a mixture of public and private partnerships.

VISION

The Mission of CIRM is:

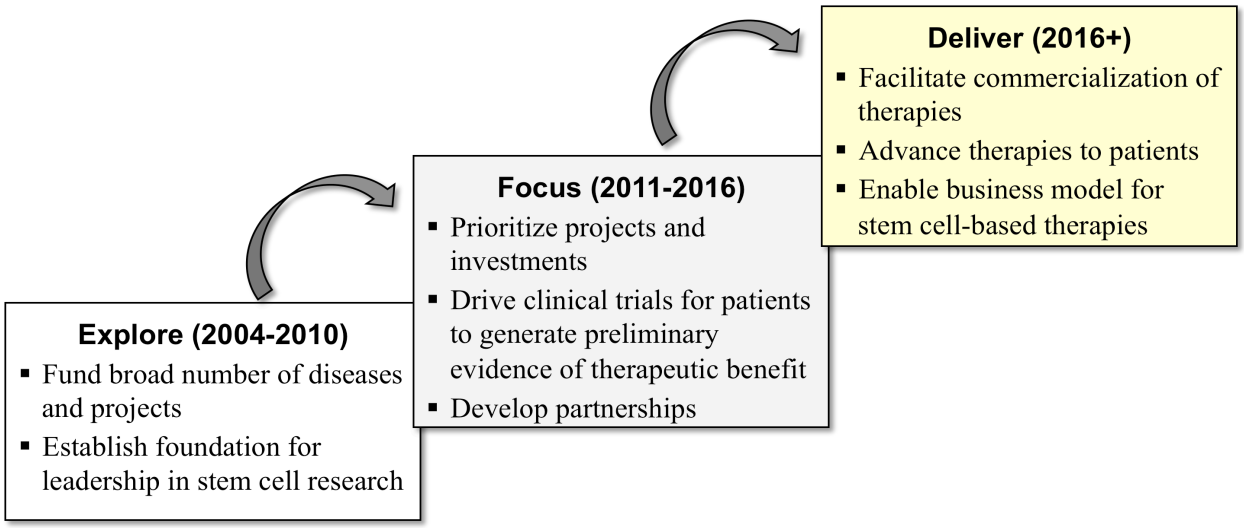
"To support and advance stem cell research and regenerative medicine under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury."

CIRM's first five years set priorities based on establishing a strong foundation for leadership in stem cell research, seeding the entire field with discoveries using a variety of stem cell-based platforms. This resulted in over $1.3 billion in awards to 59 institutions, the publication of more than 1,000 journal articles (28 percent with impact factors greater than 10, e.g., highly cited and a proxy for their relative importance in the field), the construction of 12 dedicated stem cell facilities, the relocation of more than 130 faculty level stem cell researchers to the state, and 43 translational projects in 26 therapeutic areas.

As CIRM enters its next five years, its focus will be on driving science to clinical trials that have the potential to generate evidence of therapeutic benefit for patients. We intend to fund work that will result in clinical proofs-of-concept, while maintaining the full pipeline of discovery, including the basic science that has the potential to fundamentally transform the field. By doing so, CIRM will continue to help fuel the economic engine of discovery and innovation in California by creating new jobs and by facilitating new collaborations between the public and private sectors.

As CIRM seeks to bring discoveries from the laboratory to new treatments and innovations (so called "translational medicine"), it does so with the knowledge that the cycle of discovery to translation often takes decades. CIRM is working diligently to rapidly accelerate this process, but it is important to understand that the full fruition of CIRM's investments to date will likely take many years and that this will require continued work by scientists and physicians, and continued commitments by institutions and the citizens of California. The ultimate goal is to improve the

lives of Californians, and by extension, the lives of people worldwide, and to maximize the value of Californians' investment in stem cell research.



All of CIRM's programs are a work-in-progress, whose fulfillment will unfold over the decades ahead. The investments that have been made through CIRM offer a bridge to further opportunities that will take place over time. It is important to note that these investments are already paying off. They have attracted extraordinary scientists, clinicians and leaders to California giving the state leadership in the field with the ability to form strong stem cell research teams from around the world. CIRM's investment has fostered public-private partnerships to build state-of-the-art research facilities in which groundbreaking work is being conducted and where the key tools and technologies are being developed to ensure that California remains the global leader in regenerative medicine.

Recently, CIRM released its first program designed to link CIRM funded programs with biotechnology and pharmaceutical companies. This will result in not only the leveraging of CIRM's funds but also enhancing the ability of these programs to access future funding critical to moving these programs into phase 3 clinical trials and ultimately to patients. These investments will continue to open up new opportunities – new discoveries will create new science and medical approaches and evolve new therapeutics in diseases with unmet clinical need. CIRM also anticipates fostering the creation of novel clinical programs that will bring discoveries to the citizens of California and serve as examples for business as well as national regulatory bodies such as the Food and Drug Administration (FDA). CIRM has created an unrivaled engine of innovation and discovery that will be seen as a model for the nation, especially if some of the engines for that model can be sustained for the future. These fruits of CIRM will help guide the future of this potentially transformative field and will create new jobs and opportunities and

further grow the biotechnology industry that is already so strong in California.

As a public institution, it is CIRM's intent in this strategic plan to inform, to identify what has been achieved, what has been delivered on the promise of what CIRM said it could do through its goals and objectives, and to state where CIRM is at this point in time and where the programs could be in the future.

STRATEGIC OBJECTIVES

In order to complete the transition to a new "Focused" phase, CIRM senior leadership identified four key strategic objectives that align to the overarching mission and vision.

Proposed strategic objectives for next five years			
Scientific	**Clinical**	**Economic**	**Community**
Accelerate understanding of stem cell science and its applications towards human diseases and injuries	**Advance stem cell science into clinical trials** to achieve evidence of therapeutic benefit to patients	**Drive economic development** for California from stem cell science and therapies	**Maintain California as the world stem cell leader**

Single most important key outcomes			
Scientific	**Clinical**	**Economic**	**Community**
Achieve transformative research discoveries	**Achieve clinical proof-of-concept for stem cell therapies**	**Leverage CIRM's investment in California**	**California universally recognized as the "Stem Cell State"**

Strategies for Achieving Success on the 2012 Objectives

CIRM senior leadership, with input from the Independent Citizens Oversight Committee and a wide array of stakeholders, has developed strategies for success for each of the 2012 objectives, summarized in the table below.

Scientific Strategies	Clinical Strategies	Economic Strategies	Community Strategies
▪ Foster an engine of discovery and transformative research ▪ Create a collaborative research community that enhances California's leadership and competitiveness ▪ Realign funding programs, review and decision making with current strategic objectives	▪ Foster disease-specific research toward clinical proofs-of-concept ▪ Expand multidisciplinary collaborative efforts to enhance clinical outcome ▪ Foster developing a regulatory path for stem cell therapies ▪ Boost the biotechnology sector in California ▪ Focus, prioritize and evaluate projects to move the most promising forward ▪ Enhance interactions with patients and advocates	▪ Attract co-funding and follow-on financing of CIRM projects ▪ Foster the growth of California's stem cell industry and the creation of stem cell clusters that accelerate investment ▪ Set the stage for cost savings in health care for the state and private payers ▪ Establish a platform to enable grantees, disease foundations, venture capitalists and others to pursue CIRM's mission upon the expiration of CIRM's bond funding	▪ Communicate value proposition of CIRM and the stem cell field ▪ Engage with stakeholders on why stem cell science matters to them ▪ Create an awareness among stakeholders of CIRM's role in making California the leader in the field

FIVE-YEAR GOALS

In striving towards our FY17/18 five-year goals, we will continue to be good stewards of public dollars as we seek to achieve the following:

These 5 year goals have been modified from the 10 year goals initially set forth in CIRM's 2006 Strategic Plan, which we have included in parentheses to show the changes:

- Goal I: Through research sponsored by CIRM and others, the factors regulating the self-renewal and tumor-causing potential of stem cells and their derivatives will be identified and characterized.

  (*From CIRM's 2006 Strategic Plan: Goal IX: Through research sponsored by CIRM and others, the mechanisms regulating the self-renewal and oncogenic potential of embryonic stem cells and their derivatives will have been identified and characterized.*)

- Goal II: Through research sponsored by CIRM and others, a thorough description of the steps of differentiation leading to the production of critical cells of the body desired for transplantation will be achieved.

  (*From CIRM's 2006 Strategic Plan: Goal VIII: Through research sponsored by CIRM and others, a thorough description of the steps of differentiation leading to the production of the various cells of the body will have been achieved.*)

- Goal III: CIRM will have funded new approaches for ensuring successful allogeneic cell transplantation that are in clinical development.

  (*From CIRM's 2006 Strategic Plan: Goal IV: CIRM will have funded new approaches for achieving immune tolerance for transplantation that are in pre-clinical development.*)

- Goal IV: Using stem cell research, CIRM-funded investigators will have established proof-of-principle in preclinical animal models for treatment of >10 diseases.

  (*From CIRM's 2006 Strategic Plan: Goal V: Using stem cell research, CIRM-funded investigators will have established proof of principle in preclinical animal models for the treatment of 6-8 diseases.*)

- Goal V: CIRM-funded investigators will have created disease-specific cell lines for 20-30 diseases and used them to gain new information about their underlying pathogenesis, and to identify new drug targets for discovery of new therapeutics.

  (*From CIRM's 2006 Strategic Plan: Goal VI: CIRM-funded investigators will have created disease-specific cell lines for 20-30 diseases and used them to gain new information about pathogenesis, to identify new drug targets and to discover new therapeutics.*)

- Goal VI: CIRM will have enabled development of new procedures for the production of a variety of stem and/or progenitor cells that meet requirements for clinical application.

  (*From CIRM's 2006 Strategic Plan: Goal VII: CIRM will have enabled development of new procedures for the production of a variety of stem and/or progenitor cells that meet GMP requirements.*)

- Goal VII: At least 20 CIRM funded programs will have outside capital commitments for funding development work.

  (*From CIRM's 2006 Strategic Plan: Goal III: CIRM funded projects will have achieved sufficient success to attract private capital for funding further clinical development of stem cell therapies.*)

- Goal VIII: CIRM will have funded 10 therapies in phase 1 or 2 clinical trials, in at least 5 different therapeutic areas, based on stem cell research.

  (*From CIRM's 2006 Strategic Plan: Goal II: CIRM-sponsored research will have generated therapies based on stem cell research in Phase I or Phase II clinical trials for 2-4 additional diseases.*)

- Goal IX: CIRM will have achieved clinical proof-of-concept that transplanted cells derived from pluripotent or progenitor cells can be used to restore function in disease or injury.

  (From CIRM's 2006 Strategic Plan: *Goal I: CIRM grantees will have clinical proof of principle that transplanted cells derived from pluripotent cells can be used to restore function for at least one disease.*)

- Goal X: Broaden and reinforce CIRM's efforts to educate and engage the California community in CIRM's mission and achievements, in part by increasing the number of monthly online engagements to 250,000. (*New, not in CIRM's 2006 Strategic Plan*)

ONE-YEAR GOALS

In striving towards our FY12/13 one year goals, we will continue to be good stewards of public dollars as we seek to achieve the following:

- Ensure CIRM's portfolio includes at least 2 programs with an approved Investigational New Drug (IND) filing with the US Food and Drug Administration (FDA) to enter human clinical trials

- Achieve $50 million in new, outside financial commitment for CIRM programs (ie., collaborative funding partners, industry, venture capitalists, matching funds from institutions)

- Ensure funding of potentially high-impact projects that could result in transformative research by modifying priorities in CIRM's Request for Applications

- Educate and engage the California community in CIRM's mission and achievements, in part by increasing the number of monthly online engagements from the current 70,000 to 100,000.

- Optimize CIRM's workforce staffing and processes to meet changing priorities within the 6% ceiling.

STRATEGIES AND TACTICS TOWARD SUCCESS

Scientific Objective to accelerate understanding of stem cell science and its applications toward human diseases and injuries.

Foster an engine of discovery and transformative research—CIRM has built the foundation for such an engine. With more than 1,000 research papers published using CIRM funding, 546,000 square feet of new research space either completed or near completion and more than 130 faculty level stem cell researchers attracted to the state, the agency has a solid base to build upon. Going forward tactics include:

- We expect the recruitment to California of innovators in stem cell science through CIRM's Research Leadership Award program in 2012 -13.

- CIRM will explore approaches to fund highly innovative researchers to enhance breakthrough discoveries.

- CIRM will be seeking applications under a specific RFA targeted to draw more medical researchers to bring their unique perspective to discovery and translational research that could lead to transformative therapies for patients.

- CIRM will continue to identify critical roadblocks to achieving therapies that could be overcome with basic or translational research and incorporate proposals to overcome those barriers into funding opportunities.

- Through targeted RFAs CIRM is developing iPSC cell lines and banking representing major complex diseases. This should provide California scientists and biotechnologists a major ongoing resource for disease modeling and drug discovery.

- CIRM will explore the opportunities to leverage existing high throughput compound screening and genomic screening capacities in the state to screen stem cell based disease models for drug development and toxicology.

- CIRM plans to launch a major funding initiative in stem cell genomics to develop centers of excellence, which will apply rapidly advancing developments in genomics to stem cell biology, disease modeling, and therapeutics (link to whitepaper).

Create a collaborative research community that enhances California's leadership and competitiveness— CIRM has a strong track record for creating research collaborations within institutions, across institutions and across state and international boundaries. Going forward tactics include:

- CIRM will expand and increase the effectiveness of the CIRM network of Collaborative Funding Partners, both nationally and internationally to enable the best scientists, biotechnologists and clinicians nationally, and from around the globe, to work with Californian colleagues.

- CIRM plans to continue to utilize workshops and to support critical conferences to foster collaboration with California stem cell scientists. CIRM is also exploring creation of a portal within its web site to make it easier for potential collaborators to find researchers doing complementary work.

- CIRM will continue to hold CIRM Grantee and the CIRM Bridges Trainee meetings to further foster collaboration and the community of stem cell scientists. CIRM is working towards a partnership with a leading not-for-profit conferencing agency to promote stem cell research and applications in regenerative medicine.

- The CIRM Shared Lab grants have been renewed and we have set up a web

portal for the directors of those labs to share best practices in how they teach and foster stem cell biology.

- CIRM's planned stem cell genomics program will forge new collaborations between stem cell scientists and top experts in genomics and bio-computing.

- The External Innovation component of the recently Board approved Opportunity Fund allows CIRM to identify outstanding research taking place outside California and/or within the jurisdiction of any of the agency's external network of funding partners. CIRM can fund new awards or supplement existing awards to California researchers who form partnerships with the external scientist.

- The Bridging component of the Opportunity Fund provides supplemental support to the most promising previously CIRM-funded projects, within the existing stage and defined project area, to enable the research to continue uninterrupted until next applicable round of CIRM funding or receipt of other funds.

- CIRM will continue to further enable industry participation and collaboration. Specifically:

    - CIRM will make the grant and loan process more streamlined and transparent.

    - CIRM's active management of our translational portfolio projects in conjunction with external advice will help make our stem cell projects attractive for industry collaborative investment.

    - The Strategic Partnership Funding Program, the third component of the Opportunity Fund, was designed to attract co-funding and follow on financing by the pharmaceutical industry, major biotechnology companies and the venture capital industry to support new and existing CIRM funded projects. This program will offer a biannual review, enabling CIRM to become more nimble in working with the constraints and timelines of industry

Realign funding programs, review and decision making with current strategic objectives—As CIRM moves from a broad exploratory phase to a more focused phase it must align our funding to achieve key outcomes for current strategic objectives. There must be a push for projects that deliver on clinical proof-of-concept while maintaining support for the basic and translational research that is the foundation for creative change and is necessary for the discovery of new therapeutic opportunities and new approaches to resolving barriers to progression of therapies. Going forward tactics include:

- CIRM plans to continue to aid reviewers and decision makers to incorporate portfolio prioritization considerations, where applicable, into their respective roles in making funding recommendations or funding decisions.

- CIRM will prioritize its translational, especially its development portfolio, to identify those projects that offer the most promise to patients and to regenerative medicine and actively work to enable their success.

- The Clinical and Development Advisors panel along with other industry expertise will be utilized in identifying these promising projects and in evaluating the strengths and weaknesses of our development portfolio.

Clinical Objective to advance science into clinical trials to achieve evidence of therapeutic benefit to patients.

Foster disease-specific research toward clinical proofs-of-concept — The projects in CIRM's development portfolio provide an initial base for moving selected projects toward and into early phase clinical trials. CIRM's Clinical Development Advisors panels, constituted in July 2011, are composed of experts with expertise in preclinical, manufacturing, clinical, regulatory, specific diseases, and commercial viability. They met with each of CIRM's disease teams to engage in an interactive dialog on the challenges and complexities our translational programs face in moving toward the clinic, with the intent of helping them be positioned for success. Going forward the tactics include:

- CIRM will work with the Clinical and Development Advisors panels and other industry experts to provide guidance at key milestones of ongoing disease teams to better position these projects to advance into clinical trials.

- CIRM will strengthen its robust peer review groups with additional product development, regulatory and commercial viability experts for the 2012 Disease Team Therapy Development Awards, Strategic Partnership Awards, and other future translational awards to better identify programs that have the potential to advance towards and into the clinic.

- CIRM will raise awareness of existing resources and provide more opportunities to engage with potential applicants on lessons learned to enhance potential for successful award submissions.

Expand multidisciplinary collaborative efforts to enhance clinical outcomes — CIRM's considerable effort in building collaborations to date, most notably through its Disease Teams and its network of Collaborative Funding Partners, provides a solid foundation for ratcheting up this effort in its second phase. Going forward the tactics include:

- CIRM will explore and facilitate the creation of stem cell clinics (Alpha Stem Cell Clinics whitepaper can be viewed here) in California and beyond to enhance clinical trials and delivery of stem cell based therapies for patients.

- CIRM will work in collaboration with the NIH-funded California Clinical and Translational Science Institutes and the NIH Clinical Center in Bethesda to leverage expertise and infrastructure to accelerate clinical development.

- Collaborative Funding Partners have expressed interest in the possibility of replicating the business and clinical model that may evolve from the CIRM "Alpha" Clinic network. A network of clinics for cell therapies could be expanded nationally and internationally.

- The Opportunity Fund will be used to foster collaboration and investment by industry and venture capital. As CIRM projects move through preclinical testing and Phase 1 and Phase 2 clinical trials the Strategic Partnership Funding program will be instrumental in attracting follow-on financing for the definitive Phase 3 trials.

- CIRM will provide access for academic grantees to product development, regulatory, and industry expertise during the developmental phases of research in order to improve understanding and capacity for translational and preclinical/clinical processes necessary for regulatory approval.
- CIRM will, through mechanisms that include the new translational journal (Stem Cells Translational Medicine), workshops and on-line information portals, enable opportunities to share information on experiences learned in moving a product through regulatory pathways toward and into the clinic.

Foster developing a regulatory path—CIRM has taken a leadership role by organizing webinars and face-to-face roundtables with the FDA and researchers, and co-sponsored and participated in an interactive workshop with patient advocates, FDA, industry, and researchers, focused on the role of the patient advocate in product development. These meetings and on-line presentations have addressed a wide range of issues on various aspects of regulatory consideration. CIRM is also a founding member of the Alliance for Regenerative Medicine (ARM), that is exploring a number complex issues such as "potency" of cell products and other critical matters in defining acceptable clinical parameters for cell therapies and other aspects of the regulatory pipeline. Going forward the tactics include:

- Leveraging the experience and sharing lessons learned of grantees and others on regulatory requirements for stem cell based therapies.

- Webinars and roundtables with FDA and researchers in the field will continue to address critical regulatory and harmonization issues in cell therapies and regenerative medicine.

- Members of the CIRM leadership team will continue to serve and expand their participation on committees for ARM, which is moving key scientific, regulatory and legislative initiatives forward in regenerative medicine.

- Through a targeted RFA, CIRM will support physician scientists and will explore the possibility of creating a translational fellowship program to further enhance the training of key research personnel in cell therapeutics and translation.

Boost the Biotechnology Sector in California — CIRM has recognized the importance of reimbursement for regenerative medicine and is working with industry organizations such as the Alliance for Regenerative Medicine to define a pathway. Going forward the tactics include:

- CIRM co-organized with ARM and Connect the first ever "investor and partnering" forum for the sector in 2011, which brought together 244 representatives from academia, start-up biotechnology firms, major biotechnology firms, large pharmaceutical companies and venture capital financers to discuss opportunities for collaboration and follow-on financing. CIRM will continue to support the partnering forum as an annual calendared event.

- Through the Strategic Partnering Fund, enhance the ability of industry to partner with and leverage CIRM funds and experience, to accelerate product development and clinical trials in regenerative medicine.

Focus, prioritize and evaluate projects to move most promising translational research forward— While investments in early stage discovery will continue, CIRM will institute processes that ensure investments in translational projects are focused on those most likely to progress toward and into clinical trials. Going forward tactics will include:

- CIRM will enhance the use of reviewers and advisors with product development and industry expertise when reviewing and making recommendations on the likelihood of moving projects toward and into clinical trials as well as assessment of opportunities for commercialization and application in viable markets.

Enhance interactions with patients and advocates — Patient advocates are a powerful resource for promoting awareness of clinical trials and educating the public about potential therapies. CIRM began interactive discussions with patient advocates in August of 2010. That effort started with a listening tour of one-on-one meetings summarized in a Voice of the Patient Advocate document, which directed the next phase of the project centered on information exchange. That effort has developed a list of nearly 900 patient advocates who have signed up to stay connected to the agency and receive materials on its activities. Going forward the tactics include:

- In the next phase of this project, CIRM will develop a handbook for our grantees on approaches to consider for facilitating constructive interactions with patient advocates.

- CIRM will also identify leading advocates/organizations for each disease represented in the CIRM Disease Teams and explore points of mutual interest.

- CIRM will develop an advocate venue that can be used for calls/meetings to seek input and feedback on issues related to CIRM's clinically relevant activities on a regular basis.

Economic Objective to drive economic development for California from stem cell science and therapy.

Attract co-funding and follow-on financing of CIRM projects—CIRM has been very successful in leveraging taxpayer investment. The $271 million commitment of state funds to the CIRM Major Facilities resulted in more than $800 million in private donor and institutional funds for construction, equipment and for recruitment packages for top talent. In addition, as of December 2011, CIRM's collaborative funding partners had committed approximately $60 million to CIRM-funded projects and California firms had committed considerable company resources to projects for which they had CIRM awards. Going forward the tactics include:

- CIRM will create additional research and development collaborations, co-funding arrangements and opportunities for investment in CIRM's portfolio. New approaches will include a "Bolt-On" strategy, where collaborators, including disease foundations and funding agencies, can join a project after it has ICOC approval.

- CIRM will explore collaborative funding relationships with multiple partners on the same project and early inputs sourced from collaborative funding partners.

- CIRM is exploring creating a portal within its web site to make it easier for potential collaborators to find researchers doing similar work and find other ways for our partner organizations to use existing information on our web site.

- The Strategic Partnership Funding Program is designed to attract significant amounts of co-funding and follow-on financing to California stem cell projects. This funding could come from major pharmaceutical firms, biotechnology companies, disease foundations, collaborative funding partners or venture capital.

Foster the growth of California's stem cell industry and the creation of stem cell clusters that accelerate investment — CIRM has created stem cell clusters within existing biotech clusters in the Bay Area and San Diego county and has made significant progress toward a third cluster with critical mass in the Los Angeles basin. Going forward the tactics include:

- CIRM will work closely with the state and local governments to further leverage CIRM's funding by attracting new companies to the state and to enable growth for the industry already in California.

- The Bridges Training and Creativity programs will continue to engage and advance many students who often would not have had the opportunity to consider a career in research and biotechnology. These programs provide critical personnel resources needed by our growing industry.

- The various components of the Opportunity Fund will likely attract companies to California.

- Access to CIRM resources, such as cell banks, genomic centers of excellence, clinical trial sites in Alpha Stem Cell Clinics and other opportunities will help draw companies to California.

Establish a platform to enable grantees, industry, other government agencies, disease foundations, venture capitalists and others to continue to pursue CIRM's mission upon the expiration of CIRM's bond funding – CIRM's bond funding is limited to $3 billion. Although additional funding could be a possibility in the future, it would be premature to consider another bond measure at this time. Instead, CIRM should focus its efforts on creating a platform that enables others to carry on CIRM's work. Through its funding of state-of-the-art research facilities, collaborative funding agreements, and industry engagement, CIRM has already made progress in creating this platform. CIRM's efforts will include:

- CIRM will explore and facilitate the creation of Alpha Stem Cell Clinics for the delivery of stem cell-based therapies to patients and will work with its

collaborative funding partners to replicate the model nationally and internationally.

- CIRM will continue to pursue and strengthen its joint funding efforts with state and international partners, the NIH, disease foundations, industry and venture capitalists, in order to build relationships and promote follow-on funding for CIRM's research projects.

- CIRM will work to create and bring new biotechnology companies to California and create stem cell clusters to promote collaborations with California researchers and to provide a vehicle to translate stem cell discoveries into clinical applications.

- CIRM will explore the creation of a nonprofit venture philanthropy fund to provide funding for stem cell research projects, from IND-enabling research through Phase 2 clinical trials.

- CIRM will fund the creation of an iPSC bank as a resource for California researchers and companies interested in disease modeling and drug discovery.

- CIRM will provide regulatory and product development guidance to its grantees to ensure that they have the tools necessary to take their discoveries from the bench to the bedside.

- CIRM will support efforts by its grantees to protect CIRM-funded intellectual property in order to safeguard the state's investment and promote the commercialization of CIRM-funded therapies.

Set the stage for cost savings in health care for the state and for private payers—The greatest economic impact from CIRM and the stem cell field will likely be in the reduction of health care costs, particularly in the chronic diseases of aging that currently consume more than 80 percent of our health care spending. However, most of these saving will start to materialize in years beyond the five-year scope of this revision.

- CIRM will take every opportunity to advance therapy candidates that can dramatically reduce the costs of chronic illness and injury.

Community Objective to maintain California as the world leader in stem cell research.

Communicate the value proposition of CIRM and the stem cell field—CIRM is a good investment for the state when you compare the jobs created and new tax revenue generated to the debt service on its bonds (Economic Impact Study). Additional value will develop as CIRM fosters more industry growth in the state, and in the long-term, from stem cell-related therapies with enhanced effectiveness that result in reduced cost of care for Californians, thereby lowering costs to MediCal and for employers providing health insurance. Going forward the tactics include:

- CIRM will develop tools and strategies to more broadly communicate the value of CIRM funding to state legislators, state executives, opinion leaders and the general public.

- CIRM will utilize legislative briefings, media briefings, and public speaking opportunities to inform the broad community on the value created by CIRM activities.

- CIRM will incorporate the value message in its electronic and social media and encourage broader sharing of this information

Engage with stakeholders on why stem cell science matters to them—CIRM has robust content explaining its science product to the public and to high school students. A number of advocates consider CIRM's web content some of the best and most appropriate anywhere on disease conditions and regenerative medicine. Going forward tactics will include:

- CIRM will find ways to encourage more people to visit its website so that CIRM becomes "the accepted source of stem cell information."

- CIRM will work to broaden the reach of this content and make sure that it provides the full context of the value proposition while penetrating deeper to reach a wider sector of audiences more fully.

- CIRM will use the Patient Advocate network developed to support its clinical mission as ambassadors to carry this information to their constituents.

- CIRM will increase its provision of feature story ideas to media outlets, both print and broadcast.

- CIRM will continue to investigate new tools in the constantly evolving world of social media to create a broader recognition of CIRM through content that is read and shared more widely.

- The CIRM school curriculum, while popular among those teachers who have been introduced to it, needs more users. CIRM will continue to showcase the curriculum program at national and state science teacher conventions, expand on the email marketing program and develop a summer professional development course to immerse a core set of teachers in the materials.

Create an awareness among stakeholders of CIRM's role in making California the leader in the field — CIRM's reputation for leadership among scientist stakeholders is sound and we generally have the materials to make the case to other stakeholders but a more robust and targeted effort to reach them is required. Going forward the tactics include:

- CIRM will seek further opportunities to engage elected representatives on the value of CIRM and its leadership in the stem cell field.

- CIRM intends to expand the patient advocate partnering program to reach a broader group of advocates, empowering them with more informational materials produced at a level appropriate for their constituents.

- CIRM will incorporate a patient advocate role in all appropriate communication efforts.

- CIRM will look for more opportunities for its Governing Board members to engage with stakeholders to spread the message of our leadership in stem cell science.

- CIRM will continue global public outreach through participation in Stem Cell Awareness Day, a public education opportunity we created along with our Australian partners in 2008.

- CIRM will develop more opportunities to engage with our collaborative funding partners in reaching the public to support the programs evolving from CIRM.

- With the spread of "stem cell tourism," where people spend large sums of money to access largely untested and unproven therapies at unregulated clinics around the world, CIRM intends to explore options for fostering public dialogue and awareness on this issue taking a leadership role in educating the public on the dangers involved. The Alpha Clinics cold be a valuable tool in this effort.

RESEARCH FUNDING STRATEGIES

This section is intended to provide a framework for decisions going forward on how CIRM will allocate the balance of the voter-approved funding for the conduct of stem/progenitor cell research in California to realize the strategic objectives, key outcomes and relevant 5-year goals of the 2012 Strategic Plan.

The key points are:

- There is $1.48 billion in funds not yet awarded, $695 million of which is for programs that are concept approved, $836 million is for future programs.

- The 5 year goal "CIRM will … have achieved clinical proof-of-concept that transplanted cells derived from pluripotent or progenitor cells…" drives the funding strategy given the costs, timeframes and probabilities of success associated with clinical development projects, and given the stage of maturity of the cell therapy field.

- The funding strategy proposed herein, represents a snapshot in time and should be periodically revisited to ensure that CIRM is best utilizing the remaining research funds to achieve its mission.

Funded Programs

Table 1 in Appendix D lists all programs by Request for Application (RFA) or Program Announcement (PA) where awards have been made and funding allocated. Allocated funding includes dollars disbursed and to be disbursed and is current as of February 2012. The list also assigns a category to each funded program; these categories are briefly described below.

The Facilities/Core Resources category includes programs that result in new and remodeled facilities for stem cell research as well as programs such as the Shared Laboratories Program that provides a core resource to stem cell researchers.

The Training/Career Development category includes those programs whose focus is broadening and/or strengthening the pool of stem cell researchers.

The Basic Research category includes those programs where the research focus is on addressing fundamentals of stem/progenitor cell biology.

The Translational Research category include those programs where the research focus is on translating the basic research discoveries and on addressing bottlenecks to translation through new tools and technologies.

The Development Research category includes those programs where the research is focused on the conduct of or the preparation for clinical testing of a stem cell-based therapeutics.

CIRM's Translational Portfolio, previously presented to the ICOC, includes all active projects from programs categorized as Development Research (excluding Planning Awards) as well as active projects from a subset of programs categorized as Translational Research.

The ICOC has allocated $1.28 billion to funded programs. The percentage allocation of funding by category is shown in Figure 1 below ("Funded").

Considerations for Meeting 2012 Strategic Objectives

The research funding strategy going forward is critical for positioning CIRM to achieve success with the scientific and, especially with the clinical, strategic objectives, key outcomes and associated goals. In general, achievement of the scientific objective, key outcome and associated goals are feasible within the context of the funding strategy outlined below. The following discussion focuses on considerations associated with achieving the clinical strategic objective and key outcome. Achieving the clinical key outcome necessitates planning given the costs, timeframes and probabilities of success associated with clinical development as well as the stage of maturity of the cell therapy field. The following are the specific 5-year goals proposed that addresses the clinical strategic objectives and key outcome.

Goal VIII: CIRM will have funded 10 therapies in phase 1 or 2 clinical trials, in at least 5 different therapeutic areas, based on stem cell research.

Goal IX: CIRM will have achieved clinical proof-of-concept that transplanted cells derived from pluripotent or progenitor cells can be used to restore function in disease or injury.

Industry statistics (see Appendix E for a summary of those statistics) on the duration spent in the different phases of clinical development and the probabilities of success in moving from one phase of clinical development to the next are useful in considering what it will take for CIRM to achieve clinical proof-of-concept within the next five years. The implications are:

- Over the next ~ 2 years the ICOC and CIRM must target the funding of meritorious projects already in the clinic.

- Specifically, within the next ~2 years, CIRM must fund clinical development of at least 5, and preferably more, strong candidates already in Phase 1 or in Phase 2

in order to have a reasonable chance of one successful Phase 2 outcome in 5 years (end of 2017).

- Projects that enter IND-enabling development this year are unlikely to be able to complete a Phase 2 study within five years but successful projects would contribute to CIRM's development pipeline and to the first of the above stated goals "to have funded 10 therapies in phase 1 or 2 clinical trials, in at least 5 different therapeutic areas, based on stem cell research".

Another consideration is the cost of development (see Appendix E). For the purposes of this document, assume that IND-enabling preclinical development, Phase 1 and Phase 2 studies will each cost CIRM on average $20 million.

These outcomes and the anticipated costs to achieve them are the drivers for the proposed funding strategy.

Funding to Achieve Strategies

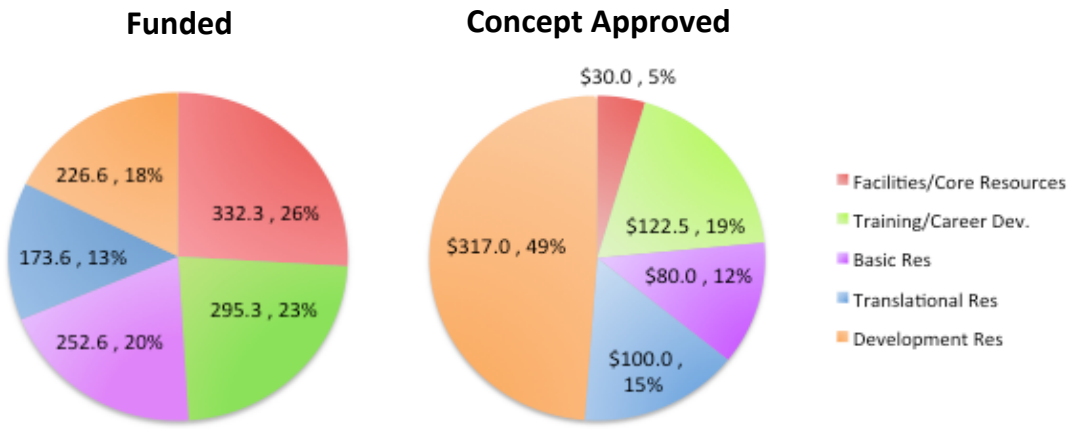
There is currently $1.48 billion in funding not yet awarded and allocated. Of that figure:

- $649 million has been approved in concept but not yet awarded, (see Table 2, Appendix D)

- $836 million is available for future programs

The percentage allocation of funding by category is shown in Figure 1 for both funded and concept approved programs. As can be seen in the figure there is shift in percentage of funding allocated to the development category when comparing the concept-approved programs to already funded programs.

Figure 1: Funded and Concept Approved Programs, Percentage allocation of funding by category



Much of the funding for Development programs that are concept approved will be awarded and funding committed in FY12/13 (see Appendix D, Figure 1). As noted in Appendix D, Table 2, assuming all the money approved in concept for Development programs is awarded, there will be an estimated addition of 16 Development projects (12 from Disease Team Therapy Development, 3 from Strategic Partnership I, and 1 from an approved transfer of the Geron Targeted Clinical Development Program). These 16 projects may include projects that are in the clinic, which could contribute to the achievement of the clinical proof-of-concept goal for a stem/progenitor–derived cell therapy

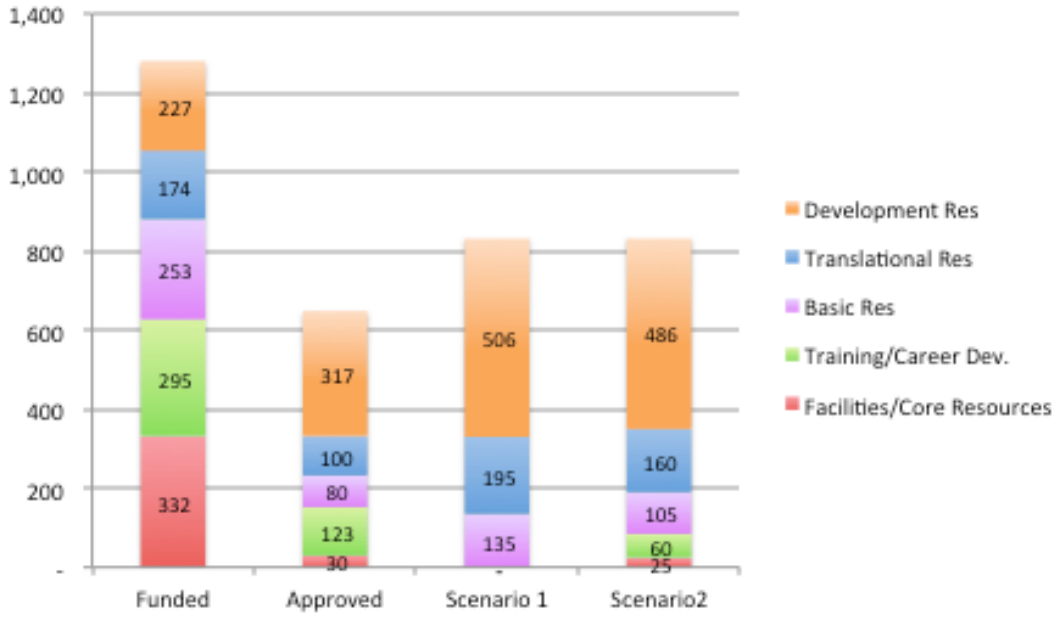
Future Funding

Given the current allocation to funded programs ($1,281 MM) and assuming full funding of all concept approved programs ($649), $836 MM is available for funding future programs.

Scenarios**:** Planning assumptions for each of 2 scenarios are outlined in Appendix D, Table 3. Differences between the two scenarios are highlighted in green. In both scenarios, development programs are front-loaded to maximize potential to achieve clinical proof-of-concept in Phase 2 for cell therapies within 5 years and to ensure that "CIRM will have funded 10 therapies in phase 1 or 2 clinical trials, in at least 5 different therapeutic areas, based on stem cell research."

The funding distribution by category for funded programs, for concept-approved programs (Approved) and for future Programs (Scenarios 1 and 2) is shown in Figure 2.

Figure 2: Funding by Category for Current, Approved and Future Programs



Implications

- Possible 25 development projects by the end of FY 13/14 (9 from either future funding scenario, 16 from concept approved programs, see above section).

- Disease Team I projects should be filing well-supported INDs in FY 13/14 and some could potentially be among the 25 projects above that receive funding to continue clinical development.

- By the end of FY13/14, at least 5 and preferably more (10) projects should be cell therapies and should be in late Phase 1 or in Phase 2, to reasonably expect clinical proof-of concept for 1 or more cell therapy candidates derived from pluripotent or progenitor cells within 5 years.

    - Key assumption: there will be 5-10 strong stem/progenitor cell derived cell therapy projects in California at these stages of clinical development in this time frame that apply for and receive CIRM funding.

- Key assumption: CIRM has the resources to support this ramp-up of activity, especially development program activity. Over the next 2 years – CIRM could go from 14 to ~39 development stage projects under active management. This entails Grants Working Group reviews of development programs 2x/year, active internal project management and periodic Clinical Development Advisors panel assessments.

Overall Funding Distribution

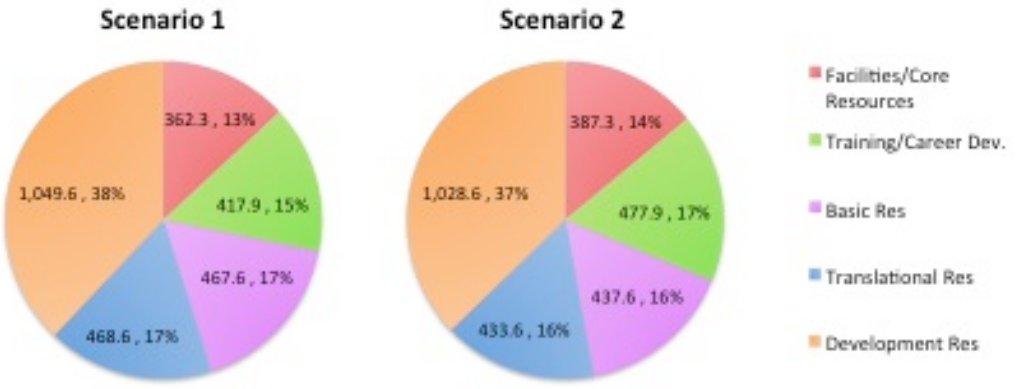
The following Table 1 summarizes the funds allocated to funded programs, the funding planned for concept-approved programs and for two scenarios for future program allocation.

Table 1: Summary of Funding Allocation

	Funded	Concept Approved	Future: Scenario 1	Future: Scenario 2	Total with Scenario 1	Total with Scenario 2
Facilities/Core Resources	332.3	30.0	0.0	25.0	**362.3**	**387.3**
Training/Career Dev.	295.3	122.5	0.0	60.0	**417.9**	**477.9**
Basic Res	252.6	80.0	135.0	105.0	**467.6**	**437.6**
Translational Res	173.6	100.0	195.0	160.0	**468.6**	**433.6**
Development Res	226.6	317.0	506.0	486.0	**1,049.6**	**1,028.6**
Total	**1,280.5**	**649.5**	**836.0**	**836.0**	**2,766.0**	**2,765.0**

Figure 3 shows the percentage distribution by category of the total of the research funding, including funded programs, concept approved programs and each of two future funding scenarios that follows from the above.

Figure 3:



This section provides a framework for discussion and decision on program funding going forward. The numbers on which it is based (funded program allocation, proposed funding for concept approved and future programs) represent the current data, which may change. Funded programs may not have all their awarded funds allocated. Similarly, program funding approved in concept may not be all awarded. What is important to consider going forward are the " buckets " of the research funding allocation in the context of the strategic objectives and the mission.

APPENDIX A - External Advisory Panel Report Summary and Senior Leadership Report on Implementation

External Advisory Panel Report

1. Executive Summary

Following a unique legislative and financing process, the California Institute for Regenerative Medicine (CIRM) began its operations in 2006. CIRM is an important new paradigm for public support of stem cell research and its translation to clinical development. After approximately six years from the initiative's approval by the voters to implementation, the organization is entering a new stage in its development. As an important part of that evolution from a start up organization, CIRM commissioned an external review of its strategy, policies and procedures.

The purpose of the review was to provide external, objective perspective and advice, to evaluate CIRM's past performance and make recommendations on changes to enable long term success. The External Advisory Panel (EAP), composed of an international group of experts in stem cell research, ethics, and business convened on October 13-15, 2010 in San Francisco and conducted comprehensive interviews with CIRM staff and its Governing Board, as well as interviews with critical stakeholder groups, including grants working group members, patient advocates, scientists, trainees and industry leaders in the stem cell community. In addition, the EAP held open public sessions on days one and three of its review and the entire session with the Governing Board's Chair and Vice Chairs was open to the public. The EAP greatly appreciated the time and effort of CIRM staff and all those who participated in this Review.

The EAP was impressed with this first stage of CIRM's operations. In a remarkably short period of time, CIRM has initiated an ambitious and comprehensive program, ranging from infrastructure support (both facilities and intellectual), the recruitment of a number of excellent young investigators to the state, training of young people, the support of a robust and broad program of research ranging from fundamental biology to preclinical to clinical trials research, strategic international partnerships and the creation of major disease teams focused on bringing novel ideas from the laboratory to the clinic. CIRM's rapid and considerable impact is further evidenced in the conclusion of a recent study by the National Science Foundation which noted that CIRM's $300 million investment in stem cell facilities, people and programs of research has already been leveraged to more than $1 billion in support.

The EAP congratulates the State of California for the foresight to create this bold initiative, as well as the Governing Board and CIRM's dedicated and talented staff for the extraordinary and rapid start up of its programs. The EAP also notes that this is

an appropriate moment for CIRM to undergo this first external review and to receive outside advice as to how best to deliver on its mandate: CIRM is about to transition from a start up to its next stage of evolution, the founding Governing Board Chair and visionary leader Robert Klein is stepping down and approximately half of CIRM's first tranche of funds have been committed to the programs summarized above.

As CIRM prepares to evolve from a young startup to a maturing organization, the EAP notes that this is a critical time for the organization: critical to ensure orderly transition of Governing Board leadership, critical that CIRM's programs evolve to ensure their alignment with the mandate from the state of California, and critical if CIRM's Governing Board decides to go back to the state of California for further support beyond its initial 10 year mandate.

It is useful to think about CIRM's organizational development of the past few years as Stage I: the Governing Board and staff are in place, many successful programs have been launched, and the impact of these programs is already becoming evident. It is now time for the leadership at CIRM, together with its stakeholders, to agree on future directions in order that CIRM move into Stage II with confidence, clarity, and appropriate programs in place. CIRM's past strategies and programs have established a strong foundation upon which it can undertake this transition. The objective of this transition into Stage II should be to position CIRM and California as a global leader in translating outstanding stem cell science into the clinic, addressing key ethical, economic, regulatory and health delivery issues emanating from regenerative medicine, and delivering health and economic benefit for California.

The EAP has a number of specific strategic recommendations for the next stage, including:

- Build on CIRM's previous and ongoing investments

- Sharpen the focus on meaningful, targeted excellence required for global leadership in the development of innovative treatments based on regenerative medicine

- Sustain a vigorous program of fundamental discovery while, at the same time, make critical choices in translating results from the laboratory to the clinic

- Transition to a much more proactive strategy of funding that aligns CIRM's peer review and other processes with its mandate of delivering new treatments to the clinic

- Adopt a porous approach to strategic opportunities, scanning the global environment for scientific advances that have the potential to enrich CIRM's portfolio

- Prioritize the investment portfolio, with input from CIRM's diverse stakeholders

- Build on and expand CIRM's current international strategy, continuing to develop strategic international partnerships that will create both scientific and financial synergies

- Assume a global leadership role in addressing not just the scientific, but also the economic, regulatory, ethical and health delivery issues associated with stem cell research and regenerative medicine

- Expand engagement with the healthcare industry and explore innovative partnerships that will catalyze the movement of research from the laboratory to the clinic

- Increase greatly public awareness within the state and internationally of CIRM's progress on all fronts of regenerative medicine and the potential and realized health and economic benefits , through outreach via patient advocacy groups, grantees and their host institutions, conferences and the internet

- Clarify the roles and responsibilities of the Governing Board and senior management and specifically between the Governing Board Chair and President in order to maximize the likelihood of success of CIRM's mission

In summary, CIRM has achieved clear and important objective measures of success in its first few years. CIRM now has the opportunity to build on these successes and make the key strategic changes required for continued progress as it transitions into Stage II of its development. California stands out for its boldness of vision in creating CIRM and funding it to scale. With continued strong leadership and vision, outstanding science, and a commitment to partnerships, the EAP believes that CIRM is well positioned to deliver significant health and economic benefits for the State of California.

Members of the External Advisory Panel

- **DR. ALAN BERNSTEIN (PANEL CHAIR)** is the Executive Director of the Global HIV Vaccine Enterprise and former President of the Canadian Institutes of Health Research.

- **DR. GEORGE DALEY** is director of Stem Cell Transplantation and the Samuel E. Lux IV Professor of
  Hematology/Oncology at Children's Hospital Boston and Dana Farber Cancer Institute, and
  Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School.

- **PROFESSOR SIR MARTIN EVANS** is a Nobel Laureate for his work on embryonic stem cells, President of Cardiff University and Professor of Mammalian Genetics at Cardiff University.

- **DR. IGOR GONDA** is the President and Chief Executive Officer of Aradigm Corporation, a public biopharmaceutical company in California specializing in the prevention and treatment of severe respiratory diseases.

- **DR. JUDY ILLES** is the Canada Research Chair in Neuroethics, Director of the National Core for Neuroethics at the University of British Columbia, Professor of Neurology, and Adjunct Professor with the School of Population and Public Health.

- **DR. RICHARD A. INSEL** is Chief Scientific Officer for the Juvenile Diabetes Research Foundation.

- **DR. RICHARD KLAUSNER** was formerly the executive director of the Program in Global Health at the Bill and Melinda Gates Foundation's, former director of the National Cancer Institute (NCI) and is a managing director of The Column Group.

- **DR. NANCY WEXLER** is the Higgins Professor of Neuropsychology in the Departments of Neurology and Psychiatry of the College of Physicians and Surgeons at Columbia University, as well as the President of the Hereditary Disease Foundation.

- **MS. SAIRA RAMASASTRY (ADVISOR TO THE EAP)** is a Managing Partner at Life Sciences Advisory, LLC, a strategic advisory services firm focused on the emerging biopharmaceutical industry

Management Response to EAP

Date: February 28, 2011
To: ICOC
From: CIRM Management

RE: Plan to Implement Recommendations of the External Review Panel

Context— As mandated in its Scientific Strategic Plan, CIRM Management organized a review of the agency's performance to assess its progress against its goals. This thorough effort culminated in December, when the report of the External Review Panel (Panel) was presented to the Governing Board.

The review was conducted by a panel of 8 experts who came from different domains that intersect with CIRM's mission. This group included stem cell scientists, leaders of private and public research funding organizations, an ethicist and representatives from the biotech industry and venture capital. To help prepare the Panel for its task CIRM Management and the Office of the Chair sent the Panel members, in advance, two documents ("A Brief History, Current Status Report and Options for Next Steps" and "Report of the Office of the Chairman to External Reviewers") designed to provide comprehensive background on CIRM's history, organization, funding programs, and accomplishments to date. Both documents are available here.

The Panel convened in San Francisco for three days in October (13-15). During that site visit the Panel met with CIRM Management, Board members and various stakeholder groups – members of the Grants Working Group, stem cell researchers, representatives of the stem cell industry, patient advocates, trainees and members of the public. Subsequently, the Panel drafted a report of its findings and recommendations and submitted it to CIRM at the end of November. The report was discussed in public at the Governing Board's meeting on December 8, 2010. Since then there have been several meetings with groups within CIRM, including one with the entire staff, to solicit input regarding the recommendations of the Panel.

In January, groups made up of members of CIRM Management and staff undertook the task of developing plans for incorporating the recommendations and spirit of the Report of the External Review Panel into CIRM's day-to-day operations. The reports from those groups were completed in early February and incorporated into this document. It is intended to stimulate strategic discussions with the Governing Board as a "next step" in defining how CIRM will reach its goals and meet its mission.

Panel Recommendations— One of the recurring messages from the Panel was to move away from traditional funding agency models. They emphasized that CIRM should adopt a "more aggressively proactive approach." CIRM should be selective;

limit its portfolio; and seek out promising projects to fund. Within that general message the Report of the Panel listed 10 specific recommendations:

1. Maintain focus on meaningful, targeted scientific excellence

2. Sustain fundamental discovery

3. Pave a path from fundamental to translational research, translational medicine, product development and healthcare delivery

4. Conduct a critical assessment and prioritization of the current portfolio with input from CIRM's diverse stakeholders

5. Develop an open innovation-focused, porous pipeline strategy

6. Assume a leadership role in the critical social, ethical, regulatory and health care delivery issues

7. Develop strategies to improve/expand engagement with industry

8. Broaden international partnerships to leverage expertise and resources

9. Expand breadth of outreach and education to ensure state-wide visibility and awareness

10. Clarify the roles and responsibilities of the Governing Board Chair and the President as it pertains to CIRM's strategic directions

Several of these recommendations have overlapping themes. Most notably, sections 3-5 all describe approaches aimed at maximizing the impact of CIRM's research investments to ensure that it reaches its scientific goals. Similarly parts of sections 3 and 7 deal with ways to better engage industry as CIRM's partner. In developing an operational plan for incorporating these recommendations, it made sense to combine some of the individual recommendations of the Panel. Thus, this document is organized into 8 sections. Some address specific recommendations of the Panel while others describe processes that are more broadly applicable and have an impact on more than one Panel recommendation.

1. Keep CIRM on the leading edge of Stem Cell Science
(Panel recommendations 1, 2)

The Panel emphasized the need for CIRM to continue funding only the best research proposals and not to lose sight of the fact that basic research will always be the engine that drives innovation. To maintain the momentum that has been created over the past four years Management believes that CIRM should:

- Develop innovative prescreening methods, such as Pre-application review, for consideration of a large number of proposals to enable selection of the most promising applications for full review;

- Continually strive to recruit world-class scientists from both academia and industry to its Grants Working Group;

- Emphasize that funding decisions should be driven by the scientific merit (score) except when there are compelling, mission-critical programmatic and portfolio reasons;

- Maintain regular, repeating funding opportunities for basic research on stem cells.

2. Optimize CIRM's portfolio (Panel recommendation 4)

The Panel encouraged CIRM to prioritize its portfolio and make difficult decisions about which programs to move forward. For programs near the translational/clinical end of the development pipeline, only those with significant promise for success in clinic trials and that have a genuine opportunity to become broadly available patient therapies should be supported. Plans for this type of prioritization review are already underway for the Disease Team projects. A Clinical Advisory Panel is being established that will include individuals with appropriate skill sets related to the delivery of preclinical and clinical research, process development and manufacturing, regulatory standards, stem cell/disease-specific biology, disease-specific clinical expertise and commercial relevance[1]. The VP, R&D will consult with these experts on project strategy, progress against milestones, and success at go-no-go decision points, and advise the President about the merit of continued support.

However, Management recommends that portfolio prioritization be examined more globally. This would require periodic surveys of the stem cell field by a group of experts to identify the most promising developments arising in stem cell science.

To perform this task, CIRM's management team and Science Office will consult with internationally recognized experts, including scientists, clinicians, regulatory experts, industry representatives, venture capitalists, and disease advocacy organizations in order to:

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[1] Members of this advisory panel will be subject to the same rigorous conflict of interest standards as scientific members of the Grants Working Group.

- Develop criteria that define projects most likely to succeed;

- Incorporate "Commercial Relevance" as a consideration in evaluating projects;

- Identify key gaps in CIRM's portfolio;

- Determine which diseases are most amenable to stem cell therapies.

These discussions will include the Chair and Vice Chairs of the Governing Board, where appropriate.

These results could then be used by CIRM Management and the Board to:

- Develop targeted translational and clinical RFAs;

- Identify specific approaches to specific diseases;

- Proactively seek to attract priority projects, research groups and companies to California.

3. Develop a proactive strategy that enables porosity of access and targets for the most promising research (Panel recommendations 3, 5, 7)

The thrust of these recommendations is that CIRM must be more aggressive and proactive in seeking out the best research, if it hopes to meet its mission. It cannot exclusively follow the traditional funding model of issuing a call for applications and then waiting to see who applies. In particular they recommended that CIRM:

- Bring promising projects into the development pipeline at all stages;

- Efficiently push forward only the most promising projects, whether or not they have been initially developed with CIRM funds;

- Find ways to better engage with industry in order to:

    - Capture industry's special capabilities (e.g. toxicity testing, manufacturing and scale-up);
    - Better meet industry timeline requirements;
    - Ensure the development projects have the best chance to attract outside investment;
    - Provide some direction to academia and industry on critical needs in specific areas based on portfolio analysis, internal assessment and external advice.

To be clear, CIRM's RFAs cover the full spectrum of the portfolio, from basic biology, to early translational to clinical development. This program encourages promising projects to enter the portfolio at any stage of development, and many have done so. However, there has been no route for scientists or companies to obtain research funds other than through the traditional RFA mechanism and there has been no concerted effort to solicit applications to support selected projects. When entities with promising new developments outside California are identified, CIRM will encourage them to partner with California institutions and apply to general or specific RFAs. The challenge is to find ways to pull projects under CIRM's umbrella while staying within the spirit and regulations that govern the Institute. Management suggests CIRM use the new advisory groups to identify the most promising stem cell research programs within and outside California.

For programs already funded by CIRM and approaching the clinical stage of the development pipeline:

- The Governing Board could create an "Opportunity Fund" to be used by the President to rapidly provide continuation funds for projects identified by VP, R&D and members of the Clinical Advisory Panel as having been highly successful and their plan to move forward is compelling and competitive as assessed against defined criteria. This process would accelerate existing promising and competitive CIRM projects and reduce the amount of time spent writing proposals and in review. CIRM already has mechanisms to discontinue or cut back projects that are not making progress. This additional tool would allow CIRM to accelerate projects that are beating expectations.

- Repeat core RFAs (Basic Biology, Early Translation, Disease Teams, and Therapy Development) on a regular basis so that new projects can enter the pipeline at the appropriate stage and those projects within the pipeline can plan for progression in the context of a competitive renewal, if they do not receive Opportunity Funds.

For Programs singled out by the priority review process but not currently funded by CIRM:

- For research groups within California, contact them and make them aware of up-coming competitions that could fund their research. Encourage collaborations among researchers with complementary expertise and invite them to apply.

- For research groups outside California, invite them to networking meetings/workshops with California researchers &/or companies that have

overlapping interests. The goals would be to establish collaborations and encourage their development in California.

The Panel emphasized that industry brings special skills and abilities to the stem cell field that are not easily handled in an academic setting or at a research institute. These include toxicity testing, product development and regulatory know-how, and the ability to develop, scale-up and optimize production for clinical use. However, many companies lack experience and expertise in grant writing, a skill perfected by academics, and their timelines are often short, especially when trying to satisfy and attract private funders.

Over the past 3-4 years CIRM has undertaken several initiatives in an effort to address concerns raised by companies interested in receiving research support. CIRM has held numerous public meetings to solicit input on intellectual property issues and on policies related to its loan program. In addition, CIRM organized a webinar on grant writing that included successful applicants from biotech companies, and it has steadily increased the number of Grants Working Group reviewers with industry experience. However, additional steps could be taken to better accommodate the private sector.

- CIRM could fund grant writing expertise for some companies that meet qualifications (e.g. at least 20 employees or $5 million in cash liquidity).

- For some RFAs in the translational arena, CIRM could require partnerships between academia and industry as a mechanism to meld the strengths from both domains.

- CIRM could create a rolling RFA that would target industry and accommodate the need for shorter timelines. The RFA would have to be specific in its focus so that only a limited number of applications would arrive at any time (for example development stage projects based on pluripotent cell-derived cell therapies). There could be 2 submission deadlines per year and review could be telephonic (as for the Research Leadership Awards) to minimize the turnaround time between submission and Governing Board decision.

4. Engage with Industry to encourage and enable commercialization of the most promising stem cell research (Panel recommendations 3, 7)

The Panel emphasized that the private sector will have to participate, if stem cell based therapies are to be readily available to doctors and patients in California. CIRM does not have adequate resources to fund Phase 3 clinical trials, and academic institutions do not have the capacity for large-scale manufacturing. If CIRM can encourage and foster stem cell related, industrial expansion in California, it will produce economic benefits to the State and health-related benefits to its citizens. In this regard, Management is proposing the following initiatives:

- Promote California-based stem cell related companies to the broader stem cell research community

    - Invite California-based research support companies to the CIRM Grantee Meeting to exhibit their stem cell related products and services;
    - Feature companies in a searchable resource portal on the CIRM website.

- Develop a process to create and recruit an Industry Advisory Board with 8-10 internationally recognized expert members representing biotech, pharma, venture capital and disease foundations. This group would be subject to the same rigorous Conflict of Interest standards followed by the scientific members of the Grants Working Group. CIRM would seek ideas from members to:

    - Make its programs attractive to industry;
    - Identify research areas most appropriate for industry;
    - Identify CIRM-funded inventions that should be patented;
    - Create opportunities for follow-on funding for CIRM-funded research programs especially those approaching clinical trial;
    - Identify and assist CIRM in fostering industry-academic partnering opportunities;
    - Identify and advance business models for regenerative medicine;

- Provide supplemental funding to grants that have already been approved by the Governing Board to help fund the costs of patent filing for the most promising stem cell technologies;

- Help broker research collaborations between academic institutions in California and pharmaceutical and large biotech companies in order to leverage CIRM's research investments, and increase the commercial appeal of candidate therapeutics;

- Create a forum for researchers to present their findings to industry and venture representatives.

5. Take a leadership role in developing national and international standards related to regulatory issues, policy and ethics (Panel recommendation 6)

The Panel recognized that CIRM's mandate, the breadth and depth of its experience and its budget give it great convening capabilities, enabling CIRM to take a leadership role on issues central to the success of the field, such as creation of regulatory pathways and standards, and social, ethical and economic issues. The Panel encouraged CIRM to take leadership roles on these matters both nationally and internationally.

In many areas this is already happening. CIRM representatives sit on the key national panels and committees that are developing these standards, and the Institute is taking the initiative to help advance the process. On-going efforts that are already in place include:

- CIRM is organizing regulatory webinars and roundtables with FDA participation.
    - CIRM has sponsored webinars focused on specific regulatory issues relevant to the stem cell field and each has included participation by FDA representatives.
    - These will continue.
    - CIRM sponsored two roundtables that brought key thought leaders to Washington, DC, to discuss issues related to regulatory oversight of stem cell research. Members of the FDA attended both. The objectives of these roundtables have included the education of researchers, CIRM and the FDA about approaches being established to ensure that breakthrough therapies will be safe and effective. CIRM plans to hold these roundtable meetings annually.
    - CIRM has conceptually approved the sponsoring of a Regenerative Medicine Translational Journal to assist information sharing in translational, preclinical and clinical research in cell therapies, including the publication of negative results.

- Members of CIRM's senior management team hold leadership positions on a number of national and international committees including:
    - International Society for Stem Cell Research (ISSCR) – the world's largest organization devoted to stem cell research;
    - Alliance for Regenerative Medicine (ARM) – a group of (mostly) industry representatives that promotes stem cell research and regenerative medicine with the federal government;
    - Interstate Alliance for Stem Cell Research (IASCR) – a national organization that promotes regulatory and ethical standards for the use of stem cells.

- CIRM must and will remain vigilant and responsive to legislative and judicial efforts to restrict stem cell research.
    - When the NIH issued new guidelines, allowing broader funding for hESC research, the NIH was sued by stem cell research opponents. While that lawsuit, Sherley v. Sebelius, was pending in the federal courts in Washington, DC, the NIH approved grant applications under the new guidelines, and research proceeded. In August 2010, the judge granted

the plaintiffs' request for an order that immediately terminated all NIH funding for human embryonic stem cell research. Following this adverse ruling the ICOC issued a resolution supporting legislation, which would permit the continued funding of stem cell research.
    - As other legislative issues arise, CIRM personnel will coordinate with the Office of the Chair to advance positions adopted by the Board.

As stem cell research advances and potential therapies move closer to the clinic, CIRM must monitor and, when possible, help resolve issues that present regulatory and ethical challenges. CIRM will need to partner with its grantees to understand these issues.

The potential challenges include:

- Donor consent – especially related to cell banking as it becomes more prevalent.

    - CIRM should consider building an educational module about consent issues for donors to banks.
    - CIRM should plan a workshop and/or develop a white paper to explore ethical issues that will arise as research with banked cells reveals health risks to the donors.

- Offshore Clinical Research – CIRM will consider decisions about overseas research where CIRM may be a collaborator– through clinical trials or co-funding partnerships on a case by case basis.

On a parallel track CIRM should develop tools on its website to educate the public on the ethics of stem cell research.

6. Expand CIRM's international partnerships and collaborations (Panel recommendation 8)

The Panel was very supportive of CIRM's network of international Collaborative Funding Partners (Collaborating Network). Not only have these collaborations leveraged funding and talent to advance CIRM's mission but they have also educated scientists around the world about the commitment to supporting stem cell research in California. The Panel recommends that this program be expanded internationally and broadened to encompass more US entities, while keeping within our legal parameters. Under Prop 71, CIRM can only fund California research.

Currently CIRM has Memoranda of Understanding ("MOU") with funding agencies in 9 countries, one state and one region within other countries, one U.S. state (Maryland), the New York Stem Cell Foundation and 1 disease foundation (JDRF).

The funding partners have made financial commitments totaling $116 million overall to these projects. The MOUs, which articulate a high level commitment to searching for opportunities to jointly support stem cell research, have led CIRM's partners to fund 15 collaborative projects through 8 RFAs. These 15 projects have leveraged $53 million in research funds from the Collaborating Networks. The main shortcomings of this program have been two-fold. First, the funding partners must work within CIRM's RFA schedule as well as its procedures, regulations and timelines. Second, collaborative projects are substantially more complex to manage and administer.

To incorporate the Panel's recommendations that these programs be expanded and that CIRM be more proactive and selective in what it funds, management recommends that CIRM, with assistance from the outside experts it consults regarding prioritization, do the following:

- Identify areas where California stem cell research community needs support from or lacks expertise that exists in other jurisdictions.

- Identify and approach additional participants for the Collaborating Network program (international and national) based upon:

    - The identified areas of California need; and
    - The strength of California's existing work and emerging programs.

- Adopt a "rolling RFA" program modeled on the CIRM Leadership Awards, which would fast-track clinical and advanced translational projects involving members of the Collaborating Network. Regular communications would allow CIRM and its partners to identify collaborative projects that satisfy the articulated criteria. Identified projects would be peer reviewed on a rolling basis.

- Develop regular communications with select disease foundations active in supporting stem cell research. Provide them opportunities to partner with CIRM in moving late stage projects into clinical development. CIRM could also include disease foundations in efforts to develop and support regulatory pathways.

To reduce some of the shortcomings of the current Collaborating Network system, CIRM should encourage selective use of a supplemental funding ("bolt-on") model as used in CIRM's agreement with JDRF and Maryland. In this model:

- Collaborating Network members would be invited to fund supplemental work by foreign scientists on projects <u>after</u> the California projects have been approved by the Governing Board.

- Under this mechanism the CIRM Science Office need not seek consensus with every Funding Partner during RFA development, grant review, and pre-funding administrative review. Collaborative grant performance monitoring could be streamlined.

- The Collaborating Network members would have more autonomy. CIRM would not set financial thresholds, timing, criteria for participation by foreign scientists, etc. In addition, Collaborating Network members would have assurance, up front, that CIRM will pay for the California portion of the projects.

7. Communicating with the public (Panel recommendation 9)

The Panel stated that CIRM has a responsibility to report to the citizens of California about the activities and successes of the Institute. It encouraged CIRM to ensure statewide visibility and awareness of the contributions that California is making to this global research effort and to provide realistic assessments of the potential benefits to the State and its citizens.

Other than funding decisions related to its largest grant programs, CIRM does not generate many hard news "pegs." Instead it needs to work with other organizations, such as its grantee institutions and patient advocate organizations to generate feature stories not pegged to specific news events.
Most scientific news related to CIRM's research investments is owned first by the scientists and institutions that CIRM funds. Thus CIRM must partner with these organizations to individually package features for broadcast and print outlets. To accomplish this CIRM should:

- Hire a Public Communications Officer who will report into the Office of the Chair – Meeting this goal will take a labor intensive process that will require fulltime attention;

- Further develop processes for interactions with the public and patient advocates;

- Develop regional strategies that pair local researchers with local patient advocates and disease organizations.

To augment this new effort on feature placements, CIRM will need to continue its efforts to place opinion pieces in key papers and to renew its efforts to reach out to editorial boards.

CIRM has now begun a concerted effort to engage with patients and disease-related

organizations and has hired a consultant team to help advance this effort. CIRM will continue to expand this engagement.

CIRM will also need to continue and increase its efforts to take information directly to the public, bypassing the old media. Over the past 3 years CIRM has made great strides in its public education efforts, most notably through a new website, fostering relationships through social media, and the development of a high school curriculum. The new website contains a robust body of information, both in written and video formats. However, early on it was of limited value to patients and disease organizations because CIRM's focus was on training, facilities and early stage research. That changed in 2010 with the first Disease Team awards. More recently, in August 2010, modifications were made to the website so that CIRM's funding portfolio can be searched in many different ways, including by disease, making it much more attractive and useful for members of the public seeking information about specific diseases. The high school curriculum will not only educate young students about stem cells, but that knowledge should also spread to family members and friends.

To expand CIRM's outreach, the Office of Science Education and Communications will:

- Summarize scientific developments associated with CIRM advances;
- Arrange webinars for direct interactions with CIRM-funded researchers;
- Create web-based interactive tools explaining how CIRM's stem cell grants are accelerating cures;
- Identify "CIRM Heroes" – Grantees who are willing and able to effectively communicate with the public about their research and other advances in the stem cell field.

For all these efforts, CIRM's Office of Science Education and Communication would need to continually provide new content for the various on-line venues to keep members of the public returning to our materials and sharing them with others. This content development effort would provide fodder for the media outreach efforts as well. The amount of effort required to produce continually renewed content cannot be under estimated.

8. Improving CIRM's governance (Panel recommendation 10)

The Panel recognized that the Governing Board had taken a very hands-on approach while CIRM was in its start-up phase, but stated, "This is an appropriate time for the Governing Board to examine its role and composition, mindful of the legal reporting, fiduciary and accountability requirements of the state of California." The Report stated that the roles and responsibilities of the Board Chair and the President need to be clearly defined, distinct and complementary.

CIRM Management agrees with that assessment.

The Governance Subcommittee and the full Governing Board have recently undertaken a survey of the Board members to assess their current views about the role of the Board Chair and the overall performance of the board as a whole. As the reviewers noted, the Board's role would be expected to evolve as CIRM's workload has grown exponentially and as CIRM has recruited a full complement of professional staff. Management looks forward to the results of that exercise and to working with the Board to implement any policy changes that are recommended.

Proposition 71 designates the President as CIRM's chief executive, while reserving several executive functions for the Board Chair. Within that legal framework, there is a need to identify the official with primary authority and accountability for each area of the agency's work. These roles will necessarily evolve as the agency matures. To succeed, the President and Chair will benefit from a cooperative working relationship and regular communication, and the flexibility to adapt as new challenges emerge.

APPENDIX B - The Process for Stakeholder Input

CIRM senior management spent considerable time from August through December gathering input for this document, first in a management retreat, then at a session with the full Science Office team and then with an extensive series of stakeholders.

CIRM's objectives of seeking stakeholder input on the 2012 Strategic Plan update were three-fold: Obtain perspectives on how well CIRM is doing in achieving its goals; determine whether the proposed revisions to CIRM's strategic objectives and strategies are appropriate; identify additional areas and/or activities for CIRM to consider or focus on moving forward. Those meetings have included:

- CIRM senior staff retreat on August 18, 2011;
- Science Team discussion on August 23, 2011;
- Process update to ICOC on August 25, 2011;
- California Stem Cell Research Leaders discussion on September 13, 2011;
- Meetings with the Public on October 25, 2011 and October 31, 2011;
- Meetings with Industry on October 27, 2011 and October 28, 2011, and meeting with Industry Advisors November 10, 2011;
- Meetings with the ICOC on October 26, 2011;
- Telecons with Collaborative Funding Partners on November 15, 2011 and November 18, 2011;
- Telecons with leaders of the Alliance for Regenerative Medicine on November 21, 2011;
- Telecons with Clinical Development Advisors on November 28, December 2, and December 5, 2011;
- Telecon with leaders of the Int'l Society for Cell Therapy on November 28, 2011;
- Telecons with Patient Advocate Organization leaders on December 2 and December 5, 2011;

Written feedback from the International Society for Stem Cell Research following

discussions internally with its Board of Directors, Executive Committee, and members of its Legislative Educational Initiative provided December 13, 2011.

These discussions were robust and insightful, often providing consistent advice across multiple stakeholder groups.

1	Established Momentum	CIRM has made great initial progress in establishing an extensive program in support of stem cell research and the advancement of science.
2	Sustainability	CIRM needs to be more aggressive in finding alternate funding resources and to implement greater creativity in identifying the types of organizations that may be able to contribute to the sustainability of CIRMs work.
3	Communication/ Public Awareness	Robust public affairs tactics are necessary, and CIRM needs to better communicate the organizational initiatives, as well as educate the public more broadly.
4	Global Networking	CIRM needs to provide greater opportunities for networking and breed collaborative projects that unite academia and industry, as well as researchers across geographic regions.
5	Process Optimization	Greater transparency in the funding process is needed, and there is a great need for the process to be less bureaucratic and easier to navigate.

The groups consistently backed the four Strategic Objectives outlined in this document.

ICOC (Board) and Stakeholder Type		Strategic Objectives: Scientific	Medical	Economic	Social
	Public Input	▪ Focus on imaging sciences ▪ Create disease "hubs" ▪ Share "lessons learned"	▪ Facilitate partnership opportunities ▪ Obtain a cure or pass a major milestone ▪ Consider surgery and somatic cell nuclear transfer	▪ Create funding opportunities ▪ Find funding partners ▪ Create three-way agreements ▪ Allow project flexibility	▪ Ensure public awareness ▪ Educate high school teachers/students ▪ Simplify presentations ▪ Create apps ▪ Create CIRM image/logo
	ICOC Input	▪ Consider sustainability	▪ Require bi-directional communication ▪ Categorize promising areas of research ▪ Reduce threshold towards translational research ▪ Define success ▪ Learn from others	▪ Create matrix to funding platform ▪ Engage and partner with HMOs ▪ Include sustainability objective to strategic objectives	▪ Promote CIRM's work ▪ Involve national stakeholder groups ▪ Create list of statistics on disease and cost ▪ Tailor strategies for various audiences ▪ Create apparatus for "stars" (i.e., "star" patients researchers) to shine
	Industry Input	▪ Share "lessons learned"	▪ Create communication bridges ▪ Split review process (academic vs. industry) ▪ Teach core processes	▪ Better communicate the details of the funding process ▪ Create a shorter approval process ▪ Create CIRM "champion" role(s)	▪ Identify and promote CIRM's expertise ▪ Educate patients on stem cell facilities as well as stem cell medicine

APPENDIX C - Progress to 2006 Five-year and Ten-year goals

Executive Summary on Accomplishments

Accomplishments to date on CIRM's five-year goals as communicated in CIRM's 2006 strategic plan serve as milestones to gauge CIRM's progress. CIRM has already met 8 of its 10 goals, is anticipated to meet a 9th goal by the end of 2012, and work is in progress on the goal of CIRM grantees demonstrating methods for transplanted tissues to evade host rejection.

Goal I – CIRM grantees will have six therapies based on stem cell research in pre-clinical development. **CIRM expects to have over 6 therapies in preclinical development before the end of 2012.**

Goal II – CIRM grantees will have developed new methods for making stem cell lines. **This strategic goal has been met.**

Goal III – CIRM grantees will have successfully created disease-specific stem cell lines for four diseases. **This strategic goal has been met**; lines for more than 4 disorders have been derived.

Goal IV – CIRM grantees will have developed methods for growing stem cells in defined media. **This strategic goal has been met.**

Goal V – CIRM will have enabled establishment of a stem cell bank. By supporting development of new lines, encouraging their registration and documentation, and ultimately providing support for self-sustaining banking and distribution efforts**, CIRM has met this strategic goal.**

Goal VI – CIRM funded investigators will have demonstrated methods for inducing immune tolerance in animal models. In June of 2010, CIRM's Stem Cell Transplantation Immunology Awards were issued to 19 investigators whose efforts are specifically devoted to understanding and overcoming immune rejection of stem cell-derived tissues. In addition to probing the immunogenic properties of stem cells, these investigators are exploring a variety of approaches for inducing tolerance or enabling transplanted tissues to evade host immunity. Several of CIRM's Disease Team grantees are also addressing this goal by devising appropriate immunosuppression and/or immunoisolation strategies as part of their preclinical development plan. It is possible that pioneering work by these groups could inform the design of similar approaches in the broader stem cell community.

Goal VII – CIRM will have increased the workforce of stem cell researchers in California. **This strategic goal has been met.**

Goal VIII – CIRM grantees will have established tools for toxicity testing based on stem cell research. **This strategic goal has been met.**

Goal IX – CIRM will have enabled effective partnerships in stem cell research between scientific teams in non-profit and commercial sectors. **This strategic goal has been met.**

Goal X – CIRM will have established national and international collaborations in stem cell research that will allow us to leverage the comparative advantage of California and our collaborators to advance toward therapies. **This strategic goal has been met.**

Accomplishments to date on CIRM's 5 year goals as communicated in CIRM's 2006 Strategic Plan

Goal I: CIRM grantees will have six therapies based on stem cell research in pre-clinical development.

CIRM defines "preclinical development" or "IND-enabling preclinical development" as the stage of translational research that includes those activities required to enable regulatory approval for the initiation and conduct of a clinical trial with a given therapeutic candidate such as process scale-up and production under stage appropriate current Good Manufacturing Practices (cGMP), GLP toxicology and other required safety studies, and pivotal preclinical pharmacology studies.

Progress: As of November 2011, CIRM has invested $225 million dollars and CIRM's Collaborative Funding Partners invested an additional S44.8 million in Disease Team Research Awards I comprising 14 grants to projects in various stages of translation ranging from late discovery research to early preclinical development. CIRM has also committed $240 million to the Disease Team Therapy Development Awards (DTTD), which will fund up to 12 projects seeking to advance a development or therapy candidate through IND-enabling or clinical studies. The first phase of DTTD launched in September 2011, when 19 groups were awarded planning grants to begin assembling teams and putting together competitive proposals for the research phase of the award. Successful applicant projects are expected to receive funding in the summer of 2012.

The goal for each Disease Team I project is an IND submission within four years, whereas the goal for Disease Team Therapy Development projects are to complete IND-enabling studies on existing development candidates and/or advance them to clinical studies within 4 years. Between these two programs alone, **CIRM expects to have over 6 therapies in preclinical development before the end of 2012.**

Outcomes:

- **14 Disease Team I Projects – the ICOC were provided an update on the Disease Teams at the March 21 session**

    - 13 projects continuing on their IND-enabling preclinical development
        - 2 projects anticipated to file IND by end of 2012
        - 1 project revised and continuing on IND-enabling preclinical development
    - 1 project did not meet Go/No-Go milestones and CIRM terminated financial disbursements in a wind down of the research on March 31, 2012

- **Disease Team Therapy Development Projects**

    - In August 2011, 19 planning grants (Part 1) were awarded to teams, many of which are in IND-enabling preclinical development, to advance development candidates to IND filing for clinical trials. Those projects that successfully compete for and obtain the research component of these awards (Part 2, to be awarded in July 2012) will allow CIRM to further surpass the milestone set forth in this goal.
    - A few additional projects, through the exceptions process, are bypassing the planning stage and will compete directly for a Disease Team Therapy Development Award, further increasing the number of projects that may impact this goal.

- **Other Projects**

    - A CIRM New Faculty grantee is performing preclinical research and development in the context of an ongoing clinical trial for treating melanoma with genetically modified CD34 cells. Specifically, an improved vector is being developed and will be produced under current Good Manufacturing Practices (cGMP). Following testing in preclinical models, the new vector could be incorporated into a parallel clinical study within the next year or two.
    - One CIRM-funded publication describes the preclinical studies of a small molecule JAK2 inhibitor that has now gone through Phase I/II studies and is the subject of several new clinical trials that are actively recruiting participants., including a phase III trial for myelofibrosis
        - Geron, I., et al. "Selective inhibition of JAK2-driven erythroid differentiation of polycythemia vera progenitors." *Cancer Cell*, 13:321, 2008. **PI: C. Jamieson (SEED, UCSD).** Demonstrated that a JAK2 (signaling kinase) inhibitor could block aberrant erythroid differentiation of polycythemia vera progenitors. Study also provided direct in vivo evidence that a particular mutation in JAK2 (JAK2V617F) is necessary and sufficient to drive aberrant myeloid differentiation characteristic of polycythemia vera. This work

provided the basis for clinical trials of the JAK2 inhibitor *TG101348 in polycythemia vera patients*.

- A publication that was co-authored by a CIRM SEED-funded grantee showed that hedgehog signaling was required for maintenance of cancer stem cells in chronic myelogenous leukemia (CML) (Zhao C., et.al. Nature 458:776, 2009). The researcher, now funded under a CIRM New Faculty II Research award, has subsequently reported in her progress report on preclinical studies on leukemic cancer stem cells with a small molecule inhibitor of the hedgehog pathway. Based in part on these studies, Pfizer has initiated Phase I clinical testing of that inhibitor in CML that is currently recruiting patients.

<u>Goal II</u>: CIRM grantees will have developed new methods for making stem cell lines.

Progress: CIRM has funded numerous projects seeking to develop or optimize methods for generating new stem cell lines. In addition to deriving new human embryonic stem cell lines from blastocysts, CIRM grantees have explored the use of transcription factors, chemicals, proteins, cell fusion, nuclear transfer, and small RNAs for generating induced pluripotent stem cells (iPSC) or other reprogrammed cell types. Investigators are creating and using new methods for producing stem cell lines with desired properties such as disease- or patient-specific phenotypes, ethnic and genetic diversity, expression of reporter constructs, correction of genetic defects, or production of therapeutic agents. In total, CIRM has funded 118 projects with the goal of a) deriving, engineering or refining a human stem cell line for research and/or development purposes; or b) developing tools or techniques for modifying or deriving stem cell line*s or derivatives. While this goal was specifically targeted by the New Cell Lines Awards, several* grants from CIRM's other initiatives have had impact, including projects from the SEED, Comprehensive, New Faculty, Tools and Technology, Early Translational, Basic Biology and Disease Team Initiatives.

Outcomes: Many CIRM grants addressing this goal are ongoing, but a number have already led to significant discoveries and insights.

- Data from progress reports indicate that 36 projects have generated novel insights and/or methods. To date, 32 publications have emerged from these studies, documenting work using small molecules and microRNAs to induce pluripotency and make significant refinements to stem cell line derivations. Some notable recent findings include:

  - Identification of a family of microRNAs whose targets promote somatic cell reprogramming in both human and mouse fibroblasts. Subramanyam et al, *Nature Biotechnology,* May 2011 and Judson et al, *Nature Biotechnology*, April 2009. **PI: R. Blelloch (SEED, New Faculty, UCSF),** with contribution from **Bridges Intern, SFSU).**

- Discovery of a rapid and efficient approach for deriving and expanding primitive neural progenitor cells from hESC, a population of keen interest to the regenerative medicine community. Li et al, *PNAS*, May 2011. **PI: S. Ding (New Faculty, Scripps**).
- New protocols for hESC derivation and xeno-free culture conditions revealed through mechanistic analyses and comparisons of hESC derived from various embryonic subpopulations. Krtolica, A., et al, *Differentiation*, April 2011. Genbacev, O., et al. *Stem Cells*, July 2011. Ilic. D, et al. *Stem Cells Dev*. November 2009. **PI: S. Fisher (Comprehensive, New Cell Lines, UCSF)**

This strategic goal has been met.

<u>Goal III</u>: CIRM grantees will have successfully created disease-specific stem cell lines for four diseases.

Progress: CIRM has funded over 40 grants with a goal of developing disease- or patient- specific stem cells lines targeting over 20 disorders. Data from progress reports indicates that many such lines have been successfully created and are being used to generate novel findings (see below).

Outcomes: Disease- or patient-specific stem cell lines (embryonic, induced pluripotent or cancer stem cell) have been created for the following disorders:

Ataxia Telangiectasia*	Lesch-Nyhan Syndrome
Alzheimer's Disease (sporadic and genetic forms)	Leukemia (CML)
apoE (Alzheimer's Disease predisposition)	Long QT Syndrome
Chronic Pulmonary Obstruction Disease	Monosomy X*
Duchenne Muscular Dystrophy	Marfan Syndrome
Ewing's Sarcoma*	Parkinson's Disease (genetic forms)*
Fanconi Anemia	$p53^{-/-}$ (cancer predisposition)*
Frontotemporal Dementia (multiple genetic forms)	Rett Syndrome*
Huntington's Disease	trisomy (various)*
ICF Syndrome	schizophrenia*

* published

Twelve publications have resulted from this work thus far. A few noteworthy examples from 2011 include:

- Byers, B. et al. *PLoS One,* November, 2011. "SNCA Triplication Parkinson's Patient's iPSC-derived DA Neurons Accumulate α-Synuclein and Are Susceptible to Oxidative Stress". **PI: R. Reijo Pera, New Cell Lines and Shared Labs, Stanford).** This study demonstrated that the relevant

Parkinson's disease (PD) mutation is intrinsically capable of perturbing normal cell function in culture, conferring a cell autonomous disease manifestation that is independent of exposure to the entire complexity of a diseased brain.

- Brennand, K. et al. *Nature,* April 2011. "Modeling schizophrenia using human induced pluripotent stem cells." **PI: F. Gage (New Cell Lines, Salk Institute) and Training Grant.** This study reports the development of hiPSC neuronal phenotypes and gene expression changes associated with schizophrenia (SCZD). SCZD hiPSC neurons showed diminished neuronal connectivity in conjunction with decreased neurite number, PSD95-protein levels, glutamate receptor expression and impairment of key signaling pathways.

- Liu, et al. *Cell Stem Cell*, May 2011. "Targeted Gene Correction of Laminopathy-Associated LMNA Mutations in Patient-Specific iPSCs". **PI: J.F. Loring (Early Translation I, Scripps Institute) and Training Grant.** The study shows that helper-dependent adenoviral vectors (HDAdVs) provide a highly efficient and safe method for correcting mutations in large genomic regions in human induced pluripotent stem cells and can also be effective in adult human mesenchymal stem cells. This type of approach could be used to generate genotype-matched cell lines for disease modeling and drug discovery and potentially also in therapeutics.

- Marchetto, M. et al. *Cell*, November 2010. "A model for neural development and treatment of Rett syndrome using human induced pluripotent stem cells." **PI: F. Gage (Comprehensive, New Cell Lines, Salk Institute).** The model generated from this data recapitulates early stages of a human neuro-developmental disease and represents a promising cellular tool for drug screening, diagnosis and personalized treatment.

This strategic goal has been met; lines for more than 4 disorders have been derived.

<u>Goal IV</u>: CIRM grantees will have developed methods for growing stem cells in defined media.

Progress: CIRM has funded 17 grants that are focused on developing methods or identifying molecules or tools that enable stem cells to grow effectively in defined, xeno-free media. In addition, efforts to develop GMP-grade cell lines or therapy candidates amongst CIRM's Development Portfolio projects could lead to insights that could further impact this goal.

Outcomes:

- Data from progress reports indicate that about 30 grants have generated new insights in this area. Some of the highlights include:

    - Use of defined, xeno-free conditions for more efficient derivation of patient-specific stem cell lines
    - Use of screening platforms and microfluidic technologies to rapidly identify ligands, chemicals and matrix formulations that promote stem cell expansion and pluripotency or replace non- defined components of culture media
    - Identification of specific molecules or compounds that promote differentiation to specific lineages including neural, cardiac and hematopoietic cell fates

- Thus far, 8 publications addressing this strategic goal have resulted from CIRM funding. Some notable findings include:

    - Hasagewa, K. et al, *Stem Cells Translational Medicine*, December 2011, "Wnt signaling orchestration with a small molecule DYRK inhibitor provides long-term xeno-free human pluripotent cell expansion" **PI: M. Pera**
    - Krtolica, A., et al, *Differentiation*, April 2011. "GROalpha regulates human embryonic stem cell self-renewal or adoption of a neuronal fate." and Ilic. D., et al. *Stem Cells Dev*. November, 2009 "Derivation of human embryonic stem cell lines from biopsied blastomeres on human feeders with minimal exposure to xenomaterials." **PI: S. Fisher (Comprehensive, New Cell Lines, UCSF)**
    - Brafman, D., et al. "Long-term human pluripotent stem cell self-renewal on synthetic polymer surfaces." *Biomaterials*, December 2010 and "Defining long-term maintenance conditions of human embryonic stem cells with arrayed microenvironment technology." *Stem Cells Dev*, March 2009. **PIs: S. Chien (SEED, UCSD), S. Varghese (New Faculty, UCSD) and K. Willert (Shared Labs, UCSD).** These publications describe the use of array technology to identify fully defined and optimized conditions for the culture and proliferation of hESCs. The authors screened extracellular matrix proteins, signaling molecules and synthetic polymers in order to develop and characterize a defined culture conditions for the long-term self-renewal of hESC lines.
    - Swistowski, A., et al. "Xeno-free defined conditions for culture of human embryonic stem cells, neural stem cells and dopaminergic neurons derived from them." *PLoS ONE*, July 2009. **PI: X. Zeng (Shared Labs, Buck Institute).** This paper describes the use of chemically defined, xeno-free media to propagate hESCs, differentiate them into human neural stem cells, induce dopaminergic neuron precursors and mature these precursors into neurons expressing midbrain and A9 dopaminergic

markers (the cells lost in Parkinson's disease). The grantee writes that this "four-step scalable process is readily transferable to a Good Manufacture Practice (GMP) facility for the production of functional dopaminergic neurons from hESCs for potential clinical uses."

This strategic goal has been met.

Goal V: CIRM will have enabled establishment of a stem cell bank.

Progress: Multiple grants have been awarded to groups developing new stem cell lines (see Five Year Goals II and III). Although CIRM has developed a system for registering and documenting these lines, recent policy changes at the National Institute of Health has led to the NIH Registry becoming the repository of choice for the research community. More recently, CIRM has developed a comprehensive initiative to support the establishment of a physical infrastructure to bank and distribute stem cells and human induced pluripotent stem cell lines of appropriate quality that have been developed, or will be developed by CIRM grantees.

Outcomes:

- As of September 2011, CIRM Grantees have reported derivation of nearly 200 human pluripotent stem cell lines, including embryonic and induced pluripotent cells, representing a diversity of disease, gender, ethnicity, and derivation methods.

- In June 2011, the ICOC approved CIRM becoming a member of the public private partnership initiative sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) at the NIH to develop and bank well characterized hiPSC lines for neurodegenerative diseases, and to make them publicly available. CIRM is contributing funds to a consortium that develops lines from patients with Huntington's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis (ALS).

- A series of RFAs are planned for 2012 to facilitate the procurement, derivation and banking of iPSC lines from patients with complex genetic disorders, and to enable banking of existing human pluripotent cell lines that have been derived by CIRM grantees and meet appropriate inclusion criteria. A cell bank will be established in California to manage and distribute these lines as a resource to the scientific community.

By supporting development of new lines, encouraging their registration and documentation, and ultimately providing support for self-sustaining banking and distribution effort, CIRM has met this strategic goal.

Goal VI: CIRM-funded investigators will have demonstrated methods for inducing immune tolerance in animal models.

Progress: In June of 2010**,** CIRM's Stem Cell Transplantation Immunology Awards were issued to 19 investigators whose efforts are specifically devoted to

understanding and overcoming immune rejection of stem cell-derived tissues. In addition to probing the immunogenic properties of stem cells, these investigators are exploring a variety of approaches for inducing tolerance or enabling transplanted tissues to evade host immunity. Several of CIRM's Disease Team Grantees are also addressing this goal by devising appropriate immunosuppression strategies as part of their preclinical development plan. It is possible that pioneering work by these groups could inform the design of similar approaches in the broader stem cell research community.

Outcomes:

- October, 2011: CIRM organized and participated in a round table discussion with the FDA to evaluate the current challenges facing cell therapy development with respect to the immune system, and the current technologies and approaches that are being used to address them.

- 19 three-year grants were awarded in the area of Stem Cell Transplantation Immunology and have been active for approximately 1 year. Approaches being explored include use of tolerogenic dendritic cells; induction of central tolerance; mixed chimerism; regeneration of thymic epithelium; manipulation of regulatory T cells or NK cells; engineering the adaptive immune system; reducing the immunogenicity of stem cells; use of *in utero* methods; various specialized biologic strategies.

- In addition to the above, CIRM has funded 10 awards across various initiatives that address this strategic goal. Data from progress reports indicate that CIRM researchers have successfully developed a tool for modulating HLA expression on hESC-derived hematopoietic stem cells; have optimized and refined protocols for differentiating pluripotent stem cells into defined populations of T cells and dendritic cells; and developed a SCID model that is capable of mounting a T cell-mediated allorejection response.

- Thus far, 6 publications addressing this strategic goal have resulted from CIRM funding. Some notable findings from 2011 include:

    - Stem cell allografts can survive when transplanted into the hippocampus. However, Chen et al (*PLoS One*, March 2011) found that MHC mismatch decreases surviving cell numbers and strongly inhibits the differentiation and retention of both graft-derived and endogenously produced new neurons. These effects were ameliorated by nonsteroidal anti-inflammatory drugs but not cyclosporine A, revealing an unexpected role for innate immunity in the survival and function of mismatched cellular grafts. **PI: T. Palmer (Comprehensive, Stanford).**
    - Cells derived from murine iPSCs elicited an immune response when transplanted into a genetically matched host, possibly due to abnormal expression of immunogenic proteins in the reprogrammed cells. This result cast doubt on the premise that autologous iPSC-derived transplants

would necessarily be tolerated, and future studies to understand and mitigate rejection of autologous tissues will be warranted. Zhao, T. et al. *Nature*, May, 2011. **PI: Y. Xu (Early Translational, UCSD**).

- Survival of human spinal stem cells after intraspinal transplantation into an SOD1 model for ALS was significantly improved by use of a combined, systemic immunosuppression regimen as opposed to monotherapy. Hefferan M., et al. *Cell Transplant*, June 2011. **PI: M. Marsala (Comprehensive)**.

<u>Goal VII</u>: CIRM will have increased the workforce of stem cell researchers in California.

Progress: CIRM continues to invest in several programs to support the training and career development of the next generation of stem cell scientists, including:

- 17 Training Grants to support graduate students, postdoctoral and clinical fellows at universities and institutes across California. These programs have recently been renewed for a third round of funding, beginning in 2012.
- 16 Bridges to Stem Cell Research Grants to provide stem cell training and education to undergraduate and Master's level students at a variety of universities and colleges across California. These programs have been extended for another three years, beginning in 2012.

- A new training program, the Creativity Awards, will be formally implemented in 2012. These grants will support summer internships for high school students in stem cell laboratories.

- $80 million has been allocated for New Faculty Physician Scientist Translational Research RFA, which will be launched in 2012.

- The Research Leadership Awards program, which enables top California institutions to recruit the most productive and rapidly rising stem cell scientists from out of state, was extended.

Outcomes:

- CIRM has supported 914 undergraduate and graduate students, postdoctoral fellows and clinical fellows through its various training grants. A pilot version of Creativity Awards supported summer internships for 22 high schools students.

- The careers of 45 investigators have been jump started through New Faculty Awards.

- Two Research Leadership Awards have enabled the successful recruitment of Dr. Robert Wechsler-Reya, from Duke University to the Sanford-Burnham Institute, and Dr. Peter Coffey from the Royal College of London to University

of California, Santa Barbara. A third award to recruit Dr. Zhigang He from Children's Hospital and Harvard Medical School to University of California, Berkeley has been approved by the ICOC.

- When last assessed, more than 130 faculty-level researchers had moved to California's non-profit institutions from around the world since CIRM began operations.

This strategic goal has been met.

<u>Goal VIII</u>: CIRM grantees will have established tools for toxicity testing based on stem cell research.

Progress: CIRM has funded two projects that explicitly target the development of assays for predicting or evaluating toxicity. In addition, a third project sought to identify agents toxic to hESCs, the insights from which could inform our understanding of developmental/reproductive toxins and their mechanisms of action. CIRM funds about 25 other projects that are seeking insights towards developing more authentic, mature heart or liver tissues, the basic tools that are needed for toxicity studies. CIRM will continue to address this goal by encouraging additional grant submissions through future Basic Biology, Early Translational and Tools and Technology initiatives.

Outcomes:

- Data from progress reports suggests that thus far, 8 projects have yielded specific tools (reporter lines, patient-specific stem cell derivatives) or insights that could be useful for predicting or evaluating developmental or cardiotoxicity.

- CIRM grantees have made excellent progress in elucidating the molecular basis of lineage specification towards the cardiac or hepatic fate, including the notable recent publication:

    - Willems, E., et al. "Small-Molecule Inhibitors of the Wnt Pathway Potently Promote Cardiomyocytes From Human Embryonic Stem Cell-Derived Mesoderm," Circ Res, July 2011. **PI: M. Mercola (Comprehensive, Sanford-Burnham)**. This study employed pharmacological inhibition of Wnt signaling via small molecules to drive human mesoderm cells to form cardiomyocytes. This method could yield novel tools for the benefit of pharmaceutical and clinical applications, including predictive toxicology.
    - Espejel, S, et al., "Induced pluripotent stem cell-derived hepatocytes have the functional and proliferative capabilities needed for liver regeneration in mice." *Journal of Clinical Investigation*. September, 2010. **PI: H. Willenbring (New Faculty, UCSF).** This study examined whether iPS cell-derived hepatocytes have both the functional and proliferative capabilities needed for liver repair in a model of liver damage and established the

feasibility of using iPS cells generated in a clinically acceptable fashion for rapid and stable liver regeneration.

- Duan, Y., et al., "Differentiation and characterization of metabolically functioning hepatocytes from human embryonic stem cells." *Stem Cells*, February 2010. **PI: M. Zern (Comprehensive, UC Davis).** This paper describes the multi-step differentiation of hESCs into cells with many of the markers and metabolic activities characteristic of primary human liver cells. While these hESC-derived hepatocytes may not be fully equivalent to mature hepatocytes, they represent an important step towards that goal and a potentially valuable tool for toxicity testing.

This strategic goal has been met.

<u>Goal IX</u>: CIRM will have enabled effective partnerships in stem cell research between scientific teams in non-profit and commercial sectors.

CIRM has funded multiple industry/nonprofit collaborations encompassing a variety of relationships and will continue to do so, particularly as more of its programs enter the translational and clinical landscapes. These partnerships are best illustrated by the Disease Team I Awards, in which teams are effectively leveraging the disparate resources and skills that will be necessary to bring such complex and ambitious projects to fruition. Examples include:

- 2 projects with principal investigators or co-principal investigators at industry and non-profit organizations

- 8 projects with academic principal investigators that include CIRM-funded, industry-based subcontracts for critical activities including GMP manufacturing, vector development, preclinical safety studies, sample and data analysis, project management, and access to specific reagents, supplies or technologies

This strategic goal has been met.

<u>Goal X</u>: CIRM will have established national and international collaborations in stem cell research that will allow us to leverage the comparative advantage of California and our collaborators to advance toward therapies.

CIRM has established 16 such partnerships and is actively pursuing additional agreements (Argentina and Brazil the end of March). From these programs, a total of 20 collaborative projects have emerged.

- **<u>Funding Agreements</u>**
  - Andalucian Initiative for Advanced Therapies (IATA)
  - State of Victoria, Australia
  - Canadian Cancer Stem Cell Consortium (CSCC)
  - Chinese Ministry of Science and Technology (MOST)
  - Medical Research Council, UK (MRC)
  - Juvenile Diabetes Research Foundation (JDRF)
  - Japanese Science and Technology Agency (JST)
  - Scottish Enterprise, Scotland
  - Spanish Ministry of Science and Innovation (MICINN)
  - Federal Ministry of Education and Research, Germany (BMBF)
  - Maryland Technology Development Corporation (TEDCO)
  - National Institutes of Health (NIH)
  - National Research Agency, France (ANR)
  - Indian Institute of Stem Cell Science and Medicine (inSTEM)
  - New York Stem Cell Foundation (NYSTEM)
  - Australia (NH&MRC)

- **<u>Awarded Projects (as of November, 2011)</u>**
  - 6 Disease Team Awards (with MRC, CSCC, BMBF, JDRF)
  - 2 Basic Biology Awards (with JST, BMBF)
  - 2 Transplantation Immunology Awards (with State of Victoria)
  - 10 Early Translational Awards (with State of Victoria, BMBF, TEDCO)
  - 1 iPSC cell line award (with NIH)

This strategic goal has been met.

Accomplishments to date on CIRM's 10 year goals as communicated in CIRM's 2006 Strategic Plan

<u>Goal I</u>: CIRM grantees will have clinical proof-of-principle that transplanted cells derived from pluripotent cells can be used to restore function for at least one disease.

In summer of 2011, CIRM issued a $25 million loan as part of its Targeted Clinical Development program to Geron Corporation, who sought to demonstrate safety and preliminary evidence of efficacy for a human embryonic stem cell-derived therapy for acute spinal cord injury. Although the study was discontinued for business reasons and funds were returned to CIRM, 5 patients have already been treated. Continued monitoring of these individuals will ensure that useful knowledge is obtained from these groundbreaking studies and inform future endeavors towards achieving this goal. In the mean time, CIRM continues to build a pipeline of potential pluripotent-derived cell therapies through the Early Translational and Disease Team Research Initiatives, which currently support 19 active projects to develop pluripotent stem cell-based therapies for 16 different indications.

Goal II: CIRM-sponsored research will have generated therapies based on stem cell research in Phase I or Phase II clinical trials for 2-4 additional diseases.

Progress: CIRM currently funds a "Development Portfolio" of 43 potential therapeutic candidates for approximately 26 different indications, a number that will increase in 2012 with funding of the Early Translational III and Disease Team Therapy Development Awards. Thirteen projects from Disease Team I are continuing in IND-enabling preclinical development, and a subset are likely to have advanced to Phase I or Phase II studies within the next few years (see Five Year Goal I).

Outcomes: CIRM has, in part, sponsored research leading to a Phase I/II clinical trial for a small molecule inhibitor of the JAK2 pathway for treating polycythemia vera and a Phase I clinical trial for a small molecule inhibitor of the hedgehog pathway for treating CML. If only a few additional IND applications emerge from the 43 potential therapeutics in CIRM's current pipeline, this goal will be achieved. Moreover, CIRM will fund several Disease Team Therapy Development Awards in 2012, some of which are expected to initiate Phase I and/or Phase II clinical studies within the next few years. Based on these estimates, CIRM is on track to reach this goal.

Goal III: CIRM funded projects will have achieved sufficient success to attract private capital for funding further clinical development of stem cell therapies.

Progress: While CIRM funded research is only just starting to move toward the clinic, CIRM is engaging in a number of actions to define pathways forward, shorten timelines and remove obstacles for those projects that demonstrate potential for clinical success. Ongoing initiatives range from promoting CIRM programs in one-on-one meetings with pharmaceutical companies, to spearheading, along with the Alliance for Regenerative Medicine, the first-ever regenerative medicine partnering and investor conference in November 2011. In addition, CIRM's board recently approved the concept for a $30 million Strategic Partnership Funding Program, which will foster collaborations of CIRM-funded researchers with partners from industry or investments from venture capital.

Outcomes: Progress towards this goal appears to be on target considering the long timeline. CIRM has learned that companies have attributed their ability to attract funding, in part, to the prospect of obtaining CIRM funding. Also, CIRM has funded, in part, research relating to the use of a small molecule inhibitor of the JAK2 pathway (owned by TargeGen), which resulted in a high impact publication prompting further research in this area. TargeGen was recently acquired by Sanofi-Aventis, who continues to explore the therapeutic potential for this drug. Viacyte very recently attracted additional funding from JDRF to their project for beta cell replacement also funded by CIRM through a Disease team I award.

Goal IV: CIRM will have funded new approaches for achieving immune tolerance for transplantation that are in pre-clinical development.

Progress: See Five Year Goal VI.

Outcomes: CIRM's Disease Team Projects are currently in IND-enabling preclinical development, each with a different strategy or consideration for addressing immune issues. One project is pursuing a novel encapsulation strategy to protect transplanted cells from host immune attack. Other projects are exploiting immune privileged sites and/or autologous cell populations to thwart or otherwise evade immune rejection. Knowledge gained from these efforts may elicit broader insights that could be applicable to other stem cell transplantation paradigms. Finally, mechanistic insights from CIRM's Stem Cell Transplantation Immunology and other research programs may lead to novel findings that will overcome existing scientific and/or regulator bottlenecks on the path to the clinic.

Goal V: Using stem cell research, CIRM-funded investigators will have established proof of principle in preclinical animal models for the treatment of 6-8 diseases.

Progress: As described previously, CIRM's Development Portfolio, which will continue to grow over the next few years, presently comprises 43 projects that are seeking to demonstrate, or already have demonstrated, proof of principle in preclinical models of disease or injury. Furthermore, several additional grants from CIRM's other programs have also led to insights and methods that impact this goal.

Outcomes:

- Diseases represented in CIRM's current Translational/Development Portfolio include type 1 diabetes, glioblastoma, cancer (hematologic and solid tumor), macular degeneration, corneal injury, epidermolysis bullosa, stroke, ALS, HIV, anemia, arthritis, Parkinson's Disease, cardiovascular damage, Alzheimer's Disease, epilepsy, muscular dystrophy, spinal cord injury, traumatic brain injury, Canavan's Disease, spinal muscular atrophy, autism, diabetic foot ulcers, osteoporotic bone fractures, liver failure and Huntington's disease.

- Analysis of recent progress reports from CIRM's ongoing grants indicate that several projects have made headway towards this goal. Examples include:

    - Demonstration of potentially beneficial effects from hESC-based cell populations in models of retinal degeneration, Parkinson Disease, radiation damage, and melanoma
    - Progress towards establishing proof of principle for bone repair, cardiovascular disease, intestinal disorder, myeloproliferative disorders, muscular dystrophy, multiple sclerosis, and HIV

- Notable recent publications include:

    - Fierro, F. A., *Stem Cells*, November 2011. "Effects on Proliferation and Differentiation of Multipotent Bone Marrow Stromal Cells Engineered to Express Growth Factors for Combined Cell and Gene Therapy." **J.A. Nolta (Early Translation, UC Davis).** This study provided scientific evidence to bolster the rationale that the therapeutic properties of mesenchymal stem cells/bone marrow stromal cells (MSCs) could be improved by genetically modifying them to express higher levels of specific growth factors. **PI: J. Nolta (Early Translational, UCD).**
    - Cho, E. et al. "MEF2C Enhances Dopaminergic Neuron Differentiation of Human Embryonic Stem Cells in a Parkinsonian Rat Model." *PLoS One* August, 2011. This publication describes functional and anatomical benefit of transplanted hESC-derived neural progenitors that are programmed to express constitutively active MEF2C in a rat model of Parkinson's disease. **PI: S. Lipton (Comprehensive, Sanford Burnham Institute).**
    - Minear, S., *Sci Trans Med*, April 2010. "Wnt proteins promote bone regeneration" **Co-Investigator: J. Helms (Early Translational, Stanford).** This study demonstrated that bone healing after injury is accelerated when Wnt signaling is increased, either by genetic mutation or upon delivery of purified Wnt3a protein to skeletal defects, which stimulates the proliferation of progenitor cells and accelerates their differentiation into osteoblasts, the cells responsible for bone growth. As Wnt signaling is conserved across mammals in tissue repair, these findings may find widespread application in regenerative medicine.
    - Rossi, S. L., et al. "Histological and functional benefit following transplantation of motor neuron progenitors to the injured rat spinal cord." *PLoS ONE*, July 2010. **PI: H. Keirstead (Comprehensive, UC Irvine).** This publication describes the transplantation of hESC-derived motor neuron progenitors (MNPs) to treat a rat model of spinal cord injury. While these MNPs didn't integrate at the site of injury, they improved endogenous neuronal survival, neurite branching and performance on a balance beam task, presumably through trophic effects.
    - Acharya, M., et al. "Rescue of radiation-induced cognitive impairment through cranial transplantation of human embryonic stem cells." *Proc. Natl. Acad. Sci. USA,* November 2009. **PI: C. Limoli (SEED, UCI).** This paper demonstrated the potential for hESCs to ameliorate radiation-induced tissue injury (such as that which occurs during treatment of certain cancers), and that such strategies may provide useful interventions for reducing the adverse effects of irradiation on cognition.
    - Blurton-Jones, M., et al. "Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease." *Proc. Natl. Acad. Sci. USA*, July 2009. **PI: F. LaFerla (SEED, UC Irvine), Postdoctoral trainee: M. Blurton-Jones.** This paper reported memory improvement following mouse NSC transplant in a mouse model of Alzheimer's disease. Dr.

LaFerla is the recipient of an Early Translational award to expand upon these findings using hESC-derived NSCs.

- Sun, L. et al. "Mesenchymal stem cell transplantation reverses multiorgan dysfunction in systemic lupus erythematosus mice and humans." *Stem Cells*, June 2009. **PI: S. Shi (New Faculty, USC).** This paper reported that allogeneic mouse mesenchymal stem cell (MSC) transplant improved multiple organ function and measures of immune function in a mouse model of systemic lupus erythematosus (SLE). This paper further demonstrated the safety and efficacy of allogeneic hMSC transplant in 4 human SLE patients, but that part of the study was performed in China and not funded by CIRM.

Goal VI: CIRM-funded investigators will have created disease-specific cell lines for 20-30 diseases and used them to gain new information about pathogenesis, to identify new drug targets and to discover new therapeutics.

Progress and Outcomes: See progress for Five Year Goal III. CIRM researchers have already developed at least 20 different disease/patient lines and have used them to explore disease pathology. Such lines are also being used to identify drug targets and novel therapeutic approaches.

Goal VII: CIRM will have enabled development of new procedures for the production of a variety of stem and/or progenitor cells that meet GMP requirements.

Progress: CIRM is currently funding 60 grants that either directly or indirectly impact this goal. Included among these are:

- 5 grants developing methods or cell lines specifically for GMP production
- 33 translational cell therapy projects (in CIRM's current Development Portfolio) which will, if successful, develop GMP and GMP-compatible methods, cell lines and banks over the course of their progression towards an IND application
- 10 projects addressing quality control of cell preparations, assays for detecting teratomas, assurance of cell integrity and functionality
- Also see Five Year Goal IV: 12 additional grants seeking to develop defined media conditions could lead to insights that may indirectly impact this goal

Outcomes: While still in the early stages, several projects have generated preliminary data by comparing and evaluating growth and behavior parameters for multiple pluripotent cell lines or cell therapy candidates using different conditions and media formulations for expansion. Most recently, CIRM investigators published

a significant report describing GMP-compatible procedures for deriving tissues from somatic cells via a pluripotent (hiPSC) intermediate (see below).

- Karumbayaram, S. et al, "From Skin Biopsy to Neurons through a Pluripotent Intermediate Under Good Manufacturing Practice Protocols" *Stem Cells Trans Med,* December 2011. The authors describe a successful framework for producing GMP-grade derivatives of hiPSCs that are entirely free of xenobiotic exposure, from collection of patient samples through reprogramming, cell maintenance, identification of reprogramming vector integration sites, and terminal differentiation of clinically relevant cells. A primary set of Standard Operating Procedures for these practices were provided to facilitate their widespread adoption. **CIRM PIs: W. Lowry** (**SEED, Basic Biology**), **K. Plath** (**New Faculty, Basic Biology), J. Zack (New Cell Lines**), **A. Clark** (**New Cell Lines**), **UCLA.**

<u>Goal VIII</u>: Through research sponsored by CIRM and others, a thorough description of the steps of differentiation leading to the production of the various cells of the body will have been achieved.

Progress: CIRM has funded about 175 projects that could inform our understanding of the mechanisms by which cell identity is established. CIRM will continue to target additional studies in this area, particularly through the ongoing Basic Biology Initiative. Currently funded grants include:

- About 70 grants studying specification of neural fate
- About 20 grants investigating the cardiac lineage
- About 30 grants focused on hematopoietic and/or immune differentiation
- Multiple grants focused differentiation towards skeletal muscle, liver, pancreas, retinal epithelium, trophoblast and other early lineages
- One or two grants each exploring specification of lung, kidney, bladder, vascular, skin, hair cells cells, bone/cartilage, germ cells, intestine, and/or dental fates

Outcomes: Major strides have been made in understanding differentiation into many cell lineages. Most of CIRM's strategic impacts, thus far, have been towards this goal and derive largely from the earliest rounds of research funding, the SEED, Comprehensive and New Faculty Awards.

- Analysis of progress reports from CIRM's active and recently concluded grants suggest that 118 grants thus have had measurable impacts on this strategic goal, many of which have yet to be published

- To date, CIRM grantees have produced about 90 publications detailing aspects of the differentiation process of stem/progenitor cells into various phenotypes. Some notable recent examples include the following:

    - Ritner, C. et al. "An engineered cardiac reporter cell line identifies human embryonic stem cell-derived myocardial precursors." *PLoS One,* January 2011. **PI: H. Bernstein (Comprehensive, UCSF).** The investigators identified heart stem cells derived from hESCs and showed that they could give rise to all of the different types of heart muscle found in the patients with heart disease.
    - Pozniak, C.D., et al. "Sox10 directs neural stem cells toward the oligodendrocyte lineage by decreasing Suppressor of Fused expression" *PNAS*, Nov 2010. **PI: S.J. Pleasure (Comprehensive, UCSF)**. Oligodendrocyte precursor cells (OPCs) are lineage-restricted progenitors generally limited *in vivo* to producing oligodendrocytes. This study shows that the certain transcription factors can induce multipotent neural precursor cells (NPCs) from the early postnatal subventricular zone (SVZ) to become OPCs in an autonomous manner. Mechanisms controlling genesis of OPCs are of interest because of their importance in myelin development and their potential for regenerative therapies in multiple sclerosis and dysmyelinating syndromes.
    - Oshima, K., et al. "Mechanosensitive hair cell-like cells from embryonic and induced pluripotent stem cells." *Cell*, May 2010. **PI: S. Heller (Comprehensive, Stanford).** In this study, the authors describe a stepwise protocol for directing mouse embryonic stem and induced pluripotent stem cells towards a hair cell-like fate. Hair cells are specialized mechanosensory cells that play a central role in hearing and balance. Cells produced from this methodology possessed sterociliary bundles and responded to mechanical stimulation. This study lays the foundation for future therapeutic advances for treating hearing loss due to hair cell damage.
    - Cordes, K.R., et al. "miR-145 and miR-143 regulate smooth muscle cell fate and plasticity." *Nature,* 2009. **PI: D. Srivastava (Comprehensive, Gladstone Institute)** MicroRNAs are regulators of myriad cellular events, but evidence for a single microRNA that can efficiently differentiate multipotent stem cells into a specific lineage or regulate direct reprogramming of cells into an alternative cell fate has been elusive. These findings demonstrate that a specific microRNA can direct the smooth muscle fate and that a combination of microRNAs functions to regulate the quiescent versus proliferative phenotype of smooth muscle cells.
    - Karumbayaram, S., et al. "Directed differentiation of human-induced pluripotent stem cells generates active motor neurons." *Stem Cells*, April 2009. **PI: W.E. Lowry (SEED, UCLA).** The authors found that human induced pluripotent stem (iPS) cells could be differentiated to form motor

neurons with a similar efficiency as hESCs. This represents the first demonstration that human iPS-derived cells are able to generate electrically active motor neurons and demonstrates the feasibility of using iPS-derived motor neuron progenitors and motor neurons in regenerative medicine applications and *in vitro* modeling of motor neuron diseases.

- Oh, S., et al. "Stem cell fate dictated solely by altered nanotube dimension." *Proc. Natl. Acad. Sci. USA*, January 2009. **PI: S. Chien (Comprehensive, UCSD); Trainee: S. Oh.** This paper demonstrated that engineered microenvironments could be used to direct the fate of stem cells. In this case, the dimensions of nanotubular-shaped surface structure (geometric cues) could be manipulated to either augment human mesenchymal stem cell (hMSC) adhesion, or specify differentiation into osteoblasts.

Goal IX: Through research sponsored by CIRM and others, the mechanisms regulating the self-renewal and oncogenic potential of embryonic stem cells and their derivatives will have been identified and characterized.

Progress: CIRM has funded 133 grants with the potential to impact this goal. Included amongst these projects are:

- Those that elucidate oncogenic mechanisms (genetic instability, tumor suppressor function) in stem cells
- Mechanisms of self-renewal in pluripotent, adult and cancer stem cells
- Mechanisms by which pluripotency can be established or maintained
- Non-viral methods for induction of pluripotency
- Evaluation and mitigation of teratoma risk in stem cells and their derivatives
- Consequences of reprogramming and culturing methods on genetic and epigenetic integrity of stem cells

Outcomes: Analyses of progress reports indicate that more than 70 projects have had substantial and/or measurable impacts on this goal, many of which have yet to be published. In addition, CIRM funding has contributed to more than 44 publications describing the mechanisms regulating the self-renewal and oncogenic potential of embryonic stem cells and their derivatives. These publications include:

- Gore, A., et al. "Somatic coding mutations in human induced pluripotent stem cells." *Nature*, Mar 2011. **PI: K. Zhang; L.S. Goldstein (Comprehensive and Training, UCSD)**. This study compared 22 human induced pluripotent stem cell lines (hiPSC) reprogrammed using five different methods and showed that each line contained an average of five

protein-coding point mutations in the regions sampled. The majority of these mutations were non-synonymous, nonsense or splice variants, and were enriched in genes mutated or having causative effects in cancers. At least half of these mutations pre-existed in the fibroblast progenitors at low frequencies, whereas the remainder occurred during or after reprogramming. These data suggest that extensive genetic screening may be necessary to ensure hiPSC safety before clinical use.

- Hawkins, R. D., et al. "Distinct epigenomic landscapes of pluripotent and lineage-committed human cells." *Cell Stem Cell*, May 2010. **PI: B. Ren (SEED, New Faculty II, Ludwig Institute).** This paper reported that hESCs differ vastly from their lineage-committed progeny in their DNA modification profile, or epigenome. The group analyzed different types of DNA modifications in different cell types using high-throughput, genome-wide approaches. The differences they discovered between hESCs and their differentiated progeny may comprise novel epigenetic mechanisms underlying pluripotency and lineage commitment in human cells.
- Lee, A. S., et al., "Effects of cell number on teratoma formation by human embryonic stem cells." *Cell Cycle*, August 2009. **PI: J. Wu (SEED, Comprehensive, Stanford).** In this paper Dr. Wu's group utilized fluorescent reporter genes and long-term, non-invasive imaging techniques to determine the minimum number of hESCs required for teratoma formation in immunodeficient mice. They found that a minimum of 100,000 hESCs transplanted into the heart and 10,000 hESCs into skeletal muscle were required, demonstrating that both cell number and transplant site play important roles in teratoma formation.
- Gaspar-Maia, A., et al. "Chd1 regulates open chromatin and pluripotency of embryonic stem cells." *Nature*, July 2009. **PI: Miguel Ramalho-Santos (SEED & New Cell Lines, UCSF).** This paper reports the identification of a protein, Chd1, required for hESC self-renewal and pluripotency as well as the epigenetic mechanism responsible for this regulation. This discovery will impact work on stem cell differentiation, reprogramming and oncogenicity.
- Xu, N., et al. "MicroRNA-145 regulates OCT4, SOX2, and KLF4 and represses pluripotency in human embryonic stem cells." *Cell*, May 2009. **Trainee: Na Xu (UC Santa Barbara).** This paper reports the identification of a novel microRNA regulator of hESC self-renewal and pluripotency. The authors demonstrated that this microRNA directly regulates known transcription factors responsible for pluripotency, and its expression inhibits hESC self-renewal. This is an important discovery with implications for controlling the differentiation and potential oncogenicity of hESCs.
- Zhu S, st al. "A small molecule primes embryonic stem cells for differentiation." *Cell Stem Cell*. May, 2009. **PI Schultz, SEED, Scripps)**. The authors utilized a high-content screen to identify stauprimide, a small molecule that interacts with NME2 and inhibits its nuclear localization, thereby leading to downregulation of c-Myc, a key regulator of the

pluripotent state. These findings identified a chemical tool that primes ESCs for efficient differentiation and reveals an important role for NME2 in ESC self-renewal.

<u>Goal X</u>: CIRM will have enabled development of new methods for tissue replacement based on stem cell research.

Progress: CIRM is funding a significant number of grants that address this goal:

- 27 grants exploring the use of matrices, biomaterials, co-culture techniques or scaffolding to control cell fate/ improve cell authenticity or function

- An additional 22 grants exploring the effects of cellular microenvironment or niche on cell behavior

Recently, CIRM has designated tissue engineering as one of several priority areas to be targeted by the Basic Biology IV Awards, which was released in November of 2011. Moreover, CIRM has organized a workshop on Tissue Engineering that convened in January of 2012. Here, leading experts in the field discussed the potential opportunities and challenges, including immunological issues, scaffold choice, translation/scale-up, and funding, in tissue engineering whereby CIRM might make a contribution.

Outcomes: While most grants in this area were funded only recently, CIRM investigators have already generated novel insights with the potential to impact our understanding of tissue architecture, particularly in the areas of cardiac biology but also in such organs as the eye, the brain, intestine and liver. CIRM has contributed funding towards 30 publications that focus on tissue engineering, tissue regeneration/replacement, and/or microenvironment interactions of stem cells. Notable examples include:

- Zhou, P., *Liver Transpl*, 2011. "Decellularized liver matrix as a carrier for the transplantation of human fetal and primary hepatocytes in mice." **PI: M. Zern (Comprehensive, UCD).** Efforts improve the level of engraftment of primary hepatocytes upon transplantation led to the discovery that decellularized liver matrix provides an excellent environment for long-term survival and maintenance of the hepatic phenotype.
- Gilbert, P. M., et al. "Substrate Elasticity Regulates Skeletal Muscle Stem Cell Self-Renewal in Culture." *Science*, July 2010. **PI: H. Blau (Tools & Technologies I, Stanford).** In this groundbreaking study, the authors report that freshly isolated muscle stem cells (MuSCs) could be maintained on a bioengineered substrate that recapitulates key biophysical and biochemical niche features. Furthermore, these MuSCs contributed extensively to muscle regeneration when transplanted into mice. This study provided novel evidence that by recapitulating physiological tissue rigidity, propagation of adult muscle stem cells was possible, renewing the promise of cell-based therapies for treating muscle wasting diseases.

- Yu, J., et al. “The use of human mesenchymal stem cells encapsulated in RGD modified alginate microspheres in the repair of myocardial infarction in the rat.” *Biomaterial*, June 2010. **PI: R. Lee (Comprehensive, UCSF).** The combination of scaffold material and cell transplantation therapy has been extensively investigated in cardiac tissue engineering. However, many polymers are difficult to administer or lack the structural integrity to restore left ventricle function. This study developed a technique using human mesenchymal stem cells (hMSCs) encapsulated in RGD modified alginate microspheres that were capable of facilitating myocardial repair. The surface modification and microencapsulation techniques were successfully combined with cell transplantation, which led to the maintenance of left ventricle geometry, preservation of left ventricle function, increase of angiogenesis and improvement of cell survival.
- Nakayama, K. H., et al. “Decellularized rhesus monkey kidney as a three-dimensional scaffold for renal tissue engineering.” *Tissue Eng Part A*, February 2010. **PI: A. Tarantal (Comprehensive, UC Davis). Trainee: K. H. Nakayama.** This paper describes the optimization of kidney decellularization techniques and the characterization of the resulting structures. The authors demonstrate that decellularized kidney sections retain critical properties necessary for use as a three-dimensional scaffold. This study represents an important first step toward new strategies for renal tissue engineering and repair.

APPENDIX D - Supporting Data for Research Funding Projections

The following Table summarizes RFA programs that have been funded by the ICOC

Table 1: Funded Programs as of 2/2012

RFA/PA	RFA Program	Concept Approved ($MM)	# Awards	Current Allocation ($MM)	RFA Status	RFA Category
RFA 07-01	Shared Research Laboratories and Stem Cell Techniques Courses (includes extension)	70.5	17	69.3	Ongoing	Facilities, Core Resources
RFA 07-03	Major Facilities Grant Program	227.0	12	270.9	Ongoing	Facilities, Core Resources
RFA 05-01	Training Program 1	46.9	16	33.2	Closed	Training, Career Dev
RFA 07-02	New Faculty Awards	85.0	22	50.6	Ongoing	Training, Career Dev
RFA 08-01	New Faculty Awards II	41.0	23	58.2	Ongoing	Training, Career Dev
RFA 08-03	Training Program II (includes extension)	94.8	17	91.3	Ongoing	Training, Career Dev
RFA 08-04	Bridges to Stem Cell Research Awards (includes extension)	45.0	16	50.2	Ongoing	Training, Career Dev
RFA 09-04	Research Leadership Awards (to date)	16.7	3	10.8	Ongoing	Training, Career Dev
PA 11-01	Visiting Faculty Supplement (to date - out of 6.6 MM)	0.2	2	0.2	Ongoing	Training, Career Dev
RFA 06-01	SEED Grant Program	24.0	73	41.5	Closed	Basic Res
RFA 06-02	Comprehensive Research Grant Program	80.0	28	66.5	Ongoing	Basic Res
RFA 07-05	New Cell Lines Awards	25.0	17	24.4	Ongoing	Basic Res
RFA 08-02	Tools & Technology Awards	20.0	23	19.2	Ongoing	Basic Res
PA 08-06	Conference Grants (0.3 MM/yr)	0.9	33	0.8	Ongoing	Basic Res
RFA 08-07	Basic Biology Awards I-1	30.0	12	15.6	Ongoing	Basic Res
RFA 09-02	Basic Biology Awards I-2 (II)	30.0	16	21.2	Ongoing	Basic Res
RFA 09-03	Stem Cell Transplant Immunology	30.0	19	24.5	Ongoing	Basic Res
RFA 10-04	Basic Biology Awards III	45.0	27	36.6	Ongoing	Basic Res
	(FP 05-2011) CIRM/NIH iPSC Consortium	0.3		0.3	Ongoing	Basic Res
RFA 08-05	Early Translational Research Awards	60.0	16	71.9	Ongoing	Translational Res
RFA 10-01	Early Translational II Research Awards	80.0	21	69.3	Ongoing	Translational Res
RFA 10-02	Tools & Technology Awards for Translational Bottlenecks (TnT II)	40.0	20	32.7	Ongoing	Translational Res
RFA 07-04	Disease Team Planning Award	1.0	22	0.9	Closed	Development Res
RFA 09-01	Disease Team Research Award	210.0	14	224.1	Ongoing	Development Res
RFA 10-03	Targeted Clinical Development Awards	50.0	1	-	N/A	Development Res
RFA 10-05	Disease Team Therapy Development Awards - Planning	3.3	19	1.7	Ongoing	Development Res
	TOTAL	**1,356.6**	**489**	**1,286.1**		

Concept Approved Programs

The following Table 2 summarizes programs that have been approved in concept by the ICOC, but where funds have not yet been awarded.

Table 2: Concept Approved Programs as of 2/2012

RFA/PA	RFA Program	Concept Approved ($MM)	# Awards (estimate)	RFA Status	RFA Category
RFA 12-02	Human Pluripotent Stem Cell Initiative: hiPSC Disease Lines Award	4.0	3-10	In Progress	Facilities, Core Resources
RFA 12-03	Human Pluripotent Stem Cell Initiative: Core hiPSC Derivation Award	16.0	1	In Progress	Facilities, Core Resources
RFA 12-04	Human Pluripotent Stem Cell Initiative: hPSC Bank Award	10.0	1	In Progress	Facilities, Core Resources
RFA 09-04	Research Leadership Awards (remaining)	33.3	6	Open	Training, Career Dev
RFA 11-01	Visiting Faculty Supplement (remaining)	6.4	28	Open	Training, Career Dev
RFA 11-04	Creativity Awards	3.0	10	Posted	Training, Career Dev
RFA 12-01	New Faculty Physician Scientist Translational Research	80.0	20	In Progress	Training, Career Dev
RFA 11-03	Basic Biology Awards IV	35.0	20	Posted	Basic Res
	Stem Cell Genomics Centers of Excellence	40.0	2	In Progress	Basic Res
	Opportunity Fund: Patent	5.0		In Progress	Basic Res
RFA 11-02	Early Translational Award III	95.0	20	Posted	Translational Res
	Opportunity Fund: External Innovation	15.0	30	In Progress	Translational, Development Res
RFA 10-03	Targeted Clinical Development: Transfer	25.0	1	TBD	Development Res
RFA 10-05	Disease Team Therapy Development Awards - Research	240.0	12	Posted	Development Res
PA 12-05	Opportunity Fund: Strategic Partner Awards	30.0	3	In Progress	Development Res
	Opportunity Fund: Bridging Fund	12.0	4	In Progress	Development Res
	TOTAL	**649.7**	**161-168**		

Scenarios

Planning assumptions for each of 2 scenarios are outlined in the following Table 3. Differences between the two scenarios are highlighted in green. In both scenarios, development programs are front-loaded to maximize potential to achieve clinical proof-of-concept in Phase 2 for cell therapies within 5 years and to ensure that "CIRM will have funded 10 therapies in phase 1 or 2 clinical trials, in at least 5 different therapeutic areas, based on stem cell research.

Table 3: Future Funding Scenarios

Category	Scenario 1	Scenario 2
Facilities & Core Resources	• No additional extension of Shared Labs program	• Shared Labs program extended
Training, Career Development	• No extensions of Training, Bridges or Creativity programs	• Bridges extended • Training III at reduced funding ($48 to $30)
Fundamental Research	• New Basic Biology RFA funding starts annually through 2016 ($35MM each thru BB7, $30 MM BB8)	• New Basic Biology RFA funding starts annually through 2015 ($35MM each thru BB7)
Translational Research	• Early Translation – 2 new rounds (ET4, $70MM; ET5 $65MM) • Tools & Technologies III @ $30MM • Translation-focused RFA @ $30MM	• Early Translation – 2 new rounds (ET4, $70MM; ET5 $65MM) • Tools & Technologies III @ $30MM
Development	• Alpha Clinics: $60 MM • New Development Programs including Disease Team (2 new rounds) and New Strategic Partner &/or Clinical Development programs (limited # projects, 2x/year); funding: – FY13/14: $180 MM – FY14/15: $100 MM – FY15/16: $100 MM – FY16/17: $60 MM • New Bridging Funding - $6 MM	• Alpha Clinics: $60 MM • New Development Programs including Disease Team (2 new rounds) and New Strategic Partner &/or Clinical Development programs (limited # projects, 2x/year); funding: – FY13/14: $180 MM – FY14/15: $100 MM – FY15/16: $100 MM – FY16/17: $40 MM • New Bridging Funding - $6 MM
Last Funding Start	FY16/17	FY16/17
Last Funding	FY19/20	FY19/20

In Figure 1, the funds awarded and funded (Notice of Grant Award issued) by fiscal year are shown for funded, concept approved and new (future) RFA programs for Scenarios 1 and 2.

Figure 1:

APPENDIX E - Drug Development Statistics

Pharmaceutical, bio-pharmaceutical and biotech industry statistics were used as benchmarks for determining the extent and timing of preclinical and clinical research and development activities likely to be necessary to achieve the clinical strategic objective and associated key outcome and 5 year goal These industry statistics are dominated by small molecule therapeutics and to a lesser extent, biologics such as monoclonal antibodies and therapeutic proteins, all of which have well understood manufacturing and regulatory paths.. There are no industry benchmarks for cell therapeutics. For the projects that CIRM funds, which tend to employ novel therapeutic approaches and novel technologies, the most conservative of a given range is probably the more realistic.

Assumptions on Phase Dwell Times

Phase	Phase Duration [1-3] (Years)
Preclinical Development	1-3
Phase 1	1.0 – 1.8
Phase 2	1.8 – 3.8

1. PAREXEL's Pharmaceutical Statistical R&D Sourcebook 2005/2006 pp. 160-162
2. Dickson, M. and Gagnon J.P. (2004): Nature Reviews Drug Disc. 3:417-429
3. PAREXEL's Pharmaceutical Statistical R&D Sourcebook 2009/2010 pp. 204, 216

Probabilities of Technical Success

	From Pre-Clinical Development to Phase 1 (%)	From Phase 1 to Phase 2 (%)	From Phase 2 to Phase 3 (%)*
Industry [5]		62	38
Industry [4]		71	44
Industry [6]	66	66	37
Industry [7]			27.5
Industry [8]			22.5

* The phase 2 to phase 3 transition probability is included here as clinical proof-of-concept, that is an indication of clinical efficacy, is typically assessed during phase 2 clinical studies and in conjunction with continued safety assessment, drives the decision to proceed to phase 3 pivotal trials.

4. DiMasi, J.A. et.al. (2004) Drug Information Journal 38:211-223.
5. Kola, I. And J. Landis (2004) Nature Reviews Drug Disc. 3: 711-15 (also in PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2009/2010, p226).
6. CMR Industry survey based on NME entering clinical phase in years 1996 -1998; tracked through end of 2001, in PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2005/2006, p. 190
7. Steven Paul, head of Lilly Research from PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2009/2010, p226
8. Trevor Mundel, global head of development at Novartis Pharmaceuticals, from PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2009/2010, p226

Assumptions on Phase Costs

Phase	Mean Cost, $MM, 2003 study (9)	Mean Cost, $MM, 2006 study (10)	Mean Cost, $MM, 2008 study (11)
Phase 1	15.2	32.2	16.8
Phase 2	23.5, 41.7*	31.6	33.6

* Mean Phase 2 cost of subset of therapeutics that were subsequently approved as compared to the mean Phase 2 cost of all therapeutics.

9. DiMasi, J.A. et. al. (2003) J. Health Econ.22:151-185 and in PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2009/2010, p198-199. Examined drugs first tested in humans in the period 1983 and 1994 with status update information through early 2001. Includes more than 500 NME (New Molecular Entities) dominated by small molecules.
10. Tufts Center for Drug Development, December 2006; from PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2009/2010, p182.
11. 2008 study from Federal Trade Commission; from PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2009/2010, p173.