

2009

2010

STRATEGIC PLAN UPDATE

Accelerating the Opportunity for Cures



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INTRODUCTION

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 over at least 10 years to support stem cell research in California.¹ The goal of the initiative 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.”

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 published its first scientific strategic plan, which served as the blueprint for CIRM’s scientific programs and procedures for program implementation. CIRM’s current leaders extend their deepest congratulations and gratitude to the authors, contributors and science team that developed the 2006 plan. The 2006 strategic plan has served the institute well and has been of enormous value in guiding CIRM to remarkable progress. CIRM continues to rely on that plan as the foundation upon which this update is based.

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 — flexible in response to its successes and failures, and opportunistic in capitalizing on unforeseen scientific developments.” Formal assessment by an outside panel and revision as necessary of the 2006 plan was 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. As we approached the halfway point to this review CIRM leadership felt it was imperative to revisit the plan and to consider:

- strategic adjustments to reflect the current state of the field; and
- the institute’s operations compared with what were outlined in the operational section of the 2006 plan (*A Fast Start: The First 1,000 Days*).

The purpose of this 2009/2010 strategic plan update, *Accelerating the Opportunities for Cures*, is to build on the solid foundation of the 2006 plan by identifying new research directions for CIRM that reflect the rapidly changing scientific landscape of stem cell science and

¹ An additional \$3 billion in interest payments will be spent over 35 years, creating the total investment of \$6 billion.

amalgamate the evolving thinking of CIRM's governing board (the Independent Citizens Oversight Committee, ICOC) and of CIRM's staff and many stakeholders regarding the most efficient means of implementing operations of CIRM's goals. The governing board and staff have already approved or implemented several strategic and operational diversions from the 2006 plan, particularly the specific steps outlined in the operational outline of *The First 1,000 Days*. More change is envisioned if CIRM is to maintain consistency with the core values and principles outlined in 2006: accountability, adaptability and innovation.

The document also includes input from its stakeholders. CIRM held four public meetings in Southern and Northern California that were attended by members of the public, patient advocates, scientific researchers and academics, and leaders in industry, soliciting their input into this update:

- February 3, 2009 (focusing on industry) at Exelixis in South San Francisco
- February 20, 2009 (focusing on industry) at Life Technologies in Carlsbad
- March 5, 2009 (focusing on the public and scientists) in City of Hope
- March 11, 2009 (focusing on the public and scientists) at Gladstone Institutes in San Francisco

This document also reflects the vision, priorities and scientific guidance of Dr. Alan Trounson, who became CIRM's president on December 31, 2007, and who initiated this planning process. Dr. Trounson is eager to move CIRM to its next level of scientific excellence and success by stimulating the development of a scientific "pipeline to cures" that bridges stem cell research from its discovery stages to its clinical applications. The 2009/2010 update thus calls for significant increases beyond the 2006 plan in the types of research targeted to elicit therapeutic candidates, and it envisions significantly more investment in "disease team" awards, translational research awards and collaboration with industry — the final critical conduit for transforming research advances into commercial therapies for patients.

The *2009/2010 Report on Operations Supplemental to the Strategic Plan Update* was developed to provide a brief description of CIRM's genesis and administrative organization and outlines the institute's achievements to date and recommendations for future improvements across the organization.

Additionally, the 2006 plan focused primarily on CIRM's scientific aspirations, strategic framework and planned scientific initiatives. This update expands on aspects that are relevant to a maturing agency, cultivating CIRM's leadership role in stem cell research and CIRM administration.

STRATEGIC OBJECTIVES

Building on the values and foundation expressed in the first plan, the specific strategic objectives of the 2009/2010 strategic plan update are as follows:

1. Acceleration of therapeutic discoveries

- A. Develop teams: Design an effective research program by linking the critical stakeholders together as committed teams to deliver clinical applications in regenerative medicine.
 - B. Respond to scientific discoveries: Create the flexibility in ongoing grants to accommodate the rapidly evolving developments in stem cell science and regenerative medicine.
 - C. Actively manage portfolio: Map a plan for accelerating progress to meet CIRM's demanding 10- to-14-year therapy goals through the "pipeline to cures" by more efficiently organizing CIRM's portfolio to bridge CIRM-funded basic stem cell research and translational, pre-clinical and clinical research.
 - D. Capture and share data: Develop robust systems for capturing and evaluating the results of CIRM-funded programs and for sharing these data in ways that accelerate the field.
 - E. Share expertise and collaborate: Propose new ways for CIRM to lead stem cell science and regenerative medicine by developing more formal mechanisms for sharing expertise and collaborations with partners in the scientific community, both nationally and around the world.
 - F. Partner with Industry: Enhance CIRM's relationships with the venture capital, biotechnology and pharmaceutical industries — relationships essential to delivering life-saving therapies based on stem cell research to patients.
2. **Regulatory certainty.** Consider methods for monitoring and improving, where appropriate, research policy and the regulations governing the ethical conduct of CIRM-funded research.
 3. **Public education.** Encourage the development of a "stem cell science culture" in California by taking a leadership role in educating and informing the general public, including special interest group, legislators and California students of all ages. Identify new procedures and methodologies that will expand public understanding and support of CIRM's research and development operations.
 4. **Economic benefit to California.** Collect and analyze information on the impact of CIRM as an economic engine and as an additional mechanism for sustaining CIRM financially.
 5. **Operational excellence.** Re-examine CIRM's internal operations to improve administrative efficiency, financial accountability, communication, education and teamwork.



STRATEGIC ADJUSTMENTS RECOMMENDED

In order to achieve the strategic objectives noted above, adjustments to the 2006 strategic plan are necessary. CIRM sought input from the research institutions, the general public, industry, patient advocates and other stakeholders. The following recommendations are the result of that consultation.

FUNDING FOCUS AND STRATEGY

1. The CIRM governing board has already approved the allocation of up to \$210 million for disease team awards, which represents a near doubling of the funds allocated to this award category in 2006. CIRM received considerable support from many different constituents for these multi-disciplinary teams as a valuable tool for CIRM's efforts on the clinical side of the research pipeline. The disease teams should subsume the clinical and tissue engineering requests for approval that were forecast in 2006.

2. CIRM clearly needs to continue to fund the full spectrum from basic to clinical research, but with the National Institutes of Health now able to fund basic embryonic research, CIRM can direct more of its basic science funding to two areas not well represented in NIH's portfolio. It can fund very directed projects that try to unlock a fundamental truth that was found to be unknown and blocking in a translational or clinical project — the critical path from bedside to the bench. It can also fund highly innovative basic projects that can sometimes yield a step change in our understanding of a particular area.

3. In light of recent science advances in using stem cells as research tools, CIRM has begun to fund molecular therapeutics based on stem cells and high throughput screening of stem cell and progenitor cell assays. As stem cell science advances in drug development, disease modeling and small molecule drug discovery, CIRM should apply its resources in these fields in ways that are in accordance with Proposition 71 — funding those projects that involve stem cell research with the most promise of advancing the field toward therapies, but that have limited capacity to attract alternative funding.

4. CIRM has consolidated many of the requests for applications (RFAs) envisioned in 2006, in part because it was not feasible to manage 12 grant cycles per year, but more importantly to move toward a smaller number of core grants, which are predictable for grantees and can have rolling priorities that reflect that state of the stem cell science at the moment of each RFA (see page 27). CIRM received considerable support from researchers for these core grants and plans to proceed in that direction.

5. The need to engage immunology in stem cell and regenerative medicine is critical, and little progress has been achieved to date in attracting immunologists to address inducing immune tolerance for allogenic cell and tissue graft survival, the need for new types of immune modulation and the apparent role of the immune system in tissue regeneration. CIRM needs to engage immunologists in working with stem cell researchers to provide the data and strategies that are essential for stem cell transplants in a wide range of diseases and injuries. An immunology and stem cell RFA is proposed, and a proactive strategy is proposed to attract central and peripheral immunologists and transplant scientists into collaborative partnerships with stem cell scientists.

6. CIRM has embarked on a series of agreements with funding entities from other countries in order to foster collaborations between Californian researchers and top stem cell scientists around the world. The agreements signed to date are outlined on page 27. In order to gain further global leverage of California's investment, CIRM plans to add several additional high ranked countries to this list that are strategically important for collaboration to California researchers. Similar agreements are under discussion with states and foundations within the United States, and CIRM is looking for opportunities for partnerships with federal agencies. Already a quarterly meeting forum has been agreed to with the Food and Drug Administration through the office of the president and general counsel.

7. CIRM has begun to proactively engage with industry recognizing the need and benefit of partnering with California's vibrant biotechnology, pharmaceutical and venture capital communities to translate basic discovery research into clinical application. A number of

changes, outlined beginning on page 21, are being made to facilitate these collaborations. CIRM has also recently appointed Elona Baum as general counsel. She is a strategic thinker with 12 years' experience at Genentech Inc. who is experienced in aligning agreements in the corporate sector and addressing complicated legal issues that involve private and public partnerships. Furthermore, CIRM proposes to recruit an experienced individual to staff (vice president of research and development) to assist in the translation-clinical research phase and who can enhance the prospects of clinical applications by working closely with teams of academic, medical, biotechnological and pharmaceutical interests.

POLICY CONSIDERATIONS

CIRM will monitor the progress of cell-based and related therapies toward the clinic and determine whether this progress is impeded because of current models for clinical trial funding or for reimbursements for the products that result. CIRM will consider the role it should play, including functioning as a convener to generate discussion between academics who model these economic issues, industry and payers.

THE CHANGING SCIENTIFIC LANDSCAPE

Many discoveries, too numerous to cite in detail here, have been made in stem cell biology since November 2004 when California voters created CIRM. For example, research teams have:

- made major strides in understanding the directive and effector molecules of the differentiation pathways that stem cells take as they divide and change into more specialized cells of the tissues of the body;
- discovered that at least one type of adult stem cell (mesenchymal cells) is itself immunosuppressive and somewhat privileged from attack and rejection by the immune system;
- used stem cells in novel ways to uncover the root causes of diseases and, in so doing, revealed targets for traditional drug therapy; and
- begun developing methods and assays to use stem cell lines to screen drug candidates for potential liver and cardiac toxicity.

Four advances in particular stand out, either for transforming the scientific landscape of regenerative medicine or for illustrating the enormous potential of this field. They are:

Induced pluripotent cells. In November 2007, companion papers emerged from the laboratories of Shinya Yamanaka² at Kyoto University in Japan and James Thomson³ at the

2. Takahashi, K. et al. *Cell* 131, 861–872 (2007).

3. Yu, J. et al. *Science* 318, 1917–1920 (2007).

4. Park, I-H et. al. *Nature* 451,141-6 (2008).

University of Wisconsin (followed rapidly by the work of George Daley and colleagues⁴) demonstrating that when adult human skin cells are transduced to express genes that are normally active together only in embryonic stem cells, they can be reprogrammed to become pluripotent (induced pluripotent stem cells or iPS cells). Like embryonic stem cells, iPS cells have the potential to generate all the cell types of the body.

Research into iPS cells will inform human embryonic stem cell biology and vice versa. Whether significant developmental differences exist between iPS cells and authentic human embryonic stem cells, which remain the gold standard for pluripotency, is currently the subject of extensive research. However, it is clear that research should continue on all types of stem and progenitor cells. The ability to reprogram mature adult cells by genes known as transcription factors, and more recently by recombinant proteins, provides the basis for personalized medicine and potentially immune compatible cell therapeutics. However, there are some concerns about the suitability of iPS cells for transplantation because of the observations of postnatal losses of mice derived from iPS cells by tetraploid complementation, and the modulations detected in the P53 (cancer associated) pathway as a result of using the transcription factors for reprogramming adult cells.

CIRM supports the use of iPS cells as models of disease, an approach that has been referred to as “diseases in a dish.” Several promising opportunities are based on iPS cell research, including establishing patient-specific iPS cells, investigating the heterogeneity of complex disease, and screening for new therapeutic drug candidates to block or delay disease expression.

iPS cells have dramatically changed the landscape of stem cell biology, opening up new avenues of research. It is possible that transcription factor manipulation of cells could enable the conversion to cell types needed by researchers and patients without the need to be pluripotential — e.g., the demonstrated conversion of pancreatic exocrine cells to β Islet cells. Ultimately, iPS cell technology holds great promise for improving the therapeutic options for patients with a variety of conditions.

Cancer stem cells. Equally significant are research studies that strongly suggest that certain cancers contain within them a rare population of insidious cancer stem cells. These stem cells were first identified in leukemia, and recent studies suggest that certain solid tumors and other blood cancers contain rare populations of stem-like cells that seed tumorigenesis. Cancer stem cells may well play a role in the recurrence of cancers or in the metastasis of cancer cells in patients who have undergone radiation and chemotherapy treatments. Although many of the solid organ cancer stem cells have not been definitively identified, research into cancer stem cells will nevertheless promote greater understanding of self-renewal, a trait shared by both tumors and stem cells. If common mechanisms of self-renewal are identified, stem cell

research could lead to novel approaches to containing cancer. This merging of the power of stem cell research and cancer biology to target the identification, isolation and elimination of cells that promote cancer's survival is a major scientific opportunity worthy of CIRM's support

Clinical trials based on stem cell research. In April 2008, the FDA convened a conference at which the safety of human embryonic stem (hES) cell-derived therapies was discussed. No hES cell-derived cell therapies had yet received FDA approval, but the conference was an important landmark in stem cell biology, opening a window on the enormous body of pre-clinical data collected by scientists in biotechnology companies that will ultimately lead to hES cell-derived cell therapies. In January 2009, the FDA granted clearance for the first hES therapy to be tested in human trials, marking an important milestone on the path to patient therapies.

In recent years there has been a rise in the number of clinical trials using bone marrow cell preparations including mesenchymal stem cells (MSCs) for severe graft vs. host disease, myocardial infarction and cardiomyopathies, autoimmune diseases such as lupus and Crohn's disease, cirrhosis, and others. These therapies are generally not regenerative, and most experts do not believe that MSCs generate new heart muscle directly; rather, they appear to provide benefit by improving the endogenous regenerative capacity of the host. Nonetheless, the experiences gained from using these stem cells, as well as cells derived from ongoing fetal and umbilical cord cell therapies, will certainly inform all of stem cell biology.

Stem cells can also be used to elucidate disease pathways and to point to novel therapies, as highlighted by the work of CIRM grantee Catriona Jamieson (UC San Diego), who identified a novel drug therapy for polycythemia vera (a disease of the red blood cells that can lead to stroke or leukemia) through her stem cell assay research. This work resulted in a clinical trial less than two years after the assays were initiated, showing the importance of stem cell-based assays to the field of stem cell biology.

Expanded federal funding for human embryonic stem cell research. As expected, President Barack Obama reversed much of the Bush administration's restrictive policies on federal funding of human embryonic stem cell research. CIRM welcomes this development and anticipates it will usher in a period of increased opportunities for collaboration and stronger partnerships targeting stem cell biology and medical applications. The elimination of institutional restrictions on using equipment purchased with federal dollars for human embryonic stem cell work will alone free up many labs for immediate collaborations, even without new dollars.

However, significant federal restrictions remain, leaving a critical role for CIRM and other private funding. The Dickey-Wicker amendment to the National Institutes of Health appropriations bill prevents the use of federal funds to create new cell lines from unwanted IVF embryos, and the issue of co-mingling federally funded equipment may still require separate facilities for this work. Also, two methods of creating cell lines without using IVF embryos, via nuclear transfer and via parthenogenesis, remain banned from federal funding, but are allowed under CIRM guidelines.

Through its first two-plus years of stem cell research funding, the institute and its grantees are well positioned to play a leadership role in this changing national environment.

IMPLICATIONS FOR CIRM

While the advances paint an enormously bright future for the stem cell field, they also create significant challenges for CIRM as a funding organization. As one of the largest funders of stem cell research in the world and a steward of public funds, CIRM has a unique responsibility to be a national and international leader in stem cell biology and regenerative medicine.

International leadership requires that CIRM be ahead of the curve in stem cell science and capitalize on the most innovative thinking in the field. CIRM must manage its agenda and expectations, recognizing that while some advances may be achieved in a few years, others will take longer, some much longer.

The unknowns in this young field are so vast that, for many goals, predicting a time frame is difficult. One example is the prospect of transplanting cells derived from pluripotent cells into patients, whether to cure disease or to replace damaged tissues. This therapy will require not only major new insights into generating and differentiating stem cells and controlling their growth and physiology, but also special guidelines crafted by the FDA to regulate the safe use of transplanted cells in patients. The FDA's approval of the first such trial January 22, 2009, was a major groundbreaking stride for the field. But that trial by Geron Corporation in recent spinal cord injury patients is just a first step of a very lengthy process.

The last few years have been marked by groundbreaking new directions in stem cell biology — some of which were impossible to predict. The next few years will likely yield similar, sudden advances. CIRM's flexibility to respond to the policy changes and new developments in science is essential to ensure that these discoveries translate into improved patient care as expeditiously as possible.

PROGRESS TO DATE

In addition to confidence in achieving the strategic objectives on page 1 and because of the rapidly changing landscape of stem cell science and CIRM's progress over the past two years, the CIRM scientific team is even more confident now than in 2006 that the five-year and 10-year goals (see Appendix 1) set in the original strategic plan are achievable, with one exception. Five-year goal number 5, creation of a stem cell bank, is no longer viewed as a valuable commitment of resources. Instead the institute is working toward creation of a registry of acceptably derived cell lines. CIRM affirms its commitment to the remainder of these goals and notes that a few have already been attained.

A good measure of progress is a review of the grant schedule proposed in the 2006 strategic plan (left column) compared with the actual RFAs released and awards made by CIRM (right column).

**RFAs TO DATE VERSUS 2006 PLAN
PROPOSED VS. ACTUAL SCHEDULE FOR RELEASE OF RFAs**

Through June 30, 2007

Shared research laboratories / stem cell techniques course (January, 2007)	RFA issued January 2007, awarded June 2007
Laboratories / research facilities (April, 2007)	RFA issued August 2007, awarded May 2008
Scientific personnel development (April – May, 2007)	New faculty RFA issued June 2007, grants awarded December 2007
Preclinical product development (May, 2007)	Determined timing was not right

July 1, 2007 to December 31, 2007

Tools and technologies (development)	RFA issued May 2008, awarded December 2008
Biology of stem cells	Included in new faculty grants awarded December 2007
Stem cell research and society (two RFAs)	To be handled via conference grants
Translational research, stage I	Determined to be premature Early translational RFA issued September 2008, awarded April 2009
Disease teams, planning grants	RFA issued November 2007, awarded June 2008
Training program, II	Decided to offer larger training II instead of renewal of training I, which was issued in 2006
Internships	Internships and technology staff training combined as Bridges to Stem Cell Research grants awarded spring 2009
Technical support staff training	

January 1, 2008 to June, 30 2008

New methods for development of stem cell lines	This RFA was combined with the next one as new cell lines grants with multiple priorities in the RFA and awarded June 2008
Generation and use of disease-specific cell lines	
Economic impact	RFP responses under review
Innovation grants	Included in the basic biology RFA issued December 2008
Banks (two RFAs)	Decided fostering a registry of existing lines was more effective
Communities of science (two RFAs)	Developed memoranda of understanding for collaboration with five countries and one U.S. foundation
Tools and technologies (sourcing)	RFA issued May 2008, awarded December 2008

**RFAS TO DATE VERSUS 2006 PLAN
PROPOSED VS. ACTUAL SCHEDULE FOR RELEASE OF RFAS**

July 1, 2008 - June 30, 2009	
Immune tolerance, initial RFA	Workshop February 2009, RFA likely late 2009
Public outreach (three RFAs)	Contract for new Web site June 2008 RFP for public relations firm awarded July 2008 RFP for high school curriculum project February 2009
Renewal of training program I	Offered larger training II instead, awarded January 2009
Cores (two RFAs)	Decided basic stem cell science RFAs more valuable Basic biology RFA issued December 2008 Basic biology II scheduled for August 2009
Internships	Bridges grants awarded January 2009
Egg and embryo research	This was included in new cell lines
Disease teams, planning grants	No need to repeat round issued December 2008
Disease team research awards	RFA February 2009
Stem cell-based tissue engineering (two RFAs)	Included in tools and technology; basic biology also covered in some of new faculty II awards issued August 2008
Clinical investigation (two RFAs)	To be determined, may be rolled into second round of disease team projects
Bio-process engineering	Held a good manufacturing process workshop to determine need and existing capacity, decided no need at this time
Innovation grants	Included as a priority in basic biology
Translational research, Stage 2	Included in disease team research awards RFA issued February 2009
Interdisciplinary research team grants	International memoranda of understanding designed to capture this intent

As of May 2009 CIRM has awarded the following grants:

- \$37.5 million for training 169 pre-doctoral, post-doctoral and clinical fellows at 16 nonprofit and academic research institutions
- \$46 million to fund 73 Leon J. Thal SEED grants to bring new ideas and new investigators into the field of hESC research
- \$72 million for 28 comprehensive research grants to support mature, ongoing studies on hESCs by scientists with records of accomplishment in the field
- \$50 million for 17 shared research laboratory grants (including six stem cell techniques courses) to fund the design and renovation of laboratory space, equipment for the new research facilities and operating expenses for three years
- \$113 million for 45 new faculty awards to encourage and support the next generation of clinical and scientific leaders in stem cell research
- \$271 million to 12 institutions for the construction of major stem cell research facilities
- \$25 million for 18 new cell line awards for the derivation and propagation of new pluripotent stem cell lines for the purpose of understanding, diagnosing and treating serious human diseases and injury
- \$1 million to support 22 disease team planning grants for multidisciplinary teams of scientists pursuing stem cell-based therapies for specific diseases
- \$19 million to support development of tools and technologies needed to move the field forward
- \$17 million for Bridges to Stem Cell Research awards
- \$40 million for training grant II awards
- \$67 million for early translational research awards
- \$16 million for basic biology I (provisionally)

ACCELERATING DISCOVERIES AND APPLICATIONS

SCIENCE PROGRAM

The science program is the heart of CIRM's operations and the catalytic hub for generating CIRM-funded research activities. As CIRM looks to the future, it seeks to (1) drive the basic stem cell discoveries upon which solutions and treatments in regenerative medicine will be based, (2) accelerate the movement of stem cell research toward clinical outcomes, (3) hone our internal processes so they more effectively support the field as a whole and (4) expand the breadth and depth of CIRM's research portfolio.

Scientists supported by CIRM should have a varied portfolio of grants that supplement CIRM awards. It is expected that NIH support should be increasingly available with the support of the Obama administration, and this should enable CIRM to concentrate support on the translation, preclinical and clinical programs that will deliver applications in cell therapeutics to patients. CIRM recognizes the need to partner with national and international agencies to enable collaborative support in the future. CIRM will seek to develop agreements with federal agencies such as the NIH and other philanthropic, patient-support, international and state granting organizations to leverage CIRM's research funds.

RECOMMENDATIONS FOR THE FUTURE

CIRM will restructure the scientific staff to include a vice president of research and development with experience in the R&D sector to increase the capacity of CIRM to work in partnership with biotechnology, pharmaceutical and investment sectors. These sectors must forge links with academic and medical center-based researchers who are driving the discoveries in stem cell and molecular biology. The disease team program is demanding on CIRM management requiring the formation of advisory committees, determining go/no-go decisions, restructuring teams and negotiating changes where necessary and creating new arrangements for advanced clinical trials. CIRM is open to negotiation with the government and the biotechnology and pharmaceutical industries, private foundations, and health insurance and venture capital institutions, within the United States and globally, to enable the efficient and cost-effective delivery of stem cell and related therapies for patients. CIRM will protect patients' access to the new developments in regenerative medicine arising from the research supported by CIRM funds.

The science program will be restructured to have grant management, grant review, basic biology, early translational and clinical trial sections. Dr. Patricia Olson, executive director of scientific activities, and the vice president of R&D will head these sections. This will enhance the ability of science staff to manage the granting process and to review and monitor progress.

Looking toward the future, CIRM's portfolio will expand as efforts are made to accelerate research that will bring stem cell technology closer to the clinic and patient care. For that

reason, CIRM is expanding the membership of the Grants Working Group to include more reviewers who are able to adjudicate applications for translational and clinical research.

Recognizing that California's biotechnology and pharmaceutical companies have the technical and commercial experience to develop and bring products to the marketplace, CIRM looks forward to offering these industries a wide variety of opportunities to apply for CIRM grants and loans. Realizing that special expertise is necessary to judge these proposals, CIRM is expanding the Grants Working Group to include scientists with industry experience in biotechnology, drug development and regulatory processes.

Given that CIRM's scientists are the front line of meeting the institute's evolving needs, other, broader modifications will be needed to enhance and monitor operations. These include:

- increasing the team's breadth of experience and domain expertise by recruiting highly qualified and motivated scientists to help with RFA writing, grant reviews and, increasingly, portfolio management and the active management of progress reports with the goal of achieving increased productivity;
- preventing reviewer burnout by keeping the grants-review process vibrant, interesting and effective and by augmenting the pool of reviewers both in number and in additional areas of expertise;
- composing new reviewer panels with biotechnology and clinical expertise to assess preclinical and clinical trial-related RFAs and appointing chairs that are appropriate for the type of RFA (e.g., basic, translational, clinical) being considered;
- adequately reimbursing specialists, reviewers and chairpersons for the number of days worked, to ensure we are obtaining the best possible advice and are protecting the state's investment and the institute's mandate as the grant applications become more complex and applied;
- ensuring that CIRM's clinical programs align with evolving FDA requirements for cell-based therapies;
- implementing a grants management system that will enable the management of reviews and provide a basis for integrating management and reporting across CIRM's growing grant portfolio;
- enhancing procedures for monitoring the progress of CIRM-funded investigators to effectively steward CIRM's investments and to identify the best CIRM-funded science to be advanced under new initiatives and make scientists aware of pertinent research outside their own institutions;
- extending CIRM's leadership role in the international community by expanding science-based outreach programs, symposia, and workshops to keep CIRM and its California-based investigators abreast of the new information continuously emerging at the frontiers of stem cell biology and regenerative medicine.

BASIC RESEARCH

CIRM will continue to build California's capacity in stem cell science by issuing RFAs to support the research of scientists at all stages of their professional careers. Recognizing that California has attracted some of the best stem cell scientists in the world, certain RFAs will support the research of these and other established scientists with large research groups. Other RFAs will be designed to serve mid-career scientists who are changing direction or applying new disciplines to the field. Cognizant of the critical and continuous need for new talent, CIRM will also continue to support young investigators who demonstrate the talent and commitment to stem cell basic research.

CIRM will explore the possibility of developing high productivity research appointments for mid-career scientists to enable recruitment opportunities in California.

CIRM expects to fund the full spectrum of research from basic to clinical, but with NIH now able to fund basic embryonic research, CIRM can direct more of its basic science funding to two areas not well represented in NIH's portfolio. It can fund very directed projects that try to unlock a fundamental truth that was found to be unknown and blocking in a translational or clinical project—the critical path from bedside back to the bench. It can also fund high-risk projects that can sometimes yield frame-shifting results.

PROGRESS TO THE CLINIC

CIRM has awarded the first early translational grants to (1) identify candidate drug molecules or cellular therapeutics derived from stem cell research, with high potential for use in regenerative medicine and (2) develop tools to overcome roadblocks and propel these applications toward the clinic. These early-stage translational research awards will support the development of animal models or the discovery of other fundamental information on molecular and cellular potency, efficacy and risk that is needed by regulatory authorities to support an investigational new drug application that the FDA requires before a clinical trial can begin. CIRM expects these RFAs to be issued annually; they will include a mixture of grants and loans to companies and nonprofit institutions, with opportunities for awards to multiple coprincipal investigators to ensure that the most senior or qualified people in the organizations are intimately involved in the research.

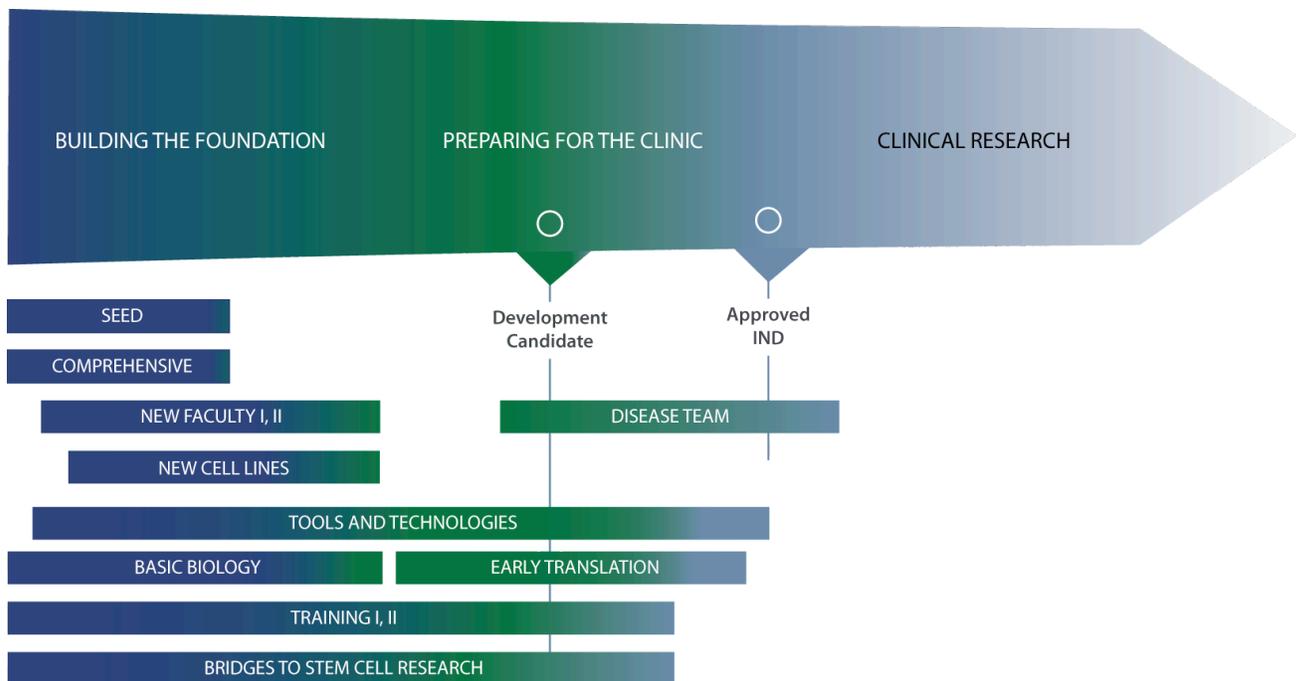
CIRM also recognizes that building the tools necessary for basic and translational research is an important step along the path toward the clinic. We anticipate that RFAs supporting the development of tools and technologies will remain an important part of CIRM's research portfolio.

Progress is being made every day in labs around the world, and some promising products are in the pipeline using pluripotential, mesenchymal, adipose, neural, and placental and umbilical cord blood stem cells. These studies represent the frontiers of stem cell therapies, and CIRM is committed to moving them along the application pipeline, particularly those that are underfunded for development and pre-clinical applications.

CIRM recently issued an RFA for disease team grants designed to move research from the laboratory to an investigational new drug application within four years. Funding of up to \$20 million per project may be available, assuming that agreed-to milestones are achieved. All teams will be required to use strict project management techniques, and oversight advisory committees will be established to help CIRM staff monitor progress. The projects will have to meet FDA guidelines for cell therapies and treatment protocols. While these have not yet been formalized, requirements for mature autologous and allogenic adult stem cell therapies are now reasonably well established. Because a large number of applications for the disease team grants were expected and 73 pre-applications were received, CIRM is testing a system to triage these brief pre-applications and direct those unlikely to be competitive to consider later RFAs. Pre-application review by external advisors and CIRM science officers makes it possible to accept an unlimited number of pre-applications submitted by an institution or company but at the same time result in a manageable number of applications for the Grants Working Group to assess. It will also minimize the time and effort of applicants who are unlikely to be funded and bring the best applications forward for these very special awards.

CIRM is also focusing on the critical need to stimulate research that links immunology with stem cell biology. Since many of the strategies being developed for stem cell therapies involve the use of allogenic cell transplantation (non-matched donors and recipients), scientists may need to induce immune tolerance to prevent the rejection of the genetically foreign stem cell transplants. This is a far more appealing strategy than current alternatives: exposing patients to long-term immunosuppression therapy. To address this obstacle in clinical applications CIRM will prepare a specific RFA addressing tolerance strategies for allogenic cell therapies that encourages immunologists to work with members of the disease teams and other CIRM-supported scientists.

The disease team RFAs will support progress of research projects into phase I clinical trials as the CIRM program progresses. There will also be RFAs developed to support clinical trials that would be expected to include partnerships with biotechnology and pharmaceutical companies, private investment, and other sources of financial support that are appropriate. This is an area of developmental responsibility for the vice president of R&D. CIRM expects that its contributions would be proportionally smaller than other contributions from companies and other financial institutions but would remain meaningful and would ensure reasonable patient access to the new therapeutics that are developed.



While CIRM's early RFAs focused on training and basic research, those in 2008 and 2009 began to move into the translational arena. RFAs will increasingly cover the entire spectrum of the pipeline, from discovery through clinical development.

SETTING THE CIRM RESEARCH AGENDA

CIRM relies on multiple sources of information to monitor progress in the stem cell field, frame issues, and identify specific areas of opportunity or roadblocks to research progress, all of which form the basis of new RFAs.

In order to develop interesting and relevant RFAs, CIRM's science officers must remain on the cutting edges of stem cell biology and regenerative medicine. Toward this end they read and debate the scientific literature, attend national and international scientific meetings, host research seminars, meet with investigators at their home institutions, and participate in frequent scientific discussions with their peers.

CIRM science officers maintain their specialty research interests by hosting presentations from visiting scientists from California and elsewhere. CIRM uses video conferencing to facilitate communication with scientists worldwide.

Other sources and resources that inform the CIRM research agenda include:

CIRM workshops. Workshops provide a valuable venue for learning about scientific fields and for convening experts to advise on how to advance various research agendas. For example, in July 2008, a workshop on the use of stem cells in predictive toxicology brought together

scientists and engineers from the pharmaceutical and biotechnology industries, national and state environmental health and regulatory agencies, and academia.

Other recent workshops have addressed cancer stem cells, stem cells and immunology, cell production in good manufacturing practice (GMP) facilities, autism, and United Kingdom and Japanese scientific linkage with California. CIRM summarizes the outcomes of these workshops and, where appropriate, moves to develop actions to address the major recommendations of the workshops.

Progress reports. The grants administration policy requires that CIRM grantees submit annual progress reports detailing the research carried out during each funding year. Science officers are responsible for evaluating these reports as they relate to the original goals of the project. In discussing these reports, the science team will suggest ways to expand on promising results and will identify potential future investigation.

To manage the flow of information, CIRM is developing and implementing a categorization system and database to store information according to disease relevance, cell types and technologies employed, research results, questions raised and answered, and possible next steps.

Analysis of progress reports may suggest the need to launch entirely new programs or reveal opportunities to make adjustments in current programs, for instance, by encouraging collaborations among investigators pursuing similar or related work in different organizations. The science team facilitates communication and collaborations among investigators, including sponsoring symposia and mini-workshops to accelerate collaborative progress. The science team may also recommend to the board additional funding to research teams for especially successful or promising programs that are directly related to achieving CIRM's mission.

Conversely, the science team is also responsible for recommending termination of failing projects. Grants will be terminated if (1) milestones are not achieved, (2) the proposed research is abandoned in favor of a project outside of the scope of the RFA without pre-consultation with CIRM or (3) the research hits a dead end. Given the high-risk nature of many of CIRM's programs, we expect negative results, but these do not necessarily represent failure; indeed, CIRM will share instructive negative results — which are often unpublishable — with its research community. These results yield substantial value in directing future research. Through diligent review by the science office, four grants have been terminated.

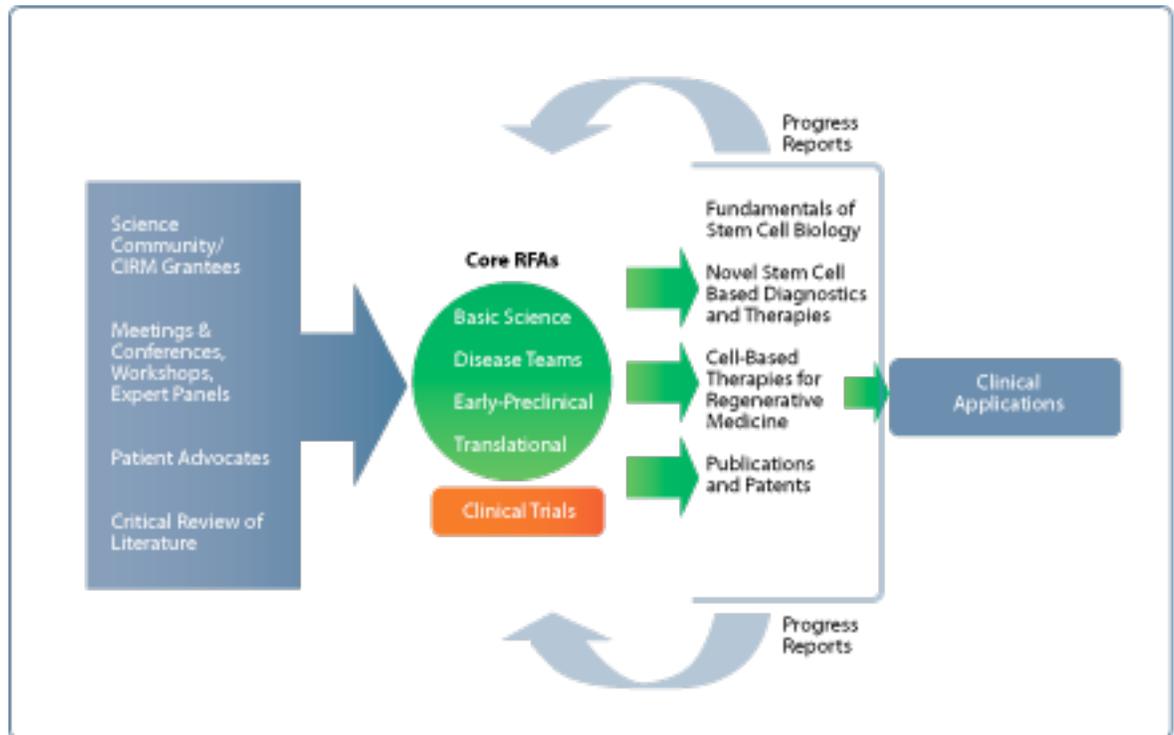
For milestone-driven clinical research projects (such as the disease team grants), beyond providing detailed data, investigators will be required to outline their go–no go decisions in evaluating stem cell–based therapeutic candidates, and to submit data to help CIRM and other monitoring committees assess progress. CIRM will also use progress reports, in conjunction with evaluations by designated monitoring committees, to identify candidate drugs, treatments or assays that deserve additional funding for follow-on stages of pre-clinical development.

Progress reports also serve a communication function, providing information that CIRM's communications office can use to update its audiences about research progress arising from CIRM-funded projects. Additionally, the reports create a record of what types of science CIRM has funded, how well this funding aligns with CIRM's strategic goals, and whether the interests of stakeholders have been fully realized and balanced.

CIRM annual conference. CIRM hosted its first grantee conference in September 2008 with more than 400 CIRM-funded scientists attending. The meeting featured lectures, posters and interactive science sessions. Prominent U.S. and international scientists attended by invitation and led stimulating discussions on subjects of high priority, including iPS cells. The conference was held under Cold Spring Harbor rules whereby data are not communicated outside the conference except at the initiation of the authoring scientist. The meeting will be held frequently, letting CIRM's science officers interact with grantees in a stimulating environment and allowing CIRM-funded scientists to forge connections and learn about each other's work. The initial conference was enthusiastically supported by grantees, with many new connections and informational exchanges made between California scientists and an obvious strong morale evident among all grantee laboratories.

Investigator-initiated conferences. Conferences initiated by CIRM investigators, which can now be co-funded through applications to CIRM, are also extremely valuable forums for information sharing and initiation of new collaborations.

Patient advocacy. Input from patient advocates is incorporated into CIRM's decision making at many levels. As members of the Grants Working Group, patient advocates have a formal role in formulating recommendations to the governing board regarding project funding. CIRM's science officers attend clinical conferences as a means of interacting not only with researchers, but also with patient advocates from around the country. As stem cell biology progresses from the laboratory to the clinic, ongoing dialogue with patient advocates, both from within California and from national disease foundations, will become increasingly important in the application of stem cell therapies.



This figure diagrams how data are fed forward into generation of RFAs, and the primary importance of feedback from progress reports in fine-tuning RFAs to advance CIRM's scientific mission.

The vast majority of patient advocates understand that each individual disease interest group is best served by following the best science no matter what disease it is studying. So they generally have a desire to keep abreast of the field as a whole. We will be sharing lay-level summaries of CIRM research results with patient advocate groups to enable them to provide informed input.

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

CORE GRANT RFAs

To ensure that opportunities for rapid and significant progress in both basic and clinical science are identified and pursued, and to be certain that technologies are evaluated and renewed periodically, CIRM intends to categorize most RFAs into four major research activities. Organizing grants in core areas will facilitate CIRM's ability to monitor research progress and to measure progress along the pathway from discovery through development and onto clinical application. It will also enable the institute to schedule RFAs for new and renewed programs more predictably, reducing the number of Grants Working Group meetings and workload on grant reviewers.

CIRM's core or primary grant areas are as follows:

1. Basic innovation in stem cell biology. Basic stem cell research conducted by a broad spectrum of researchers is essential for moving this technology from the bench to the bedside. In its short, four-year history, CIRM has aggressively funded innovative basic research projects that are likely to advance the field and CIRM's mission. CIRM will continue to build on the critical mass of scientific excellence and to fund creative projects with the potential to lead to clinical applications.

2. Early translational research. These awards will support research that advances stem cell-derived candidate therapies or assays to a development candidate stage ready for consideration for preclinical development and enabling a regulatory filing. The candidate therapies may be stem cells or their derivatives, small molecules, proteins, antibodies, genetic manipulations or any pharmaceutical that is identified using stem cell technologies.

3. Disease teams. As described elsewhere, CIRM plans a major investment to support disease team grants aimed at achieving an Investigational New Drug application within the four-year grant/loan funding period.

The scope (and therefore funding) for disease teams will differ, depending on the maturity of the candidate therapy. Disease team grants will be milestone driven and monitored on a regular basis by project managers and oversight committees. CIRM will make a special effort to identify teams making singular progress toward a clinical application and to accelerate their translational research efforts by facilitating appropriate collaborations and further funding.

4. Clinical trials. The program of clinical trials will be developed in partnership with other funding sources as a special interest of the VP R&D. The program will be focused on the delivery of research arising from the work in California on stem cells and related technologies and ensures the continuation and delivery of discoveries in basic stem cell biology into the clinic.

5. Research fellowships and training programs. CIRM training grants have greatly expanded the cadre of California researchers skilled in the techniques of growing and manipulating stem cells, and thus have played a critical role in accelerating stem cell research capacity in the state.

Funding for the first round of training grants will end during the winter and spring of 2009. A second round of such grants was awarded in January 2009, though funding was delayed pending state issuance of sufficient bonds to cover CIRM programs the board deemed higher priority. These funds were released in June 2009.

While CIRM has determined that continuity in these training opportunities provides value, the institute will consult with the research community to determine whether a third round of trainees is needed to drive the CIRM mission and if additional young stem cell researchers can reasonably expect the field to accommodate them.

Similarly, the first two rounds of new faculty awards have given talented young faculty the security of five years of steady funding. Before considering another round of new faculty awards, however, CIRM will review the funding landscape. While a main goal of the institute remains ensuring a sufficient pipeline of scientists to pursue all viable avenues of regenerative therapies, CIRM must balance this aim with the capacity of the field to use new talent.

The Bridges program is designed to introduce students in community and state colleges to careers in the biomedical sciences in general and stem cell science in particular. The governing board approved the first round of these grants in January 2009 and released the funds for them in March 2009. Because of anticipated ongoing needs to grow the pool of research personnel and diversify the community of researchers, CIRM expects this program to continue.

From time to time CIRM will also release RFAs that address programmatic needs, such as tools and technologies, immunology, toxicology testing and CIRM research leadership awards. These programs are needed to support and supplement the core programs noted on the prior page. CIRM also recognizes the need to attract and recruit the most productive mid-career scientists and retain these champions in the California research environment.

COLLABORATING WITH INDUSTRY

As the effort to cure or treat disease using stem cell technologies moves closer to the clinic, CIRM will need to call upon expertise in clinical trials, regulatory requirements and large-scale good manufacturing practices. The greatest reservoir of these skills resides in pharmaceutical and biotechnology companies. Without the injection of such expertise into CIRM programs, either independently or through formal collaborations between industry, universities and other nonprofit organizations, CIRM's ability to accomplish its mission will be jeopardized. Therefore, one of CIRM's primary goals is to promote and facilitate the involvement of corporations in its programs to harness the resident expertise and resources in regulatory, clinical, manufacturing and R&D.

To achieve these goals, CIRM proposes five strategies:

1. Ensure that CIRM's internal programs, policies and regulations embrace industry participation.

In each aspect of its work, CIRM will be mindful of the benefits of industry participation as well as the impact of CIRM policies and practices on such participation, removing obstacles where appropriate. Toward that end, CIRM must ensure that:

- its grant and loan programs are conducive to industry participation, amending them as necessary to facilitate collaboration with pharmaceutical and biotech companies;
- CIRM's business loan program is implemented on terms that encourage industry participation while including provisions to assure preferential pricing for California local and state government entities and access by the uninsured; and
- CIRM's rigorous peer review encourages industry participation, for example, by including on the Grants Working Group industry experts who are qualified to recognize what is necessary for commercial success.

2. Reach out to the pharmaceutical and biotechnology industry to better understand its needs and encourage its participation in CIRM programs.

CIRM recognizes that the nonprofit and business communities, while sharing the goal of using stem cell research to improve the lives of patients, have different missions, capabilities and cultures. To promote industry involvement, CIRM must:

- consult regularly with representatives from the pharmaceutical and biotechnology sectors concerning industry trends and needs to help evaluate CIRM's interactions with this sector;
- join or establish a formal liaison with industry groups with a stake in stem cell research at the state, national and international levels, such as BIO, PhRMA, CHI, BayBio and BIOCOM;
- include, as appropriate, topics with industry focus in CIRM-hosted and sponsored events and promote industry representatives as participants and speakers; and
- take visible leadership roles at conferences, panels and professional meetings addressing industry participation and concerns in stem cell research.

3. Serve as a resource to support industry involvement in stem cell research and development.

CIRM should provide:

- a conduit for communication with the FDA and other federal agencies to broadly disseminate information concerning regulatory issues and experiences relevant to research and development of stem cell products to help reduce uncertainty concerning the regulatory process that creates inefficiencies in the stem cell product pipeline and discourages potential investors;
- a forum and resources for reimbursement models for stem cell therapies that go beyond traditional economic models, which are generally premised on chronic treatment and may not provide adequate incentive for commercial involvement in the field of "one dose" stem cell therapies;

- opportunities and guidance for joint collaborative projects involving industry and nonprofit entities;
- useful information on best practices in intellectual property licensing and trade secret issues;
- information on, and guidance in, grant and loan application writing and best practices in CIRM-specific grant and loan management;
- information on intellectual property prosecution and other relevant legal developments, which may require CIRM to consider establishing a network or panel of IP and licensing attorneys with strong client bases in the commercial stem cell arena that could meet periodically to share best practices and advise the institute;
- help in both monitoring “blockers” to industry participation and using CIRM resources and influence judiciously to resolve logjams;
- opportunities to facilitate the lawful exchange of information between companies regarding stem cell manufacturing and regulatory experience, with the aim of avoiding duplication of effort and repetition of mistakes;
- advocacy for policy changes and clarifications of various state and federal agency rules that hinder industry involvement in stem cell research and development, which might involve submitting amicus briefs in various legal proceedings, submitting “white papers” to government agencies and testifying before governmental bodies.

4. Educate key stakeholder constituencies about industry’s critical role in accomplishing CIRM’s mission.

Key constituencies should be educated about the close links and cascade effects between health/economic benefits for Californians on the one hand, and industry innovation/intellectual property protection on the other. To improve understanding, CIRM should:

- regularly update the governing board about relevant developments in the pharmaceutical and biotechnology sector;
- help raise public awareness about industry’s unique ability and extensive track record of success in bringing valuable therapies to patients and the need for pharmaceutical or biotechnology companies’ involvement to help drive similar stem cell–based therapeutics;
- raise the awareness of state legislators about the importance of industry involvement in CIRM’s mission; and
- encourage other funding organizations, especially those with whom we have established memoranda of understanding, to fund industry research and development efforts.

5. Provide loans to support later stages of research leading to clinical trials and new therapies.

Bringing new and more effective treatments and therapies into practice is a complex, expensive process, and financing is becoming more difficult for small biotech companies. As CIRM believes these companies will be important partners for California’s world-class

academic and nonprofit research institutions in bringing stem cell therapies to market, finding ways to support their efforts is essential.

CIRM is already providing opportunities for for-profit companies to apply for support of basic and translational science through its grant programs. In the next few months the institute will introduce a loan program that will provide significant new funding to biotech companies while maximizing CIRM's ability to achieve its goals by recycling monies repaid from loans into new research programs. Key features of the loan program include:

- RFAs for preclinical and clinical development will make loans available for for-profit companies;
- applications for loans will undergo the same rigorous peer-review process as applications for grants;
- standards will be developed for assessing financial feasibility and risks associated with loans and industry grants;
- underwriters will be identified to manage the financial aspects of the loan program; and
- loan funds repaid to CIRM will be recycled and used to support the institute's mission, including funding additional research RFAs.

To summarize, California's biotechnology and pharmaceutical companies are among the best in the world in their ability to develop innovative technologies and products to meet the needs of patients. In collaboration with California's leading nonprofit research sector, they are an invaluable and essential resource to bring stem cell therapies to patients. They are enthusiastic about CIRM and eager to contribute to the institute's success. Working together, CIRM and its industry partners have unlimited potential to realize CIRM's lifesaving mission. To maximize this potential, CIRM must remain aware of the sector's specific needs for technology and information and work diligently to provide opportunities for industry to engage — without hurdles — with both CIRM and its nonprofit partners.

NATIONAL AND INTERNATIONAL LEADERSHIP

“Advance the biotech industry in California to world leadership, as an economic engine for California’s future” (Proposition 71)

Thanks to the vision, generosity and foresight of California voters who overwhelmingly supported the passage of Proposition 71, and due to the growing success and impact of CIRM’s programs, California is rapidly becoming recognized as the primary international hub of stem cell research. CIRM-funded research had resulted in more than 300 scientific publications by June 2009 (see Appendix 2). Stem cell scientists from around the country have identified California as the most desirable location for their research (see sidebar this page), and many leading scientists have moved here from other states and countries to carry out their work.

The tasks and challenges CIRM faces in bringing stem cell technology to patients within 10 to 14 years loom large by any estimation. Additional assets, both intellectual and financial, will accelerate the march to success, as will leveraging CIRM programs through collaborative interactions with talented people and biotechnology interests outside California.

COLLABORATIONS AND JOINT PROGRAMS

Collaborations with scientists from outside California play a valuable role in advancing CIRM’s research agenda. International collaborations allow California to significantly leverage both its financial and intellectual investment in the field. These collaborations will be facilitated by agreements with external funding agencies via competitive RFA programs. A number of agreements have either already been forged or are in late-stage discussions with research agencies in other countries and philanthropic foundations that support research in specific diseases. These arrangements will be expanded over time to create a national and worldwide network of scientists, biotechnologists, clinicians and business interests working together to accelerate progress on stem cell therapies and their transition to the clinic.

Stem Cell Researchers Around the Country Are Noticing CIRM’s Role

When a Georgia Tech researcher asked scientists from around the country to rank the top states in their discipline, nearly 90 percent of stem cell scientists ranked California in the top three, compared with about half the non-stem cell scientists. A similar percent of stem cell scientists were aware of California’s commitment to fund stem cell research on a large scale.

See Nature Reports Stem Cells 10 July 2008 - Levine A (2008) Policy considerations for states supporting stem cell research: evidence from a survey of stem cell scientists. Public Admin. Rev. 68: 681-94. 2008

CIRM Funding is Attracting Researchers to California

- Twenty-four national and international leaders in stem cell research have moved to California from 10 U.S. universities and six foreign countries.
- Thirty-three young investigators have decided to launch their careers in the state after studying in labs in 16 different U.S. institutions and three foreign countries.
- A sample of five CIRM-funded institutions has increased the number of stem cell researchers from 134 in 2004 to 463 by November of 2008, a 455 percent increase.

These collaborations will:

- allow CIRM to expand its research portfolio and intellectual capacity by involving scientists from institutions and companies located in other states in the United States and abroad, in joint study and research programs;
- create opportunities for CIRM funding to leverage additional financial support from other organizations;
- reduce duplication of both effort and facilities in projects of shared interest;
- accelerate opportunities for clinical applications; and
- pursue collaborations with the FDA and NIH that may accelerate research and development in a wide spectrum of areas and more efficiently enable clinical trial applications.

COLLABORATIVE RELATIONSHIPS AS OF AUGUST 2009

ORGANIZATION	COLLABORATION
State of Victoria, Australia	Broad in scope, immunology strengths
Canadian Cancer Stem Cell Consortium	Cancer stem cells
Medical Research Council, UK	Broad in scope
Juvenile Diabetes Research Foundation	Diabetes
Japanese Science and Technology Agency	Broad in scope, iPS cell focus from Japan
Spanish Ministry of Science and Innovation	Broad in scope

CIRM has received numerous inquiries from organizations eager to engage in collaborative funding. As CIRM considers entering into partnerships it is:

- establishing criteria for determining appropriate partners and circumstances;
- ensuring that all joint-funding arrangements are consistent with CIRM’s scientific and ethical standards and with all of CIRM’s governing statutes and regulations, including rigorous peer review; and
- strengthening mechanisms for monitoring progress, to enable CIRM to rapidly identify and seek new partnerships in promising research areas.

In summary, with CIRM programs and operations now firmly established in California, the institute is extending its reach and influence both nationally and internationally, playing a leadership role and benefiting from the scientific progress of others.

APPENDIX 1

FIVE-YEAR GOALS (FY11/12)

These five-year goals will be milestones to gauge our progress:

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

The disease team research awards will target this goal. In addition, CIRM funds over 50 grants that include research that may result in therapeutic candidates for preclinical development. Such research includes testing stem cells or their derivatives for engraftment or disease/injury-modifying activity in relevant models and using stem cells for in vitro disease modeling, drug discovery or strategies to enhance activity of resident adult stem cells in vivo.

- Goal II: CIRM grantees will have developed new methods for making stem cell lines. CIRM funds research focused on the development and optimization of various methods for deriving new cell lines including SCNT and induction of pluripotency with transcription factors, chemicals, proteins and microRNAs.

Outcomes: To date, CIRM grantees have produced 13 publications documenting work using small molecules and microRNAs to induce pluripotency and refine methods for stem cell line derivation. One notable paper is

- Judson, R.L., et al., "Embryonic stem cell-specific microRNAs promote induced pluripotency." *Nature Biotechnology*, 2009. PI: R. Blelloch (SEED, UCSF). This report demonstrates that introduction of microRNAs specific to embryonic stem cells enhances the production of mouse induced pluripotent stem (iPS) cells. The paper suggests that these microRNAs are downstream effectors of cMyc during reprogramming; however, unlike cMyc, they induce a homogeneous population of iPS cell colonies.
- Goal III: CIRM grantees will have successfully created disease-specific stem cell lines for four diseases.

CIRM currently funds 17 grants that are deriving disease-specific cell lines. Targeted conditions include:

- Neurological and neurodevelopmental disorders: Alzheimer's disease, frontotemporal dementia, Parkinson's disease, Huntington's disease, fragile X syndrome, amyotrophic lateral sclerosis
- Skeletal muscle, bone and connective tissue disorders: muscular dystrophy, Marfan syndrome, Loeys-Dietz syndrome
- Chromosomal abnormalities: Down syndrome, trisomy

- Metabolic disorders: Hurler syndrome, adrenoleukodystrophy, Tay-Sachs disease, Canavan syndrome
 - Others: cystic fibrosis, melanoma, cardiac arrhythmia, age
- Goal IV: CIRM grantees will have developed methods for growing stem cells in defined media.

CIRM currently funds at least seven grants where this is a primary focus. The work proposed includes:

- using signaling ligands in serum-free media to optimize and maintain the pluripotency of stem cells in culture;
- screening for compounds that promote self-renewal and differentiation in the absence of biological agents;
- developing lines more efficiently using serum-free, chemically defined media; and
- using microfluidics to improve scale up and culture integrity.

In addition, 10 grants propose to develop cells or lines under good manufacturing practice, which is required for clinical grade material.

Outcomes: Four papers have been published based on CIRM-funded research describing the development of methods for growing stem cells in defined media. One notable paper was published in July 2009:

- 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*, 2009. **PI: X. Zeng (Shared Labs, Buck Institute)**. This paper describes the use of chemically defined, animal cell-free media to propagate hESCs, differentiate them into human neural stem cells (hNSCs), 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."
- Goal V: CIRM will develop a registry of stem cell lines that are suitable and available to California researchers.
- CIRM is working toward a system of documenting eligible stem lines, which will identify pertinent lines that meet state and national guidelines/regulations. Currently, CIRM has received documentation for 12 stem cell lines.
- Goal VI: CIRM-funded investigators will have demonstrated methods for inducing immune tolerance in animal models.

This goal will be specifically targeted by an RFA on stem cell transplantation immunology planned for release in late 2009. Currently, there are five grants addressing immune bottlenecks to stem cell therapies. Various strategies are being investigated, including:

- designing less immunogenic hESCs and derivatives;
- engineering T cells; and
- suppressing immune system function in animal models or reengineering immune systems with hematopoietic derivatives of hESCs.

- Goal VII: CIRM will have increased the work force of stem cell researchers in California.

CIRM has funded 279 graduate students, postdoctoral fellows and clinical fellows through its training grants and has jump-started the careers of 45 young faculty through its new faculty grants.

- Goal VIII: CIRM grantees will have established tools for toxicity testing based on stem cell research.

CIRM is currently funding three grants specifically focused on developing tools for assessing or predicting toxicity (cardiotoxicity or hepatotoxicity). However, CIRM is also funding more than a dozen grants exploring ways to develop more authentic, relevant and mature hepatocytes and cardiomyocytes, the basic tools needed for toxicity studies. In addition, one early translational proposal has been funded to identify compounds that are selectively cytotoxic to hESCs, a finding that could inform our understanding of developmental/reproductive toxicity as well allow the development of tools for identifying agents with similar mechanisms of action.

- Goal IX: CIRM will have enabled effective partnerships in stem cell research between scientific teams in nonprofit and commercial sectors.

CIRM has funded several industry/nonprofit collaborations, including:

- projects with key research personnel at both industry and nonprofit institutions (tools and technology RFA);
- academic projects with industry subcontracts (early translational RFA);
- industry projects with academic consultants (tools and technology RFA); and
- at least two industry-based projects with academic co-investigators sponsored by CIRM's collaborative funding partners.

Similar partnerships are expected to be funded by the disease team research awards.

- 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.

CIRM has established a number of such partnerships. See page 25.

Outcomes: Four early translational research grants have been approved for funding include international collaborators through CIRM's collaborative funding partner program with the State of Victoria, Australia.

Collaborative funding partners including the MRC (United Kingdom), the CSCC (Canada) and the MICINN (Spain) are participating in the disease team research awards program.

Ten-Year Goals (FY16/17)

CIRM commits to the following 10-year goals:

- **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.

CIRM, through its early translational research and disease team research awards programs, is building its portfolio and presence in therapeutic development. CIRM plans to develop its clinical trial award program over the next 18 months.

- **Goal II:** CIRM-sponsored research will have generated therapies based on stem cell research in Phase I or Phase II clinical trials for two to four additional diseases.
 - Geron I., et al., "Selective inhibition of JAK2-driven erythroid differentiation of polycythemia vera progenitors." *Cancer Cell* April 2008. **PI: Jamieson C (SEED UCSD); Kavalchik E (Training)**. This paper describes how researchers transferred human cord blood stem cells, engineered to contain the mutant JAK2 gene, into mice with a suppressed immune system, to find whether over-expression of a single gene could drive, or initiate, the disease. These stem cells were introduced directly into the liver, the main site of blood development in the newborn mouse. As a result, the stem cells over-expressing the mutant gene led to overproduction of human red blood cells, and the mice developed a disease that looked like PV. The researchers corroborated these results by injecting actual stem cells from patients with PV into the same mouse model, achieving similar results. "... the JAK2 mutation was necessary and sufficient, by itself, to drive the disease." A selective JAK 2 inhibitor, TG 101348 was shown to be effective in blocking the mutant JAK2 gene and is now being used in Phase I and II clinical trials to reverse the human disease — polycythemia vera.
- **Goal III:** CIRM-funded projects will have achieved sufficient success to attract private capital for funding further clinical development of stem cell therapies.

Several projects, including item in Goal II above, have attracted such funding.

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

CIRM will be releasing in late 2009 a request for application, stem cell transplantation immunology, specifically focused on new approaches for achieving immune tolerance for transplantation. See also five-year goal VI for description of current grants addressing this and other immune bottlenecks.

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

As stated under five-year Goal I: approximately 50 grants are testing stem cells or their derivatives for engraftment or disease/injury-modifying activity in preclinical models. Diseases and conditions being targeted by these and other grants include PD, HD, ALS, several cancers, spinal cord injury, stroke, deafness, retinal degeneration, Alzheimer's disease, heart disease, renal disease, epilepsy, muscular disorders, HIV, diabetes, liver disease, intestinal and lung conditions, ischemia, hematopoietic disorders.

Outcomes: CIRM-sponsored publications describing preclinical proof of principle for human ES-derived therapies have yet to emerge, as currently funded projects are still in their early stages. However, several publications have been reported describing proof of principle using analogous animal stem cells and disease models, establishing the necessary groundwork to move into work with human cells. Notable papers include:

- Blurton-Jones, M., et al., "Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease." *PNAS*, 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. Frank 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*, 2009. **PI: Songtao 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 four 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 to 30 diseases and used them to gain new information about pathogenesis, to identify new drug targets and to discover new therapeutics.

CIRM is funding many ongoing efforts. See progress for five-year Goal III.

- **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.

CIRM has funded at least 10 grants that specifically indicate they will develop cell lines using GMP. In addition, over a dozen grants are targeting clinical bottlenecks that will impact the ability to produce GMP-compliant cell lines, including:

- several projects developing methods of addressing bottlenecks in scale-up, cell sorting and handling;
- several projects addressing quality control of cell preparations, assays for detecting teratomas, reducing the risk of tumorigenesis and assessing or improving cell integrity; and
- multiple projects exploring cell features, seeking markers for indicating functional and behavior relevance of differentiated cell populations.

Outcomes: CIRM grantees have produced two publications demonstrating development of GMP procedures. One publication of note:

- 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*, 2009. **PI: X. Zeng (Shared Labs, Buck Institute)**. This publication demonstrates a defined medium system providing a path to a scalable GMP-applicable process of generation of dopaminergic neurons from hESCs for therapeutic applications, and a ready source of large numbers of neurons for potential screening applications.

- **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.

CIRM is currently funding more than a hundred grants with a focus on differentiation:

- About 40 investigate general neural development pathways, most for motor neuron specification but a few with glial or sensory cell focus.
- About 15 investigate cardiac pathways.
- About 14 investigate hematopoietic pathways.
- Others investigate skeletal muscle, intestine, liver, germ cells, pancreatic tissue, intestinal, bone/cartilage, hair, lung, kidney, vascular tissues, retinal, breast and other tissues.
- In addition, several grants investigate progenitor cells (NSCs, MSCs, etc.) and their behavior, as well as progenitor cell differentiation.

Outcomes: Major strides have been made in understanding differentiation into many cell lineages. CIRM grantees have produced 38 publications detailing aspects of the

differentiation process of stem or progenitor cells toward various lineage fates. Notable publications include:

- 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)**. The authors demonstrate that a specific microRNA can direct the smooth muscle fate and that a combination of microRNAs function 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*, 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." *PNAS*, 2009. **PI: S. Chien (Comprehensive, UCSD); Postdoctoral Trainee: S. Oh**. This paper demonstrated that engineered microenvironments can 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.

There are approximately 60 active grants pursuing this strategic goal:

- About 15 address safety (teratoma formation).
- About 24 address self-renewal.
- About 17 address reprogramming.
- About four address cancer/oncogenic potential.

Grantees are exploring various mechanisms underlying the biology of self-renewal and oncogenic transformation. Included among these are microRNA pathways, methylation patterns and chromatin remodeling, transcriptional circuits underlying pluripotency and fate control, stem cell proliferation and signaling mechanisms, cell migration and apoptosis, mitochondrial characteristics, and the roles of the microenvironment and stem cell niche in fate determination. More recently, several new grants are attempting to develop safer ways to induce pluripotency (non-viral methods).

Outcomes: CIRM funding has supported 16 publications investigating the mechanisms regulating the self-renewal and oncogenic potential of embryonic stem cells and their derivatives. Notable publications include:

- Xu, N., et al. "MicroRNA-145 regulates OCT4, SOX2, and KLF4 and represses pluripotency in human embryonic stem cells." *Cell*, 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.
 - Gaspar-Maia, A., et al. "Chd1 regulates open chromatin and pluripotency of embryonic stem cells." *Nature*, 2009. **PI: Miguel Ramalho-Santos (SEED, New Cell Lines grants, UCSF). Contributing Authors: Kathrin Plath (New Faculty, UCLA), Rupa Sridharan (Trainee, UCLA)**. 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.
- Goal X: CIRM will have enabled development of new methods for tissue replacement based on stem cell research.

CIRM is currently funding the following grants that address this strategic goal:

- three tissue engineering grants;
- about 20 grants investigating the microenvironment and stem cell niche, either in context of organism or in vitro culture. These concepts are also being explored in context of degenerative environments (neural, muscular and retinal degeneration); and
- More than 50 grants investigating cells with focus toward eventual therapy.

These grants have potential to impact our understanding of tissue architecture in several areas, most notably in cardiac biology but also in organs such as the intestine, eye, liver and vasculature.

APPENDIX 2

RESEARCH PAPERS FUNDED IN WHOLE OR IN PART BY CIRM

- "Inhibition of mTOR Attenuates Store-operated Ca²⁺ Entry in Cells from Endarterectomized Tissues of Patients with Chronic Thromboembolic Pulmonary Hypertension." **Ogawa A, Firth AL, Yao W, Madani MM, Kerr KM, Auger WR, Jamieson SW, Thistlethwaite PA, Yuan JX.** *Am J Physiol Lung Cell Mol Physiol* 7/24/2009, Pub Med ID. # 19633069
- "Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease." **Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Müller FJ, Loring JF, Yamasaki TR, Poon WW, Green KN, Laferla FM.** *Proc Natl Acad Sci U S A* 7/24/2009, Pub Med ID. # 19633196
- "PARP-1 deficiency increases the severity of disease in a mouse model of multiple sclerosis." **Selvaraj V, Soundarapandian MM, Chechneva O, Williams AJ, Sidorov MK, Soulika AM, Pleasure DE, Deng W.** *J Biol Chem* 7/23/2009, Pub Med ID. # 19628872
- "A regulatory pathway involving Notch1/beta-catenin/Isl1 determines cardiac progenitor cell fate." **Kwon C, Qian L, Cheng P, Nigam V, Arnold J, Srivastava D.** *Nat Cell Biol* 7/20/2009, Pub Med ID. # 19620969
- "Digital RNA allelotyping reveals tissue-specific and allele-specific gene expression in human." **Zhang K, Li JB, Gao Y, Egli D, Xie B, Deng J, Li Z, Lee JH, Aach J, Leproust EM, Eggan K, Church GM.** *Nat Methods* 7/20/2009, Pub Med ID. # 19620972
- "Regeneration of the mammalian inner ear sensory epithelium." **Wei D, Yamoah EN.** *Curr Opin Otolaryngol Head Neck Surg* 7/15/2009, Pub Med ID. # 19617827
- "Naturally derived myocardial matrix as an injectable scaffold for cardiac tissue engineering." **Singelyn JM, Dequach JA, Seif-Naraghi SB, Littlefield RB, Schup-Magoffin PJ, Christman KL.** *Biomaterials* 7/14/2009, Pub Med ID. # 19608268
- "Xeno-free defined conditions for culture of human embryonic stem cells, neural stem cells and dopaminergic neurons derived from them." **Swistowski A, Peng J, Han Y, Swistowska AM, Rao MS, Zeng X.** *PLoS One* 7/14/2009, Pub Med ID. # 19597550
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- "Nkx6-1 controls the identity and fate of red nucleus and oculomotor neurons in the mouse midbrain." **Prakash N, Puelles E, Freude K, Trümbach D, Omodei D, Di Salvio M, Sussel L, Ericson J, Sander M, Simeone A, Wurst W.** *Development* 7/10/2009, Pub Med ID. # 19592574
- "Polysialic acid governs T-cell development by regulating progenitor access to the thymus." **Drake PM, Stock CM, Nathan JK, Gip P, Golden KP, Weinhold B, Gerardy-Schahn R, Bertozzi CR.** *Proc Natl Acad Sci U S A* 7/8/2009, Pub Med ID. # 19587240
- "Chd1 regulates open chromatin and pluripotency of embryonic stem cells." **Gaspar-Maia A, Alajem A, Polesso F, Sridharan R, Mason MJ, Heidersbach A, Ramalho-Santos J, McManus MT, Plath K, Meshorer E, Ramalho-Santos M.** *Nature* 7/8/2009, Pub Med ID. # 19587682
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