Organizational Profile

California Institute for Regenerative Medicine: the road ahead

The California Institute for Regenerative Medicine (CIRM) has completed 4 years of full operation and has allocated over US\$1.1 billion for buildings, laboratories, training, foundation research, basic research and, more recently, translational and preclinical research. CIRM was recently reviewed by an external committee and will make some adjustments to the program to address their primary recommendations. This will include a closer working relationship with industry and a more proactive approach to linking the best and fastest moving stem cell science from around the world with scientists and the biotech industry in California, USA. While basic stem cell science must be supported to remain innovative and strong, CIRM will encourage the translation of discoveries to clinical application and facilitate the rapid adoption of safe and effective therapies that are evolving from the program.

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The California Institute for Regenerative Medicine's breadth of activity

The California Institute for Regenerative Medicine (CIRM) was founded in November 2004 with the passing of Proposition 71 in California that authorized the sale of US\$3 billion state general obligation bonds at a maximum rate of \$300 million/year for the support of stem cell research and regenerative medicine. Funding was initiated in April 2006, using bond anticipation funds provided by private donors and a loan from the Governor of California, Arnold Schwarzenegger. CIRM was defending the constitutional validity of CIRM against legal challenges in the state courts between 2004 and 2006 and was unable to sell state bonds to fund the research. By the end of 2010, there were seven new major CIRM-funded Stem Cell Institutes opened in Californian Universities with another five due to be completed in 2011. CIRM's investment of \$271 million was more than matched by >\$800 million in private donor and institutional contributions to these buildings and their contents. By 2010, training and seed grants for basic and physician

scientists and mid-career scientists changing disciplines were awarded, comprehensive awards made to established scientists, new faculty appointments made and an innovative 'Bridges Program' established to enable Californian state university and college students to gain training and internships at the major stem cell research programs in academia and industry (see FIGURE 1). Over the initial 4 years of operation, CIRM has committed \$321 million in physical infrastructure and equipment, \$220 million in intellectual infrastructure, \$227 million on foundational basic research and \$300 million on translational research.

The impact of CIRM has already been dramatic [101]. In the last 3 years the training grants have supported 279 predoctoral students and postdoctoral and clinical fellows in 219 laboratories across California. These scholars have contributed as authors to 358 publications (as of August 2010). There were a total of 584 publications from all CIRM grantees at that time, 23% of which were in the high profile, high impact journals. CIRM-funded research has contributed to the initiation of several early-stage clinical trials and the creation of a major pipeline of translational and

preclinical studies focused on the development of clinical trial registrations. We expect that the front line of these studies will result in clinical trials in the next 3–4 years for the treatment of Type 1 diabetes, glioblastoma, HIV/AIDS, leukemia, heart disease, blood cell cancers and solid tumors, and macular degeneration. A little further back are potential treatments for stroke, amyotrophic lateral sclerosis, sickle cell disease and the inherited skin disorder known as epidermolysis bullosa.

The California Institute for Regenerative Medicine funds research involving both stem and progenitor cells. This includes pluripotent stem cells (both embryonic stem cells and induced pluripotent stem [iPS] cells), mature stem cells (fetal and adult stem cells), small molecules and biologics that evolve from stem cell research – including those that target cancer stem cells (CSCs) or mobilize endogenous stem cells (FIGURE 2). Work on progenitor cells that differentiate from stem cell populations are also targets for CIRM support. The program has a substantial tools and technologies component that is needed for support of basic research and translation, and we support work on tissue engineering.

Moving the research program forward

To date, the approach taken by CIRM has been to support a bottom-up approach where grants are solicited from scientists and technologists in areas that are general and broad (e.g., basic, translational, tools and technologies). These applications are reviewed by a panel of exceptional non-Californian scientists and patient advocates from the CIRM Board. The recommendations for funding are provided to the CIRM Board for a final decision. CIRM has a number of collaborative funding partners including: the Canadian Cancer Stem Cell Consortium, State of Victoria Australia, Japan Science and Technology Agency, State of Andalucía and the Federal Ministry of Science and Innovation (Spain), UK Medical Research Council, Germany's Federal Ministry of Education and Research, China's Ministry of Science and Technology and the Indian Institute for Stem Cell Biology and Regenerative Medicine. CIRM also has collaborating relationships with the State of Maryland, the New York Stem Cell

Figure 1. The California Institute for Regenerative Medicine (CIRM) timeline.

Figure 2. Number of projects awarded by the California Institute for Regenerative Medicine (CIRM) from 2006 to 2010 in the various categories of stem cell types.

hAdult SC: Human adult stem cell; hCSC: Human cancer stem cell; hESC: Human embryonic stem cell; hiPS: Human induced pluripotent stem; hSCNT: Human somatic cell nuclear transfer; Other: Nonhuman cells or no cell use.

Foundation and the Juvenile Diabetes Research Foundation. Grants awarded for collaborating projects are jointly supported by CIRM and the funding agency that relates to the collaborating scientists. This enables the best teams from around the world to work together and significantly leverages CIRM investment in research (TABLE 1). CIRM is further expanding the collaborating partner program and expects to have arrangements in place in the near future with several additional European and other leading stem cell research countries. The aim is to link the most advanced laboratories and biotechnology companies in the world with the fast moving Californian regenerative medicine programs and companies.

The California Institute for Regenerative Medicine is able to respond very rapidly to developments in the field (see FIGURE 3) because of the abbreviated grant evaluation time. Nominally we seek grant applications on a rolling 12-month basis for basic stem cell research, but that could be contracted if a new platform of research opportunities arise. We are considering the area of direct reprogramming of cells as one of those that could establish a new direction for basic and applied research and may attract a specially targeted request for applications (RFAs). In another area we are exploring the merger of stem cells and genomics where we believe there is substantial potential to link disease areas and medical

Table 1. Collaborative partner participation in the California Institute for Regenerative Medicine (CIRM) request for applications.

RFA	CSCC	BMBF	JST	MRC	Victoria	Total
Early translation		US\$1,880,999 (3)			US\$3,868,934 (4)	US\$5,749,933
Disease teams	US\$36,414,513 (2)			US\$8,394,738 (2)		US\$44,809,251
Basic biology			US\$900,000 (1)			US\$900,000
Immunology					US\$1,094,454 (2)	US\$1,094,454
	US\$36,414,513 (2)	US\$1,880,999 (3)	US\$900,000 (1)	US\$8,394,738 (2)	US\$4,963,388 (6)	US\$52,553,638

Note: () – Number of collaborating grants awarded.

BMBF: Federal Ministry of Education and Research; CSCC: Cancer Stem Cell Consortium; JST: Japan Science and Technology Agency; MRC: Medical Research Council; RFA: Request for applications; Victoria: The State of Victoria.

records with iPS cells and genomics and epigenomics at a level never envisaged before. This has the potential to help us understand the mechanisms of disease, determine the heterogeneity of human disease and identify targets for treatment and cure of severe diseases. Centers of excellence in stem cell genomics may have a very important part to play in improving global human health.

The preclinical development program at CIRM (Disease Team Therapies) integrates academic scientists and biotech company teams [1] who have innovative flair, are responsible for driving discovery, and have the experience and focus that is essential for the requirements of clinical trial registration. CIRM and a consortium of partners (Regenerative Medicine Consortium) have been working closely with the US FDA to become well acquainted with the expectations for cell and molecular therapies. In addition, key executives from CIRM are closely involved on the board of the industry organization, the Alliance for Regenerative Medicine, which is also working to establish standard operating procedures for the regulatory pathway. The benefits of combining academic and industry members include a deep intellectual capacity in academic basic research that can solve problems encountered in

development of the therapeutic product and the relevant experience that exists in company project management needed to logically address the translation process necessary for completing registration for a clinical trial. This includes activity-based budgeting that is designed to complement the activities needed for completing the project.

How to deliver the evolving cell therapies to the patient

Most small molecule and biologic therapies that develop from stem cells will pass through the new drug development pathway and be taken up by the biotech and pharmaceutical companies. For example, work supported by CIRM identified that a particular mutation in JAK2 (JAK2V617F) is necessary and sufficient to induce aberrant myeloid differentiation in the disease of polycythemia vera [2]. The JAK2 inhibitor TG101348 effectively reverses the phenotype and was used by the company TargeGen for an early Phase I clinical trial with very encouraging results for patients with polycythemia vera. This clinical work will progress under the direction of the pharmaceutical company Sanofi Aventis US. In a similar example, a CIRM-funded project showed the hedgehog signaling pathway was needed to maintain cancer stem cells in chronic myelogenous leukemia [3]. Further work on preclinical studies on leukemic CSCs with a small molecule inhibitor of the hedgehog pathway has resulted in Pfizer initiating Phase I clinical testing in chronic myelogenous leukemia.

However, not all stem cell-derived therapies can be delivered in this model of a drug therapy. In particular, cases requiring manipulation of the patients' own cells, or the delivery of cells to specific sites in the body, may be more amenable to delivery through tertiary clinical centers in a model that is more akin to the bone marrow transplant units, cancer centers or *in vitro* fertilization clinics. The presence of committed clinical expertise, cell and molecular biologists, experienced nursing staff and patient counselors will be necessary for clinical applications of cell therapies. The approach that we term the Alpha Stem Cell Clinic model could be established in major cities and involve the presently approved studies with bone

Figure 3. Major stem discoveries above the timeline and the California Institute for Regenerative Medicine (CIRM) grant awards seeking applications on these discoveries below the timeline.

iPS: Induced pluripotent stem; RFAs: Request for applications.

marrow and mesenchymal/adipose stem cells to treat patients with appropriate conditions. While these may not be the most effective therapies or cures, they may be the most appropriate treatments presently available. These Alpha Clinics could be sites for the evolving cell therapy trials for newer and more effective cell therapies. The capacity to closely monitor patients for extended periods, to provide patients with the full information on what is genuinely available in terms of treatment and expected outcome, and to provide the necessary good manufacturing practice facilities, surgeries and expertise to handle and manipulate cells is absolutely critical. CIRM will explore this concept of seeding Alpha Clinics in California to initiate the cell therapy practices that are moving through the clinical pipeline for patients.

Connecting with industry

The California Institute for Regenerative Medicine has already supported a number of Californian biotech companies with grants and loans where the company is the lead investigator. This includes companies such as ViaCyte, Calimmune, BioTime, VistaGen Therapeutics, Gamma Medica Ideas, Vala Sciences, Fluidigm and iPierian. CIRM is working closely with resources and technology from other companies such as Geron, Sangamo Biosciences and Life Technologies. We will be working to facilitate a more comprehensive linkage with the biotech and pharmaceutical industry in the next few years. Access to CIRM loans will be enabled by revisions to the loans program to make them more attractive. The developmental pipeline will be made more accessible to companies by abbreviating the grant and loan review processes, making the pipeline more 'porous' for entry into translation, preclinical and clinical trial awards. Where there is major technology rapidly evolving outside California, CIRM will become proactive in linking with it through our collaborative funding partners or encouraging partnerships with Californian researchers and companies. These connections may be assisted by advice from key scientists and technologists. In addition CIRM seeks to become better informed of the early-stage venture capital industry approaches to supporting innovative bioscience.

There is an increasing interest from the major pharmaceutical companies in stem cell technology, particularly in the area of iPS cells, which represent a valuable asset for the study of human disease and its diversity even within specific diseases. The development of 'disease in the dish' models that CIRM and others are creating can provide an extremely valuable screening method for new small molecule drug candidates that may be effective for controlling pathologies in some sections of the disease population whilst being ineffective or adversely effective in some other patients. Diagnosis of these variant populations will advance personalized medical therapies. The iPS cells will also be informative of the nature of the disease mechanism, which is important in complex diseases governed by several or many genes and environmental factors. Some of this will be illuminated by stem cell genomic or epigenomic analyses.

The California Institute for Regenerative Medicine will be looking to connect with major biotech, service and pharmaceutical companies in order to advance clinical trials and applications of stem cell discoveries. This is necessary for the manufacturing of therapeutic products and their development for clinical marketing. Options may include the co-development of certain areas of common interest and co-funding of some specific RFAs or particular research opportunities.

Addressing roadblocks to global success

Linking scientists across the globe is relatively easy when governments and industry see the financial and social benefits. CIRM has a robust collaborating partner program that has very strong support from senior scientists from the best laboratories in the world. Current economic pressures hamper some government agencies from participating with CIRM in individual RFAs and for some extended time frames. However, the benefits of partnering are substantial. Scientists in collaborations push each other hard and work goes on around the clock. Communications are now relatively easy and immediate. The opportunity to partner with biotech companies can be very worthwhile and lead to the sharing of commercial benefits and clinical trials

for patients. Scientists in these partnerships have open exchange of critical reagents and information from experiments and analyses. This accelerates progress and provides further competitive advantages for all members of the collaboration. Scientific manuscripts are more quickly composed and revisions and additional data more easily collated. This again leads to enhanced reputations and recognition of productivity. All this can strengthen the research environment. Critically, patients can benefit from international clinical trials and can become strong advocates for the global collaborative endeavors.

The California Institute for Regenerative Medicine has substantial but limited resources, which means that we cannot support projects beyond Phase II. Hence the pipeline of developments needs connection to other government or industry bodies to enable the programs to eventually reach the patient. There will be connections to the pharmaceutical industry and we will engage other partners to help facilitate the therapies that are desperately needed. A cure for HIV/AIDS evolving from CIRM support needs to progress to an effective vaccine for global health-care and other stem cell-based therapies need to be made available at a cost that is amenable to use everywhere. These are great challenges that can be met by working together. A bond initiative that was developed by the World Bank for preventing HIV/AIDS could draw international scientists together in an extraordinary way that could be successful when based on the rapid developments that are now occurring in cell biology and cell therapies, genomics and immunology. The savings in current medicine and social support for a disease such as HIV/AIDS is very large and the benefits would offset the cost of the bonds.

Looking forward

Progress has been extremely rapid in stem cell biology. The developments in iPS cells and the direct reprogramming of cells from one lineage type to another (transdifferentiation) happened quickly and may herald a new platform

for application in regenerative medicine. This means that patient immune-compatible cells will become available for clinical use. The optimism that is apparent and well founded [4] is likely to provide cellular products, engineered tissue products, new drugs and biologics for mobilizing tissue-specific stem cells and for targeting metastasizing CSCs that will become available for patients. It is very possible, in the next 10 years, that CIRM will continue to be financed and will be funding these important developments. Science is very likely to become globally united with the resources to begin to relieve humanity from the burden of major diseases, poverty and the despair of the effects of pandemics that decimate susceptible populations.

Financial & competing interests disclosure

A Trounson is an employee of the Californian Institute for Regenerative Medicine (CIRM). The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Bibliography

- 1 Trounson A, Baum E, Gibbons D, Tekamp-Olson P: Developing a model for successful translation of stem cell therapies. *Cell Stem Cell* 6(6), 513–516 (2010).
- 2 Geron I, Abrahamsson AE, Barroga CF *et al.*: Selective inhibition of JAK2-driven erythroid differentiation of polycythemia vera progenitors. *Cancer Cell* 13(4), 321–330 (2008).
- 3 Zhao C, Chen A, Jamieson C *et al.*: Hedgehog signalling is essential for maintenance of cancer stem cells in myeloid leukaemia. *Nature* 458, 776–779 (2009).
- 4 Trounson A, Gibbons D: The promise of regeneration in: 2030: seven visions of the future. *COSMOS* 33, 58–59 (2010).

Website

- 101 CIRM: Report of the External Advisory Panel www.cirm.ca.gov/files/PDFs/Administrative/CIRM-EAP_Report.pdf