June 2010

# Matching the expenditure of CIRM's authorized $3 billion to its Strategic Goals

This document follows internal discussions at CIRM about the pace at which CIRM is funding its research. It began as an effort to estimate the projected longevity of the $3 billion but evolved into an analysis of whether CIRM's funding programs are best targeted to achieve the goals laid out in the 2006 Strategic Plan.

Progress toward many of these goals is quite impressive. As CIRM approaches five years of research funding, its grantees are on target to accomplish most, if not all, of the 5-year benchmark goals listed in the 2006 Strategic Plan. Some, like increasing the stem cell research work force, have already been achieved. Similarly, many of the 10-year goals appear to be within reach. Thus this document will focus on the most ambitious and difficult 10-year goals, related to moving stem cell therapies into the clinic.

## Initial assumptions

Over the past year CIRM has been developing a regular schedule of RFAs that will repeat on an annual basis. There are several advantages to such a schedule. It provides predictability for our grantees and co-funding partners; it allows the staff to plan well in advance; and it creates a basis for projecting the expenditure of CIRM's funds. However, it is also clear that not all RFAs should repeat annually – e.g. training – and not all future programmatic needs can be anticipated now. Therefore, in planning future RFAs to carry through the entire $3 billion, it is important to allow for flexibility and some one-time offerings.

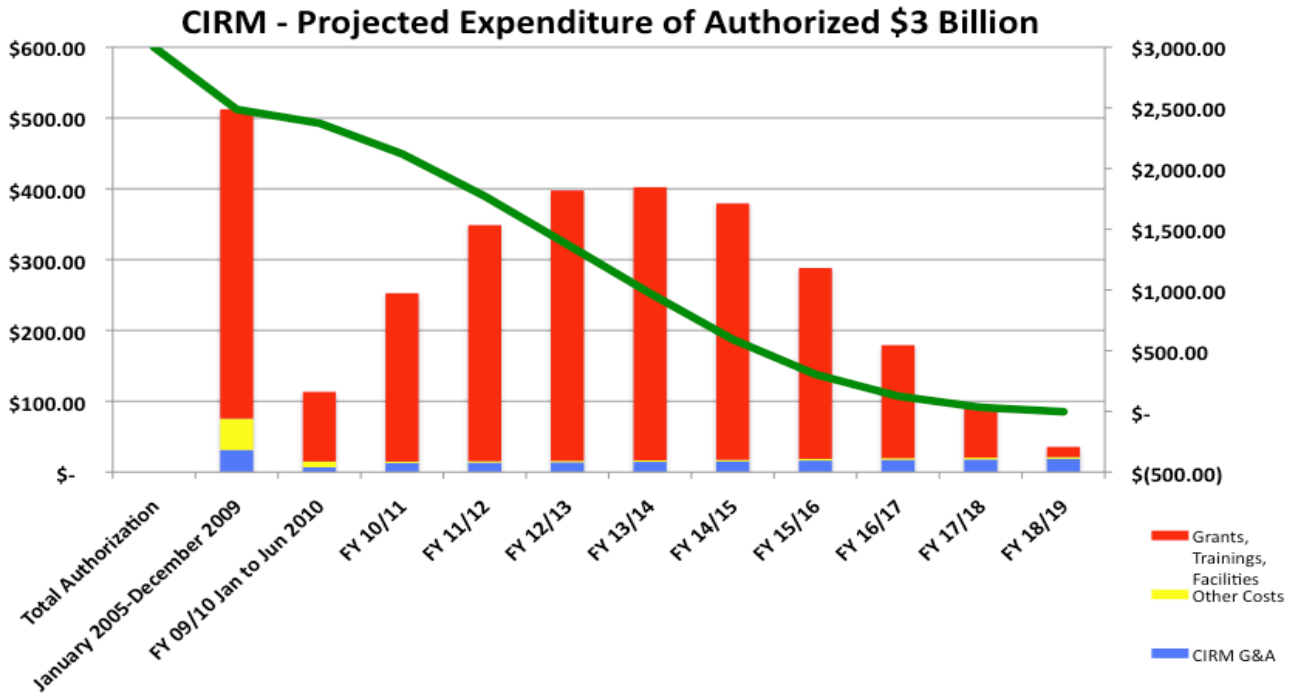
With these requirements in mind a plan for future RFAs was constructed with input from the President and the Science Office. That plan is shown in Table 1. It includes four RFAs that would repeat annually. Three of those are core RFAs – Basic Stem Cell Biology, Early Translational and Diseases Teams – that address different stages in the research pipeline and the dollar amounts assigned to each are based on previous rounds of funding by the ICOC. The fourth has been designated "to be determined". It is intended to provide the flexibility needed to address new research challenges that result from advances and obstacles that arise as the field of stem cell research matures. It is projected at $30 million per year. Also included are RFAs for Tools and Technologies ($40M) and Clinical Development ($50M), which have already received concept approval from the ICOC, and three one-time programs that are anticipated for the near future. They include an RFA related to iPS cell banking and one additional round each for Training and Bridges, two programs that have been highly successful.

**Table 1**

| Program | Frequency | Next ICOC Decision | Total/RFA |
|---|---|---|---|
| Early Translational | Every 12 months | October 2010 | $80M |
| Basic Stem Cell Biology | Every 12 months | April 2011 | $40M |
| Variable - To Be Determined | Every 12 months | June 2011 | $30M |
| Disease Teams | Every 12 months | August 2011 | $230M |
| Tools and Technology | One time | January 2011 | $40M |
| Clinical Development | One time | July 2011 | $50M |
| iPS Cell Banking | One time | TBD 2011-12 | $25M |
| Training 3 | One time | June 2012 | $45M |
| Bridges 2 | One time | June 2012 | $20M |

When these programs are projected forward the outcome is illustrated in Figure 1 which is a graph summarizing the expenditure of the full $3 billion. Under this scenario the final RFA would be Disease Team 5. It would be released early in 2014 and would be presented to the ICOC for approval in August of that year. If it were a four-year program, like Disease Teams 1, all funds would be expended by early 2019.

**Figure 1** – The columns in this graph show the annual expenditures for research and facilities (red), operations (blue) and other expenses (yellow – capitalized interest, bond issuance) based on the RFA schedule outlined in Table 1. The first column on the left (Jan 05-Dec 09) is based on actual expenditures and the others are projections. For each column, the values are indicated by the numbers along the vertical axis on the left (in $millions). The green line indicates the total amount of CIRM's $3 billion authorization remaining to be expended with the amounts indicated along the vertical axis on the right (in $millions). Thus the line begins at $3 billion (upper left) and declines to zero in FY 18/19 (lower right).




This scenario raises the concern that CIRM may be pushing its programs forward too fast to meet its mission. Stem cell science is a rapidly progressing, fast moving field. However, it is still a young discipline. The next big advances to come out of basic research can only be imagined but it is not unreasonable to expect additional paradigm-shifting results in the next couple of years that will rival the initial development of iPS technologies. CIRM may well be in position to contribute to those breakthroughs but will it have enough money and time remaining to push them into the clinic? Currently, there are programs in the pipeline with potential for significant clinical benefits but, given the early stage of stem cell research and the well-documented studies of success rates in drug development, it is difficult to predict how many, if any, of them will fulfill that promise. However, as the field matures there will surely be many more therapeutic candidates and it is reasonable to predict that some of the later ones will have a greater chance of success because they will be able to take advantage of more advanced technologies.

This is a difficult issue that requires some crystal ball gazing. One could argue that the future directions of the field are unknown, so CIRM should invest as much funding as possible now to push it along, and assume that other funding sources will be available to develop CIRM-funded discoveries.

Alternatively, one could make the case that the greatest benefits (health-related and economic) from CIRM's investments will come from clinically proven therapies, so funds should be reserved to support those efforts when the field is more advanced. This could be accomplished by reducing the frequency of RFAs or by reducing their targeted budgets. Either (or a combined) approach would spread out CIRM's funds; permit additional cycles of funding (including Basic Biology, Early Translational and Disease

Teams); and allow the field to mature an additional year or two before starting the last clinical programs.

CIRM's Strategic Plan

One instructive way to evaluate CIRM's funding strategies is to benchmark CIRM's RFA schedule against its strategic aims and industry standards for developing new therapeutics. In CIRM's strategic plan, the first, and most ambitious, of its 10-year goals states that "CIRM grantees will have clinical proof-of-principle that transplanted cells derived from pluripotent stem cells can be used to restore function in at least one disease." (i.e. will have completed a Phase 2 trial for a pluripotent-derived cellular therapy that shows safety and efficacy). What must CIRM do to be confident that it can achieve that goal? How long will it take?

In many cases, research into potential therapeutics in the early stages of development (e.g. Early Translational 1 and most Disease Team 1 projects) does not result in submission of an IND that is accepted by the FDA. Further, a number of studies show that only about 20% of drugs that enter Phase 1, first–in-man clinical trials succeed in demonstrating safety and efficacy in Phase 2 trials. Of that 20%, only about half eventually succeed in Phase 3 and make it to clinical practice. These statistics are based on small molecule drugs and biologics, such as monoclonal antibody therapeutics, and not on novel cell therapeutics for which there are very limited data and regulatory history. Nevertheless, these odds indicate that CIRM should plan to have at least 5 pluripotent cellular therapies accepted by the FDA for Phase 1 clinical trials in order to be confident that at least one will show effectiveness in a Phase 2 study. Based on reported probabilities, *twice* that many will be required for development of a useful therapy. Further, it takes 5-10 years for a drug to get from Phase 1 through Phase 3 and to patients, but it is likely that this process will take longer for the initial pluripotent stem cell therapies because of the novelty of the therapeutic strategy, the lack of a well defined regulatory framework and, most importantly, the safety concerns inherent with pluripotent cell-derived cellular therapeutics.

Currently, five of CIRM's Disease Team awards support research programs that will use pluripotent stem cells to develop therapies. They are slated to submit INDs to the FDA by 2014; while some will make or, perhaps, even beat that target, others probably will not. The next round of disease team applications is scheduled to go to the ICOC for approval in August 2011 and a Clinical Development RFA is being planned that could fund up to two projects using pluripotent stem cells for Phase 1-2 trials beginning in 2011.

To determine the number of INDs, the time and the investment required to reach the above stated goal of developing a pluripotent cell-based therapy through Phase 2 trials, the following assumptions were used:

1. A minimum of 5 FDA-accepted INDs will be required (10 preferred).

2. Half of the Disease Team awards that fund projects using pluripotent stem cells will lead to FDA-accepted INDs in 5 years (4 years to submission plus 1 for acceptance).
3. In 2011 CIRM will provide support for clinical trials for 2 pluripotent cellular therapies with FDA authorization to initiate testing in humans.
4. The time period from IND approval to the completion of a Phase 2 trial (not Phase 3) will be 5 years.
5. Each project with an accepted IND will require $25 million from CIRM to proceed through a Phase 2 trial (if additional funds are required, they would come from other sources).

Table 2 summarizes these assumptions and projected timelines.

**Table 2 –** In column 3 (Pluripotent SC projects) all numbers are estimates except for Disease Team 1. In this model it is assumed that Disease Teams 3 would be restricted to cellular therapies using pluripotent cells. In column 4 (INDs in 5 years) the numbers are estimated. However applicants for Clinical Development funding in 2011 must already have an FDA-accepted IND by the time of funding.

| RFA | Start Date | Pluripotent SC projects | INDs in 5 years | Clinical trial funding date ($25M each) | Phase 2 - completion date |
|---|---|---|---|---|---|
| Disease Teams 1 | 2010 | 5 | 2 | 2015 | 2020 |
| Clinical Development | 2011 | 2 | 2 (obtained) | 2011 | 2016 |
| Disease Teams 2 | 2011-12 | 6 | 3 | 2016-17 | 2021-22 |
| Disease Teams 3 | 2012-13 | 6 | 3 | 2017-18 | 2022-23 |

Based on the assumptions used to create Table 2, it seems unlikely that the goal - "…clinical proof-of-principle that transplanted cells derived from pluripotent stem cells can be used to restore function in at least one disease" – can be reached in the original 10-year time frame (by 2016) unless a recipient of a Clinical Development Award proceeds quickly and successfully through Phase 2. It is more reasonable to anticipate that this milestone would be achievable by 2021 or 2022, but for that to happen CIRM would have be make clinical trial funding commitments in 2015, 2016 and possibly 2017. Based on the current RFA pattern and projections described at the beginning of this document, all CIRM funds will be committed by 2014.

An alternative approach is presented in Table 3, which is a modification of Table 1. It summarizes a revised RFA schedule that is intended to address the needs outlined

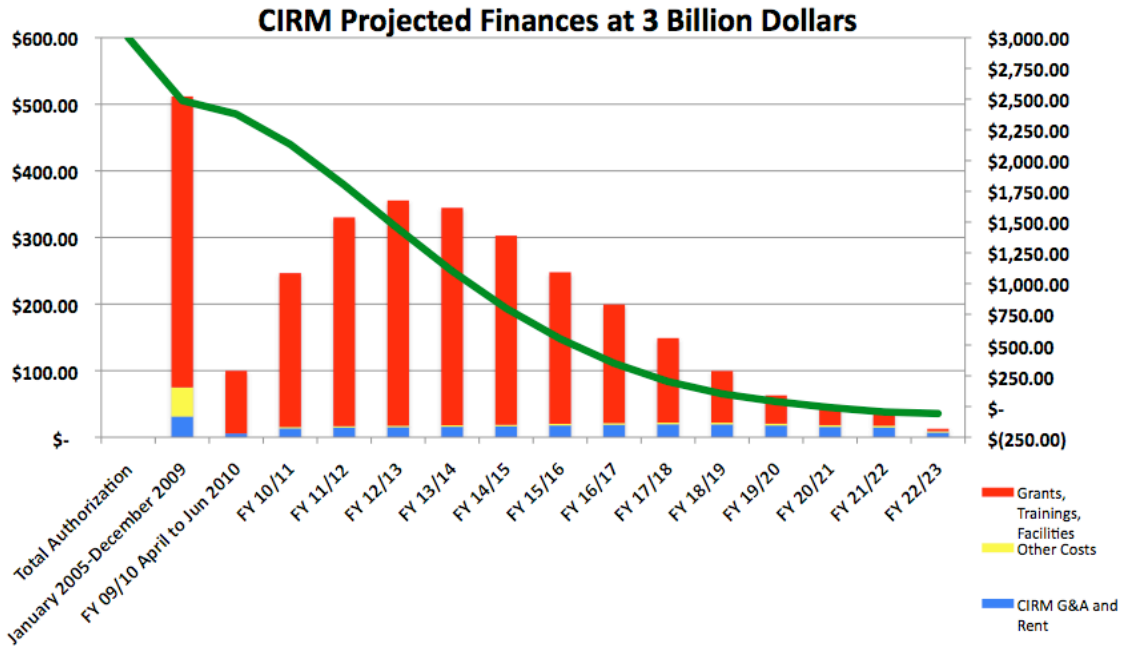
above and in Table 2. The total allocated for research funding is the same as in Table 1 but the time-period during which RFAs will be issued is extended from 2014 to 2017. It also incorporates new clinical trial RFAs to fund projects from Disease Teams 1-3 that have moved through the IND approval process ("Clinical Trials - Follow-on", highlighted in green). In order to do this, the amounts allocated to each future Disease Team RFA was reduced significantly, although an additional round of Disease Team funding was added (Disease Teams 6). Smaller reductions were also made in other repeating core RFAs. All programs that are reduced relative to Table 1 are highlighted in yellow and a full list of RFAs based on this plan is provided as Appendix 1.

**Table 3**

| Program | Frequency | Next ICOC Decision | Total/RFA |
|---|---|---|---|
| Early Translational | Every 12 months | October 2010<br>October 2011 et. al | $80M<br>$65M |
| Basic Stem Cell Biology | Every 12 months | April 2011 | $35M |
| Variable - To Be Determined | Every 12 months | June 2011 | $30M |
| Disease Teams | Every 12 months | August 2011<br>August 2012 et. al | $200M<br>$120M |
| Clinical Trials - Follow-on | Every 12 months | August 2015<br>August 2016<br>August 2017 | $50M<br>$75M<br>$75M |
| Tools and Technology | One time | January 2011 | $40M |
| Clinical Development | One time | July 2011 | $50M |
| iPS Cell Banking | One time | TBD 2011-12 | $25M |
| Training 3 | One time | June 2012 | $45M |
| Bridges 2 | One time | June 2012 | $20M |

A summary of the expenditure of the full $3 billion based on this extended RFA schedule is shown in Figure 2. Under this scenario the final RFA would be the third Clinical Trial Follow-on. Awards would be made by the ICOC in 2017 and the program would be complete by early 2023, assuming a funding period of five years.

**Figure 2** – As in Figure 1, the columns show the annual expenditures for research and facilities (red), operations (blue) and other expenses (yellow – capitalized interest, bond issuance). In this case the projections are based on the RFA schedule in Table 3. For each column the values are indicated by the numbers along the vertical axis on the left (in $millions). The green line indicates the total amount of CIRM's $3 billion authorization remaining to be expended with the amounts indicated along the vertical axis on the right (in $millions). Thus the line begins at $3 billion (upper left) and declines until the last program terminates in FY 22/23 (lower right).




There are other important issues to consider in evaluating these plans.

1. When making adjustments to the RFA schedule an effort was made to segregate funds into programs designed to accomplish a specific goal listed in the strategic plan of 2006. However, programs were also retained (e.g. later rounds of Basic Biology, Early Translational and Disease Teams) that would continue supporting projects at all stages along the research pipeline until the end of the Institute's lifespan, even though CIRM would not be able to deliver many of those projects to the clinic. This approach was supported in the 2006 Scientific Strategic Plan and it ensures that CIRM would always be funding research at the leading edge of the stem cell field. Assigning proportionality in this funding approach is an important strategic decision.

2. Increasing funding for Disease Team programs in the next 2 rounds (2011 and 2012) is not likely to help CIRM reach its first strategic goal prior to 2021 since it is estimated that it will take about 10 years from the start of a Disease Team project to completion of a Phase 2 clinical trial.

3. This plan focuses only on the first of the Ten-Year Goals listed in CIRM's Strategic Plan and there are nine others (see Attachment 2). For example, the second Goal states – "CIRM grantees will have therapies based on stem cell research in Phase 1 or Phase 2 clinical trials for 2-4 additional diseases." Given the breadth of this goal, it is quite reasonable to expect that it will be achieved. In fact, one clinical study of polycythemia vera already meets this standard. However, future projects in this category may need support from CIRM in order to initiate Phase 1 and/or Phase 2 trials and no such funds are currently allocated

in Table 3. Support for a few (e.g. 1-3) could easily come from funds targeted at other future RFAs but, if CIRM hopes to be able to support a large number of such projects (e.g. 10-20), the cost could rise to hundreds of millions of dollars.

4. There are eight additional Ten-Year Goals listed in the 2006 Strategic Plan. Many of them will rely heavily on basic research, if they are to be achieved, so CIRM cannot stop investing in the early phases of the research pipeline.

5. CIRM makes its research funding predictions based on the expectation that the approved research programs will be successful. However, it is possible that some research investments will be returned, if projects fail to meet go-no-go milestones or if they are terminated for other reasons. The amount that might be returned is very difficult to predict, especially since the first projects with go-no-go decision points are just beginning. If it is assumed that 10% of all research investments from this point forward will be returned to CIRM to be used for future RFAs, the total would be less than $200 million (10% of the remaining, uncommitted $1.9 billion). Such funds could be used to increase the amounts of future RFAs or to support additional RFAs, including clinical trials.

6. Should the 2006 Strategic Plan be modified? The external review of CIRM that is to be completed during this calendar year will provide an opportunity for highly regarded experts to evaluate CIRM's performance and benchmark its progress against the goals laid out in the 2006 Strategic Plan. That review will provide a timely opportunity to consider revisions to the goals and/or timelines presented in the Strategic Plan.

**APPENDIX1**

This table is a full list of RFAs based on Table 3.

| RFA | RFA Number | Amount | Stage | Start Date |
|---|---|---|---|---|
| Training 1 | RFA 05-01 | 37,253,385 | Current Program | |
| Seed | RFA 06-01 | 42,233,826 | Current Program | |
| Comprehensive Research | RFA 06-02 | 67,313,412 | Current Program | |
| Shard Labs | RFA 07-01 | 49,047,039 | Current Program | |
| New Faculty 1 | RFA 07-02 | 53,720,258 | Current Program | |
| Major Facilities | RFA 07-03 | 270,946,931 | Current Program | |
| Disease Team Planning | RFA 07-04 | 1,175,368 | Current Program | |
| New Cell Lines | RFA 07-05 | 24,449,174 | Current Program | |
| New Faculty 2 | RFA 08-01 | 59,292,558 | Current Program | |
| Tools and Technology 1 | RFA 08-02 | 19,253,974 | Current Program | |
| Bridges to Stem Cell Research 1 | RFA 08-04 | 23,873,044 | Current Program | |
| Training 2 | RFA 08-03 | 44,988,409 | Current Program | |
| Basic Biology 1 | RFA 08-07 | 16,288,581 | Current Program | |
| Early Translational 1 | RFA 08-05 | 70,401,825 | Current Program | |
| Conference Grants | RFA 08-06 | | Current Program | |
| Disease Team 1 | RFA 09-01 | 224,984,899 | Current Program | |
| Basic Biology 2 | RFA 09-02 | 30,000,000 | PFAR Stage | July/September 2010 |
| Immunology | RFA 09-03 | 30,000,000 | Review Stage | July/September 2011 |
| CIRM Leadership Award | RFA 09-04 | 44,800,000 | Review Stage | April/June 2010 |
| Early Translational 2 | RFA 10-01 | 80,000,000 | Review Stage | January/March 2011 |

| RFA | RFA Number | Amount | Stage | Start Date |
|---|---|---|---|---|
| Tools and Technology 2 | RFA 10-02 | 40,000,000 | Review Stage | April/June 2011 |
| Clinical Trials | | 50,000,000 | Concept Approved | July/September 2011 |
| IPS - banking | | 25,000,000 | Future Program | July/September 2011 |
| Basic Biology 3 | | 35,000,000 | Future Program | July/September 2011 |
| Disease Team 2 | | 200,000,000 | Future Program | December/March 2011-12 |
| Early Translational 3 | | 65,000,000 | Future Program | January/March 2012 |
| Bridges 2 | | 20,000,000 | Future Program | July/September 2012 |
| Training 3 | | 40,000,000 | Future Program | July/September 2012 |
| Basic Biology 4 | | 35,000,000 | Future Program | July/September 2012 |
| TBD | | 30,000,000 | Future Program | July/September 2012 |
| Disease Team 3 | | 120,000,000 | Future Program | December/March 2012-13 |
| Early Translational 4 | | 65,000,000 | Future Program | January/March 2013 |
| Basic Biology 5 | | 35,000,000 | Future Program | July/September 2013 |
| TBD | | 30,000,000 | Future Program | July/September 2013 |
| Disease Team 4 | | 120,000,000 | Future Program | December/March 2013-14 |
| Early Translational 5 | | 65,000,000 | Future Program | January/March 2014 |
| Basic Biology 6 | | 35,000,000 | Future Program | July/September 2014 |
| Disease Team 5 | | 120,000,000 | Future Program | October/December 2014 |
| Disease Team 1 Follow-on | | 50,000,000 | Future Program | January/March 2015 |
| Early Translational 6 | | 65,000,000 | Future Program | January/March 2015 |
| Basic Biology 7 | | 35,000,000 | Future Program | July/September 2015 |
| Disease Team 6 | | 120,000,000 | Future Program | December/March 2015-16 |
| Disease Team 2 Follow-on | | 75,000,000 | Future Program | December/March 2016-17 |

| RFA | RFA Number | Amount | Stage | Start Date |
|---|---|---|---|---|
| Disease Team 3 Follow-on | | 75,000,000 | Future Program | December/March 2017-18 |

**APPENDIX 2**

**Ten-Year Goals** (from "CIRM Scientific Strategic Plan" - December, 2006 – pp 34-36)

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.
- 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.
- Goal III: CIRM-funded projects will have achieved sufficient success to attract private capital for funding further clinical development of stem cell therapies.
- Goal IV: CIRM will have funded new approaches for achieving immune tolerance for transplantation that are in pre-clinical development.
- 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.
- 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.
- Goal VII: CIRM will have enabled development of new procedures for the production of a variety of stem and/or progenitor cells that meet GMP requirements.
- Goal VIII: Through research sponsored by CIRM and others, a thorough description of the steps of differentiation leading to the production of the various cells of the body will have been achieved.
- Goal IX: Through research sponsored by CIRM and others, the mechanisms regulating the self-renewal and oncogenic potential of embryonic stem cells and their derivatives will have been identified and characterized
- Goal X: CIRM will have enabled development of new methods for tissue replacement based on stem cell research.