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Matching the Expenditure of CIRM's Authorized $3 Billion to its Strategic Goals

This document follows internal staff discussions about the pace at which CIRM is funding its research. It began as an effort to estimate the 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 schedule of core RFAs that will repeat on a regular 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 will repeat regularly 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 some one-time offerings and to anticipate that changes will occur as new challenges and opportunities arise.

With these requirements in mind a plan for future RFAs was constructed with input from the President and the Science Office. That plan is summarized in Table 1. It includes three core RFAs that repeat regularly – Basic Stem Cell Biology, Early Translational and Diseases Teams. Each addresses different stages in the research pipeline and the dollar amounts assigned to each are based on previous rounds of funding by the ICOC and anticipated future needs. Also included are two RFAs that are planned for the near future - Tools and Technologies 2 and Clinical Development - which have already received concept approval from the ICOC; six one-time programs; and two Disease Team Follow-on RFAs. Finally two RFAs are included in 2013 and 2014 that are titled, "To Be Determined". A complete list of all RFAs, based on the assumptions in Table 1, including those that have already been approved and funded is provided as Appendix 1. It is important to note that the purpose of this list is to stimulate discussion and predict longevity for CIRM's funds. It merely provides and example of how CIRM's remaining funds could be allocated.

Table 1 – RFA Schedule Based on Current Assumptions

Program	Frequency	Next ICOC Decision	Total/RFA
Early Translational	Every 15 months	October 2010	$80M – 60M
Basic Stem Cell Biology	Every 12 months	May 2011	$45M
Disease Teams	Every 24 months	August 2012	$240M – 120M
To Be Determined	Not regular	March 2014	$30M
Tools and Technology 2	Not regular	January 2011	$40M
Clinical Development	One time	May 2011	$50M
Shared Labs 2	One time	October 2011	$30M
Training 3	One time	May 2012	$45M
Bridges 2	One time	May 2012	$20M
iPS Cell Banking	One time	July 2012	$25M
Alpha-Clinic	One time	December 2012	$70M
Disease Team Follow-on	Two times	January 2014 & 16	$75M

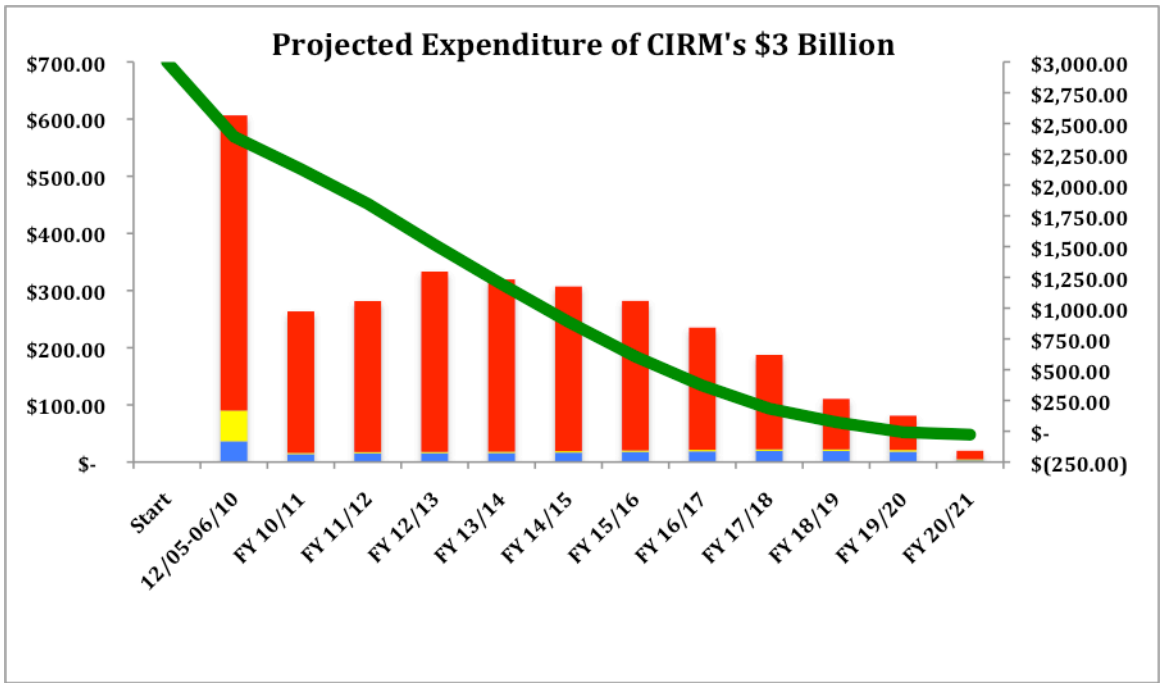
Before projecting forward to the full expenditure of CIRM's $3 billion, it is important to first explain the assumptions used in addition to the RFA schedule described above. These assumptions include the following:

1. All of the money targeted for each RFA will be committed by the ICOC. It is not unusual for the ICOC to approve projects that total more or less than the amount originally targeted for any given RFA. In this analysis it is assumed that those variances will balance.
2. It is assumed that all funds that are committed will be expended. For some RFA programs (Early Translational and Disease Teams) go-no-go decision points could result in the early termination of projects. Similarly, awards could be terminated early if the PI moves out of state or fails to make progress on the project. In those cases the amount ultimately expended would be less than the amount committed. However, CIRM is not able to predict when such savings might occur or how much they might total, so no dollar value has been assigned. See below (4 on page 7) for additional discussion of this issue.
3. No new funds will come to CIRM from revenue sharing from grantees whose CIRM-funding research is commercialized. Those funds will go to the General Fund of the State.
4. No new funds will come to CIRM from its Loan Program prior to 2020. Funds resulting from the repayment of loans or the sale of warrants will return to CIRM to support additional research. However, only one loan has been issued to date ($20 million) and it is not scheduled for repayment until 2020. Additional funds could be generated from the sale of warrants received as part of this or other loans, but CIRM's expectation is that this will not occur prior to 2020. As shown below it is likely that CIRM's $3 billion will be fully committed long before that date.
5. California will not approve additional funding for CIRM beyond the current authorization of $3 billion. It is likely that an effort will be made to extend CIRM's authorization beyond $3 billion. However, it is too early to gauge the likelihood of

that effort succeeding. It will depend on the future economic status of California and the success of CIRM's programs in producing health and economic benefits to Californians.

With these assumptions and the RFA schedule described above and listed in Appendix 1, it is possible to project the full expenditure of CIRM's $3 billion. This is illustrated in Figure 1. Under this scenario the final RFA would be presented to the ICOC in the summer of 2016 and would terminate by the end of 2020. If any of the assumptions described above change, the projection would have to be adjusted accordingly.

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 and the assumptions listed above. 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).



Is this an appropriate plan and rate for expending CIRM's $3 billion? 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 (direct re-programming; de-differentiation?) but it is not unreasonable to expect additional paradigm-shifting results in the next couple of years that will rival the impact of iPS technologies. CIRM will likely be in position to contribute to those breakthroughs but will it have enough money 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 in the future 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 combination) approach would spread out CIRM's funds; permit additional cycles of funding; 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 antibodies, and not on novel cellular 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 may 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, 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 are likely to 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 June 2012 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 mid-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.
2. Half of the Disease Team awards that fund projects using pluripotent stem cells will lead to FDA-accepted INDs in 4 years.
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 $15-25 million (mean $20 million) from CIRM to proceed through a Phase 2 trial (if additional funds are required, they would have to 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. It is assumed that the RFAs for Disease Teams 2 will be valued at $240 million and will include 6 projects with pluripotent stem cells. In column 4 (INDs in 4 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 4 years	Clinical trial funding date ($20M each)	Phase 2 - completion date
Disease Teams 1	2010	5	2	2014	2019
Clinical Development	2011	2	2 (obtained)	2011	2016
Disease Teams 2	2012	6	3	2016	2021

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 can be achievable by 2021, but for that to happen it is likely that

CIRM would have to make clinical trial funding commitments in 2014 and 2016 as indicated in Table 1. This plan allows for such funding.

Final Points:

1. This analysis of CIRM's RFA schedule has focused on one specific goal listed in the strategic plan of 2006. However, programs were also retained (e.g. 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 will 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. 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. Therefore, reserving more funds for later in CIRM's lifespan could certainly benefit these projects too.

3. 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.

4. CIRM makes its research funding predictions based on the expectation that the approved research programs will be successful. However, it is likely that some research commitments will not be expended and the amounts could be significant if large projects (Early Translation or Disease Teams) fail to meet go-no-go milestones or if they are terminated for other reasons. However, the amount that might be recycled by CIRM is very difficult to predict, as is the timing, especially since the first projects with go-no-go decision points are just beginning. If it is assumed that 10% of all research commitments made from this point forward will not be expended and are thus available 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. However, CIRM's management elected to not make strategic decisions about future research funding based on projects that might fail. Instead it is assumed that all projects will succeed and adjustments will be made later, if additional funds become available.

APPENDIX1 - This table is a full list of RFAs based on Table 1.

RFA	RFA Number	Amount	Stage	Review Date	ICOC Date	Start Date
Training 1	05-01	37,253,385	Current Program			
Seed	06-01	42,233,826	Current Program			
Comprehensive Research	06-02	67,313,412	Current Program			
Shard Labs	07-01	49,047,039	Current Program			
New Faculty 1	07-02	53,720,258	Current Program			
Major Facilities	07-03	270,946,931	Current Program			
Disease Team Planning	07-04	1,175,368	Current Program			
New Cell Lines	07-05	24,449,174	Current Program			
New Faculty 2	08-01	59,292,558	Current Program			
Tools and Technology 1	08-02	19,253,974	Current Program			
Bridges to Stem Cell Research 1	08-04	23,873,044	Current Program			
Training 2	08-03	44,988,409	Current Program			
Basic Biology 1	08-07	16,288,581	Current Program			
Early Translational 1	08-05	70,401,825	Current Program			
Conference Grants	08-06		Current Program			
Disease Team 1	09-01	224,984,899	Current Program			
Leadership Award	09-04	44,800,000	Review Stage	Variable 2010-11	Variable 2010-11	Variable 2010-11
Basic Biology 2	09-02	30,000,000	Current Program			July - Sept 2010
Immunology	09-03	30,000,000	Current Program			Oct-Dec 2010
Early Translational 2	10-01	80,000,000	Review Stage	Sept 2010	Oct 2010	Jan - March 2011
Tools and Technology 2	10-02	40,000,000	Review Stage	Nov 2010	Jan 2011	April - June 2011

RFA	RFA Number	Amount	Stage	Review Date	ICOC Date	Start Date
Clinical Trials		50,000,000	Concept Approved	Feb 2011	May 2011	July - Sept 2011
Basic Biology 3		45,000,000	Concept Approved	March 2011	May 2011	July - Sept 2011
Disease Team 2 Planning		3,300,000	Concept Approved	May 2011	Aug 2011	Oct – Dec 2011
Shared Labs 2		30,000,000	Future Program	Sept 2011	Oct 2011	Jan - March 2012
Stem Cell Genomics		30,000,000	Future Program	Oct 2011	Dec 2011	Jan – Mar 2012
Early Translational 3		80,000,000	Future Program	Nov 2011	Jan 2012	April - June 2012
Bridges 2		25,000,000	Future Program	Feb 2012	May 2012	July – Sept 2012
Training 3		45,000,000	Future Program	Feb 2012	May 2012	July - Sept 2012
Disease Team 2 Award		240,000,000	Future Program	Apr 2012	June 2012	Oct – Dec 2012
IPS - banking		25,000,000	Future Program	May 2012	July 2012	April - June 2012
Basic Biology 4		45,000,000	Future Program	June 2012	Aug 2012	Oct - Dec 2012
Tools and Technology 3		30,000,000	Future Program	Sep 2012	Oct 2012	Jan - March 2013
Alpha Clinic		70,000,000	Future Program	Nov 2012	Dec 2012	April – June 2013
Early Translational 4		80,000,000	Future Program	Feb 2013	May 2013	July/Sept 2013
Basic Biology 5		45,000,000	Future Program	June 2013	Aug 2013	Oct - Dec 2013
Disease Team 3 Planning		3,300,000	Future Program	Sept 2013	Oct 2013	Oct - Dec 2013
Clinical Follow-on 1		75,000,000	Future Program	Nov 2013	Jan 2014	April-June 2014
To Be Determined 1		30,000,000	Future Program	Jan 2013	Mar 2014	July-Sep 2014
Basic Biology 6		45,000,000	Future Program	Apr 2014	June 2014	Oct - Dec 2014
Disease Team 3 Award		180,000,000	Future Program	June 2014	Aug 2014	Oct - Dec 2014
Early Translational 5		60,000,000	Future Program	Sept 2014	Oct 2014	Oct - Dec 2014
To Be Determined 2		30,000,000	Future Program	Oct 2014	Dec 2014	April – June 2015
Disease Team 4 Planning		3,300,000	Future Program	June 2015	Aug 2015	Oct – Dec 2015
Early Translational 6		60,000,000	Future Program	Oct 2015	Nov 2015	Jan - March 2016
Clinical Follow-on 2		75,000,000	Future Program	Nov 2015	Jan 2016	Apr-June 2016
Disease Team 4 Award		120,000,000	Future Program	April 2016	June 2016	Oct – Dec 2016

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.