Research Funding Strategy

March 11, 2011

This document is intended to provide a framework for a discussion on how the ICOC and CIRM will allocate the balance of the voter- approved funding for the conduct of stem/progenitor cell research in California to realize the strategic objectives, key outcomes and relevant 5-year goals of the 2012 Strategic Plan. Initially, I will briefly review the funding allocated to awarded programs ($1.28 billion), then summarize the strategic objectives, key outcomes and relevant 5-year goals and outline the implications for funding. I will next address the programs that are concept approved but not yet funded and finally I will outline scenarios for future funding programs that are compatible with realizing the strategic goals and CIRM's mission.

The key points are:

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

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

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

Funded Programs

Appendix A is a list of all programs by Request for Application (RFA) or Program Announcement (PA) where awards have been made and funding allocated. Allocated funding includes dollars disbursed and to be disbursed. The list also assigns a category to each funded program; these categories are utilized throughout this document and are briefly described below.

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

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

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

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

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

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

The ICOC has allocated $1.28 billion to funded programs. The allocation of funding to the different categories of funded programs is highlighted in the following Figure 1. The percentage allocation of funding by category is shown in Figure 2.

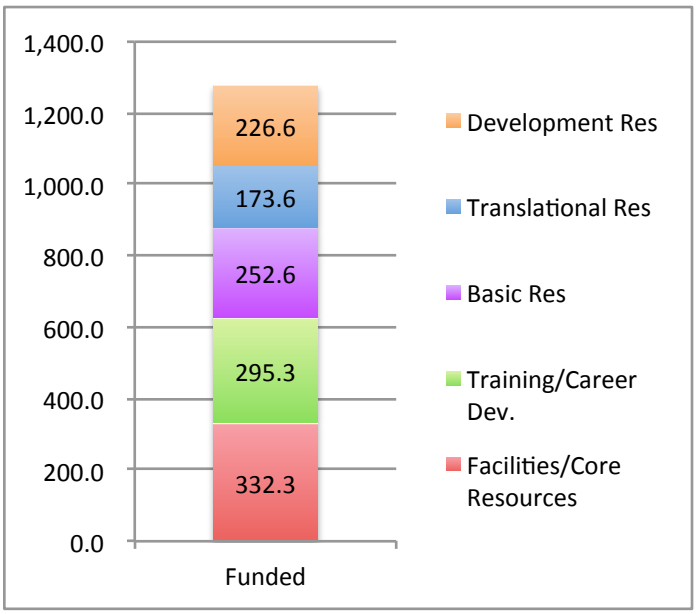

Figure 1: Funded Programs, $MM allocated by category

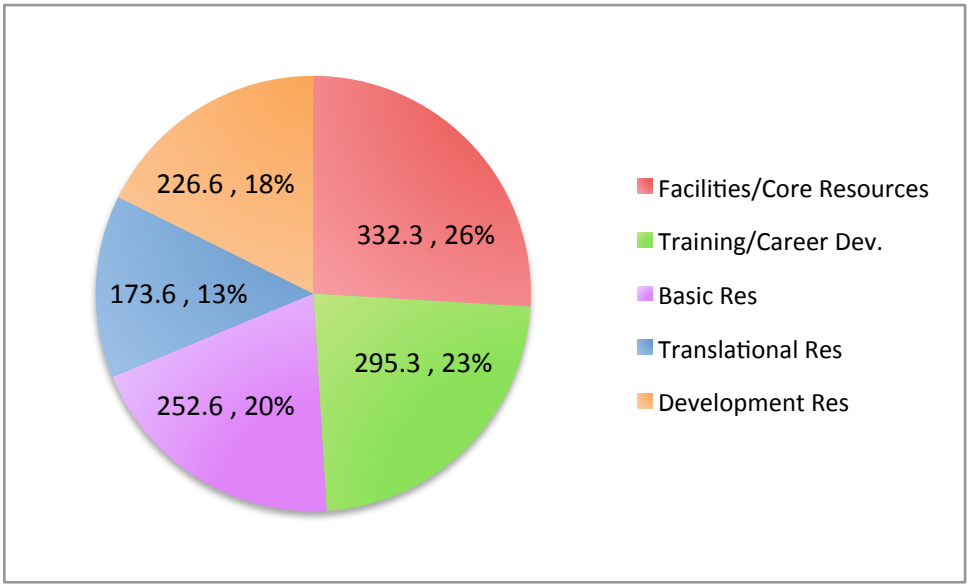

Figure 2: Funded Programs, Percentage allocation of funding by category

Strategic Objectives and Considerations

As CIRM moves into its next 5 years, the following are strategic objectives and associated key outcomes proposed for the 2012 revision of the Strategic Plan.

Category	Strategic Objective	Key Outcome
Scientific	**Accelerate understanding of stem cell science** and its applications towards human diseases and injuries	**Achieve** transformative research discoveries
Clinical	**Advance stem cell science into clinical trials** to achieve evidence of therapeutic benefit to patients	**Achieve** clinical proof of concept for stem cell therapies
Economic	**Drive economic development** for California from stem cell science and therapies	**Leverage** CIRM's investment in California
Community	**Maintain California as the world stem cell leader**	**Achieve** universal recognition of California as the "Stem Cell State"

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

as the stage of maturity of the cell therapy field. The following is the specific 5-year goal proposed that addresses the clinical strategic objective and key outcome.

Goal: CIRM will have funded 10 therapies in phase I or II clinical trials, in at least 5 different therapeutic areas, based on stem cell research, and have achieved clinical proof-of-concept that transplanted cells derived from pluripotent or progenitor cells can be used to restore function for at least one disease or injury condition.

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

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

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- Specifically, within the next ~2 years, CIRM must fund clinical development of at least 5, and preferably more, strong candidates already in Phase I or in Phase II in order to have a reasonable chance of one successful Phase II outcome in 5 years (end of 2017).

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

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

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

Funding to Achieve Strategy

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

- $649 million has been approved in concept for but not yet awarded
- $836 million is available for future programs

Concept Approved Programs

The following Table 1 summarizes programs that have been approved in concept by the ICOC, but where funds have not yet been awarded.

Table 1: Concept Approved Programs

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

The percentage allocation of funding by category is shown in Figure 3 for both funded and concept approved. As can be seen in the figure there is shift in percentage of funding allocated to the development category when comparing the concept-approved programs to already funded programs.

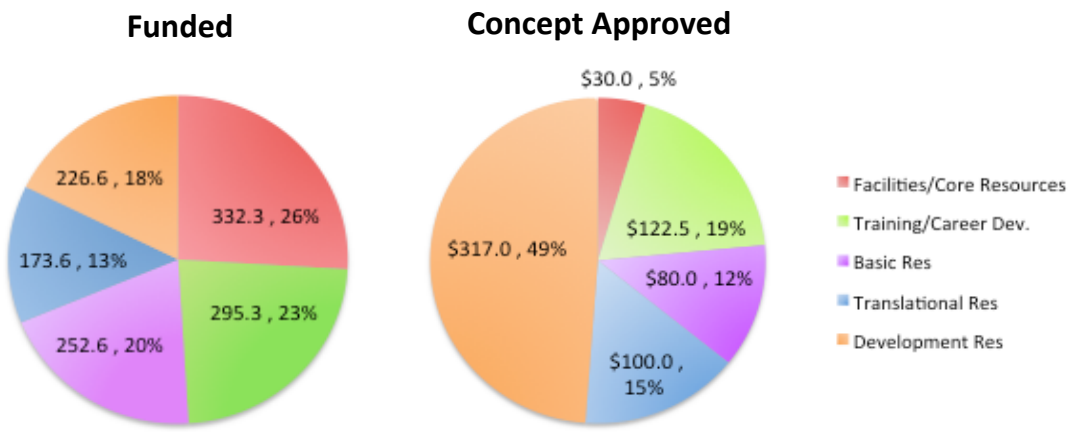


Figure 3: Funded and Concept Approved Programs, Percentage allocation of funding by category

The distribution of funding by category to funded programs and to concept-approved programs is shown in Figure 4.

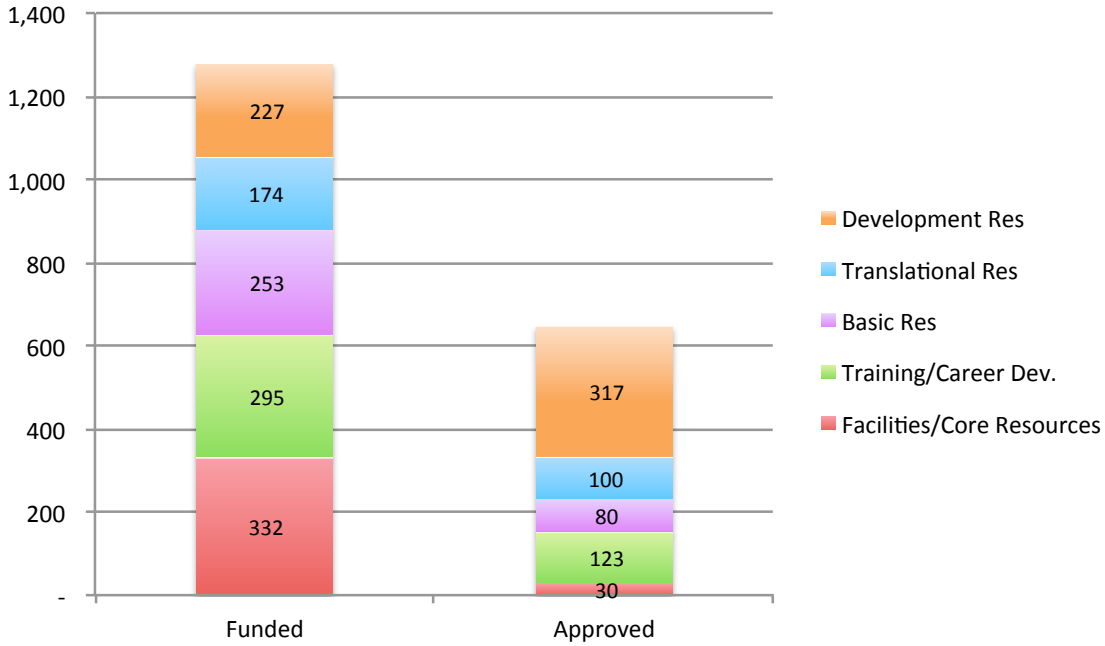


Figure 4: Funded and (Concept) Approved Programs, $MM by category

Much of the funding for Development programs that are concept approved will be awarded and funding committed in FY12/13 (see Figure 7 below). As noted in Table 2, assuming all the money approved in concept for Development programs is awarded, there will be an estimated addition of 16 Development projects (12 from Disease Team Therapy Development, 3 from Strategic Partnership I, and 1 from an approved transfer of the Geron Targeted Clinical Development Program). These 16 projects may include projects that are in the clinic, which could contribute to the achievement of the clinical proof-of concept goal for a stem/progenitor–derived cell therapy

Future Funding

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

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

Table 2: Future Funding Scenarios

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

	– FY13/14: $180 MM – FY14/15: $100 MM – FY15/16: $100 MM – FY16/17: $60 MM • New Bridging Funding - $6 MM	– FY13/14: $180 MM – FY14/15: $100 MM – FY15/16: $100 MM – FY16/17: $40 MM • New Bridging Funding - $6 MM
Last Funding Start	FY16/17	FY16/17
Last Funding	FY19/20	FY19/20

The funding distribution by category for funded programs, for concept-approved programs (Approved) and for future Programs (Scenarios 1 and 2) is shown in Figure 5. The percentage distribution by category for the scenarios is shown in Figure 6.

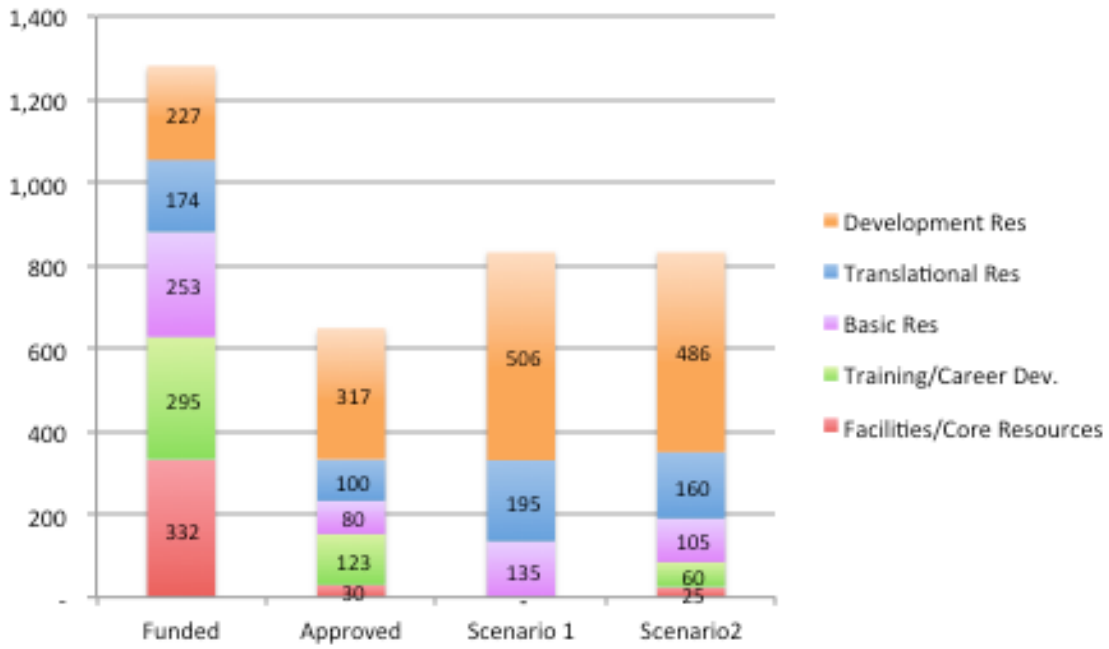


Figure 5. Funding by Category for Current, Approved and Future Programs

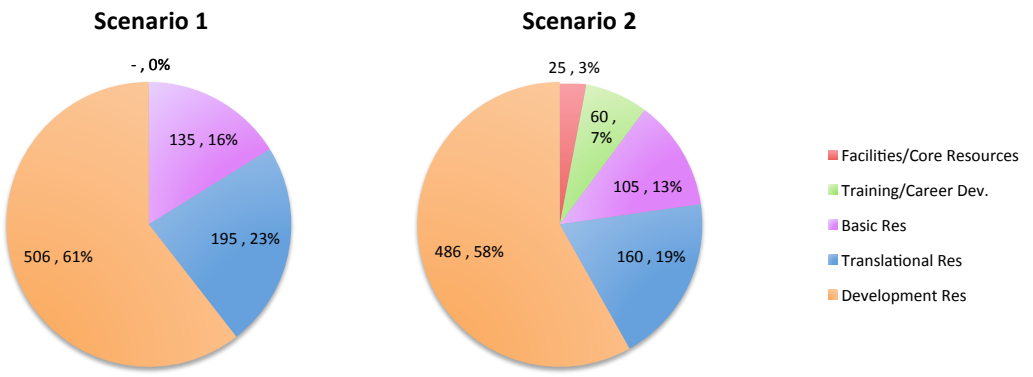


Figure 6. Scenarios for Future Funding, Percentage allocation of funding by category

Implications

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

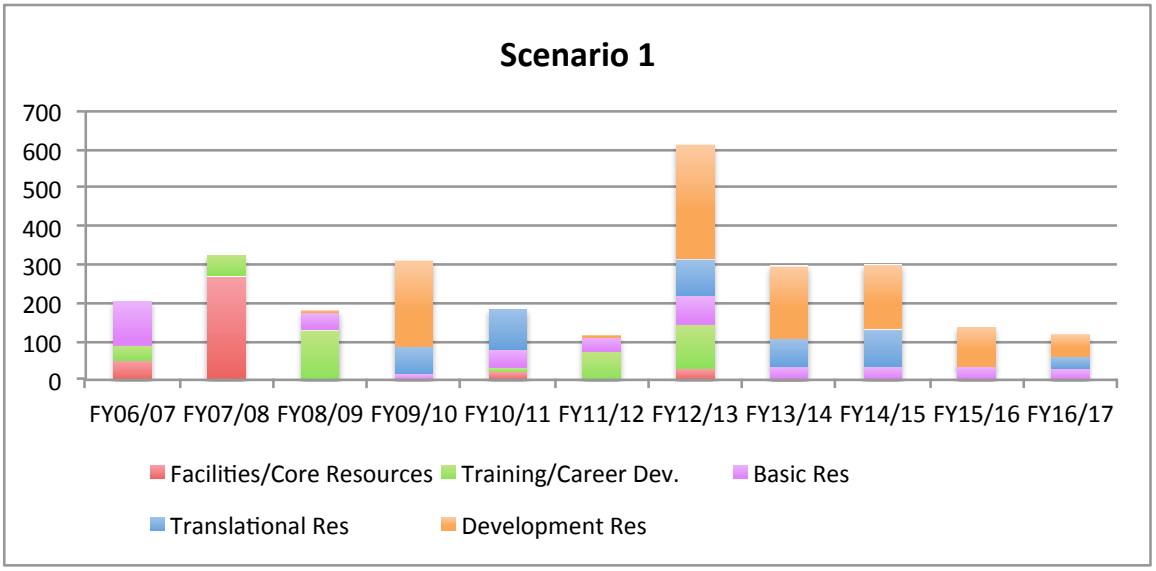
- Disease Team I projects should be filing well-supported INDs in FY 13/14 and some could potentially be among the 25 projects above that receive funding to continue clinical development.

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

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

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

In Figure 7, the funds awarded and funded (Notice of Grant Award issued) by fiscal year are shown for funded, concept approved and new (future) RFA programs for Scenarios 1 and 2.



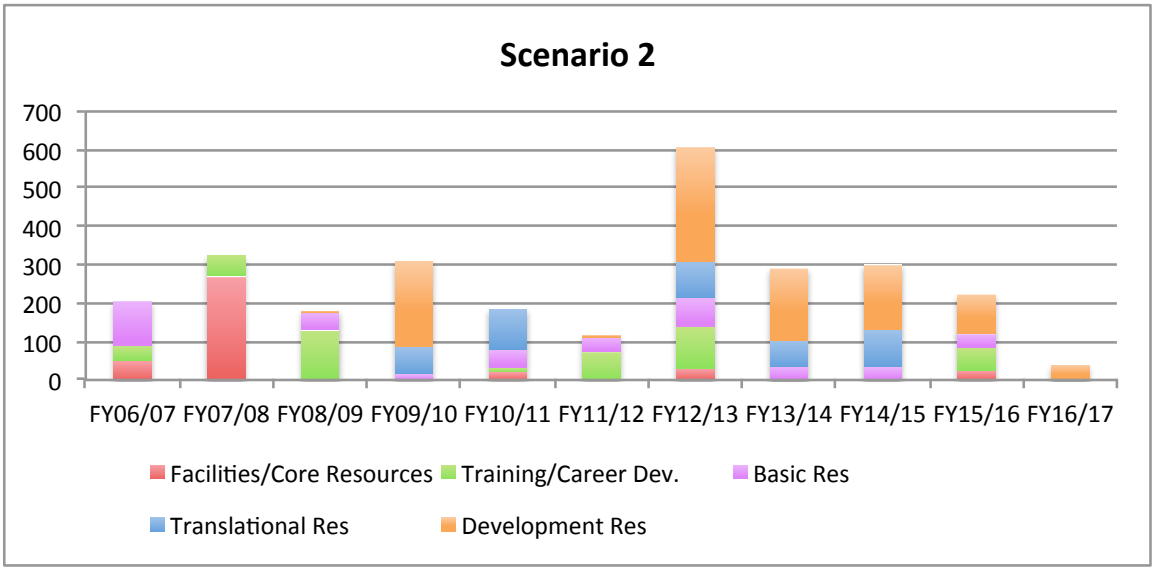


Figure 7. Funding by fiscal year by category for already funded, concept-approved, and future (Scenarios 1, Scenario 2) programs.

Overall Funding Distribution

The following Table 3 summarizes the funds allocated to funded programs, the funding planned for concept-approved programs and for two scenarios for future program allocation. Figure 8 shows the percentage distribution by category of the total of the research funding, including funded programs, concept approved programs and each of two future funding scenarios that follows from the above.

Table 3: Summary of Funding Allocation

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

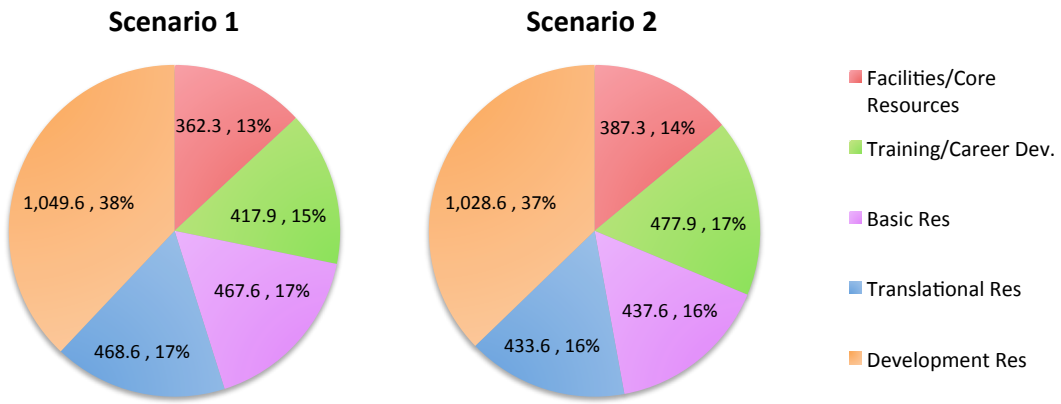


Figure 8. Percentage distribution by category of the total research funding, including funded programs, concept approved programs and each of two future funding scenarios (Scenario I, Scenario 2)

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

Appendix A

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

Table 4: Funded Programs*

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

* Data is as of 2/2/2012

Appendix B: Drug Development Statistics

Pharmaceutical, bio-pharmaceutical and biotech industry statistics were used as benchmarks for determining the extent and timing of preclinical and clinical

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

Assumptions on Phase Dwell Times

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

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

Probabilities of Technical Success

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

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

4. DiMasi, J.A. et.al. (2004) Drug Information Journal 38:211-223.
5. Kola, I. And J. Landis (2004) Nature Reviews Drug Disc. 3: 711-15 (also in PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2009/2010, p226).

6. CMR Industry survey based on NME entering clinical phase in years 1996 -1998; tracked through end of 2001, in PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2005/2006, p. 190
7. Steven Paul, head of Lilly Research from PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2009/2010, p226
8. Trevor Mundel, global head of development at Novartis Pharmaceuticals, from PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2009/2010, p226

Assumptions on Phase Costs

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

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

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

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