Executive Summary

Introduction

"Against all odds, we shall succeed. We have a moral obligation to every patient, to every family, to every Californian - to every American - to succeed; and so we shall."
-Robert Klein,
ICOC Chair

The extraordinary possibilities of human embryonic stem cell research promise to introduce a new era of science and medicine. The defining features of embryonic stem cells – their ability to expand indefinitely when cultured *in vitro* and their ability to differentiate into virtually all of the specialized cells of the body – have given rise to the compelling dream of being able to restore function after disease or injury by replacing damaged cells with healthy new cells. The remarkable developmental potential of stem cells suggests that it may be possible to use them for a wide range of diseases, including diabetes, spinal cord injury, neurodegenerative diseases, blood disorders, arthritis, retinal disease and burns, among others. Stem cells may eventually provide the cellular components for the even more ambitious task of reconstructing entire tissues *in vitro*. Finally, stem cells offer a powerful tool for understanding diseases such as cancer, Alzheimer's disease, and autism, so that targets for new therapeutics can be defined.

The possibilities seem limitless – but to achieve them will require time and effort in countless laboratories and clinics around the world. Proposition 71 offers Californians the opportunity to fully participate in this effort by authorizing the expenditure of $3 billion over 10 or more years for stem cell research in California. The Scientific Strategic Plan of the California Institute for Regenerative Medicine (CIRM) that is described here offers a blueprint for how this money will be spent to make the possibilities of stem cell research a reality.

The challenge is daunting. Human embryonic stem cells were first identified only eight years ago and there is much that we do not understand about them. Their ability to divide, for example, is of great benefit in producing large numbers of cells, but also means that they have the potential to form tumors, so that understanding how to regulate and control stem cell growth will be essential. Once a therapeutic possibility is identified, the road to having it approved as a wide-spread therapy is long and expensive, with most therapeutics that begin clinical trials falling by the wayside. The aims of the Scientific Strategic Plan are: to show evidence that cell replacement therapy using derivatives of human embryonic stem cells is effective for at least one disease; to provide a rich pipeline of therapeutic candidates for a number of other diseases; and to lay a broad foundation of knowledge about stem cells and disease mechanisms on which future researchers can build to devise new therapies. In addition to exploring the possibilities of using human embryonic stem cells as therapeutics, which is our primary task, CIRM will also seek to advance therapies based on multipotent and progenitor cells found in fetal and adult tissues and in cord blood. CIRM will further seek to advance the use of embryonic stem cells and their derivatives as diagnostics and as tools for use in research, drug discovery, preclinical

and clinical development. These may be nearer-term opportunities for commercialization and economic benefit.

Overview of the Planning Process

Development of the Scientific Strategic Plan began with a scientific meeting held on October 1-2, 2005, "Stem Cell Research: Charting New Directions for California". An international group of stem cell scientists addressed the question of developing scientific priorities for CIRM. Data-gathering continued through interviews with over 70 leading scientists, clinicians, patient advocates and others; through three scientific conferences on specific topics for the ICOC and the public; and through two focus meetings. Two ICOC meetings were used to develop a mission statement, values and strategic principles. A Strategic Plan Advisory Committee met periodically to discuss strategic questions and advise the CIRM staff in plan development.

"Curing a disease like Type 1 diabetes, doing embryonic stem cell research, or doing cell therapy is not rocket science; it's a lot harder."
- Allen Spiegel,
Albert Einstein College of Medicine

Mission

In accordance with the mandate of the citizens of California, as specified in the California Stem Cell Research and Cures Act, the mission of the California Institute for Regenerative Medicine 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.***

Values

The values that will guide and imbue our efforts and activities are:

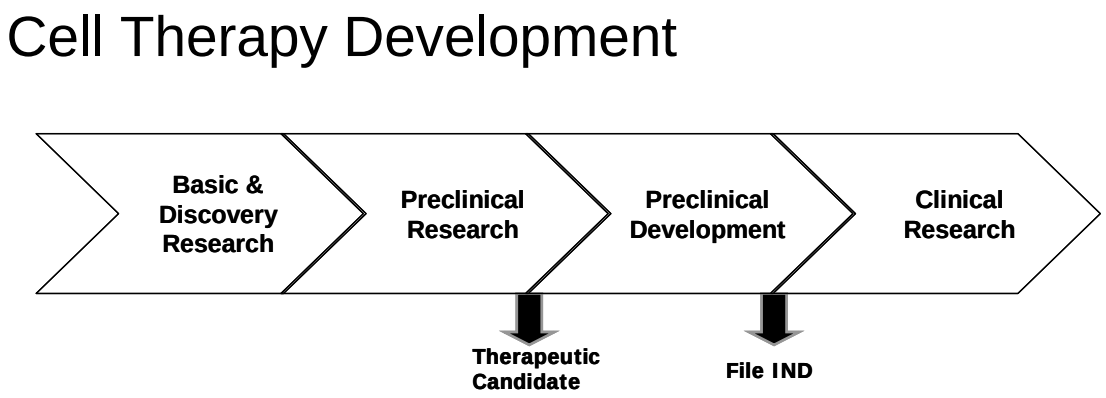
- Accountability
- Adaptability
- Collaboration
- Diversity
- Excellence
- Innovation
- Integrity
- Service
- Urgency

Strategic Objectives: Aspirations and Commitments

The Scientific Strategic Plan seeks to express ambitious and visionary goals, but also to have a realistic plan with achievable milestones against which we and others can measure our progress. To achieve these aims, we define two types of goals: *aspirational* goals that reflect our highest hopes and *commitment* goals that represent a realistic view of what we might achieve based on industry experience. The former is our dream; the latter represents the goals for which we will be accountable.

The principal aspirational goal for CIRM is simple: to use stem cells to cure a wide variety of diseases. Although the challenges for meeting it are many, this goal drives all of our efforts. A second aspiration is to make California the world-wide leader in stem cell research and the global center for stem cell science in the biotechnology and pharmaceutical industries.

CIRM's commitment goals are our covenant with the people of California for what we will accomplish over the next ten years to make the promise of stem cell therapy a reality. Given the time (8-10 years) and expense ($800 million) for development of small molecule therapeutics, it is unlikely that CIRM will be able to fully develop stem cell therapy for routine clinical use during the ten years of the plan. Within that time span, however, we will be able to advance therapies for several diseases to early stage clinical trials, and to have therapies for other diseases in the pipeline. To provide a framework for our ten year goals, we provide a plausible model for the development of a cell therapy, based on the development of small molecule and biological therapeutics:



In the model, development is described as occurring in four discrete stages:

- *Basic and discovery research*, which provides the foundation for therapy development.
- *Preclinical research*, where strategies for disease treatment are explored.
- *Preclinical development*, where the studies necessary to meet the Food and Drug Administration (FDA) regulatory requirements for an Investigational New Drug (IND) application prior to testing in humans are conducted.
- *Clinical research*, where the efficacy and safety of a treatment is tested in humans.

Clinical trial research is further subdivided into three sequential phases, as shown below:

Phase	Purpose	Numbers of Patients
Phase I	Safety	Tens
Phase II	Dose, regimen, efficacy signal; safety	Tens to hundreds
Phase III	Statistical proof of efficacy; safety	Hundreds or more

Ten Year Goals

CIRM commits to the following ten 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 grantees will have therapies based on stem cell research in Phase I or Phase II clinical trials for 2-4 additional diseases.
- Goal III: CIRM grantees will achieve a level of success that will 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 preclinical development.
- Goal V: Using stem cell research, CIRM-funded investigators will have established proof-of-principle in preclinical animal models for treatment of 6-8 diseases.
- Goal VI: CIRM-funded investigators will have created disease-specific cell lines for 20-30 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 be achieved.
- Goal IX: Through research sponsored by CIRM and others, the factors regulating the self-renewal and oncogenic potential of embryonic stem cells and their derivatives will be identified and characterized.
- Goal X: CIRM will have enabled development of new methods for tissue replacement based on stem cell research.

Five Year Goals

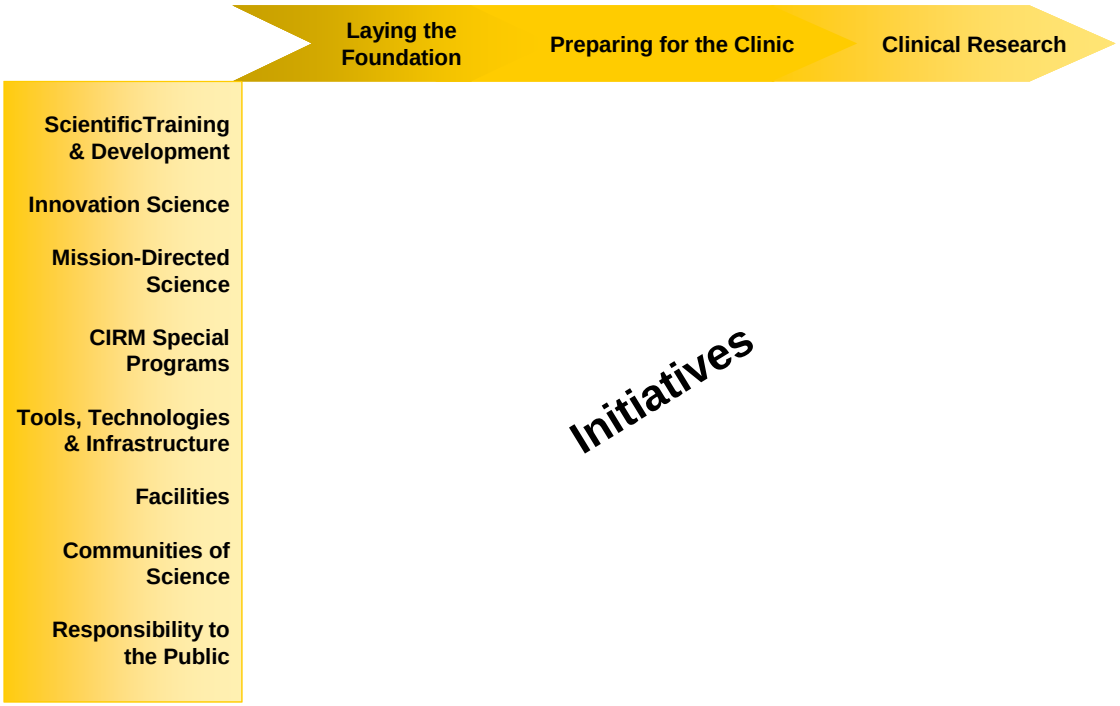
These five year goals will be milestones to gauge our progress:

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

- Goal II: CIRM grantees will have developed new methods for making stem cell lines.
- Goal III: CIRM grantees will have successfully created disease-specific stem cell lines for four diseases.
- Goal IV: CIRM grantees will have developed methods for growing stem cells in defined media.
- Goal V: CIRM will have enabled establishment of a stem cell bank.
- Goal VI: CIRM-funded investigators will have demonstrated methods for inducing immune tolerance in animal models.
- Goal VII: CIRM will have increased the workforce of stem cell researchers in California.
- Goal VIII: CIRM grantees will have established tools for toxicity testing based on stem cell research.
- Goal IX: CIRM will have established effective partnerships in stem cell research between scientific teams in non-profit and commercial sectors.
- 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 of our collaborators to advance toward therapies.

The Strategic Planning Framework: Charting the Path to Therapies

CIRM will achieve its strategic objectives through a series of initiatives that, taken together, will define the CIRM research program. To place these initiatives within a strategic framework we define a "space", using two coordinate systems, one related to progress from the laboratory bench to the clinic and the other representing the resources that will be deployed:



Laying the Foundation

There is general agreement that before human embryonic stem cells (hESCs) can be developed for widespread clinical use, much work on their fundamental biology must be done. Many of the questions that CIRM will attempt to explore are outlined in this section.

An early challenge is to understand what defines an embryonic stem cell and how different hESC lines differ from each other and from non-embryonic stem cells. Our understanding of both of the two characteristic features of embryonic stem cells, their capacity for self-renewal and their ability to produce a wide variety of specialized cells, is incomplete.

If stem cells are to be used as therapies, it will important to have available a large number of stem cell lines of diverse genetic backgrounds that represent the range of human populations and to understand the influence of those backgrounds on these lines. In particular, the availability of embryonic stem cell lines with genetic mutations that lead to disease will be a powerful tool for understanding the cellular basis of pathogenesis for many disorders and for drug discovery.

In the body, stem cells occupy special locations, or niches, whose components interact with stem cells to regulate cell division and to influence differentiation. Understanding the role of the niche is important in guiding *in vitro* attempts to regulate stem cells and to understand the behavior of endogenous stem cells, which may be mobilized to combat disease and injury.

Preparing for the Clinic

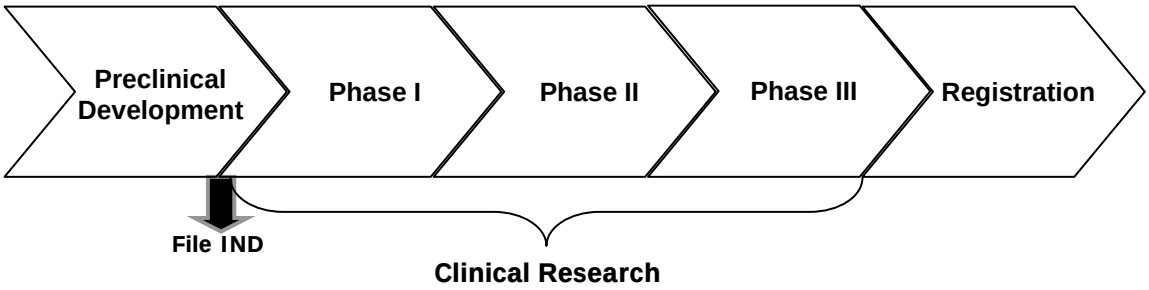
Preclinical research and development involves the identification of a potential therapeutic for a particular disease, demonstration of proof-of-principle in a cellular or animal disease model and preparation of the therapeutic for use on humans. Before approval can be obtained from the FDA for an Investigational New Drug (IND) for testing in humans, a therapeutic agent must be shown to be safe and effective in non-human models. The quality of a therapeutic agent must be assessed, including demonstrations of its purity and its ability to be reproducibly produced. An early challenge for preclinical development of stem cell therapies will be to develop methods for production of the cells in Good Manufacturing Practices (GMP) facilities.

To bring stem cell therapy to widespread use in the clinic, the problem of immune rejection must also be addressed. Currently, for allogeneic transplants, immune suppression is required to prevent rejection of the tissue by the recipients, leading to unwanted or life-threatening complications. For some indications, patient-based stem cell lines offer a potential solution, but the current expense and difficulty of creating a tailor-made cell line makes this solution unlikely to be practical on a large scale. Another more general solution is to replace the immune system to make it compatible with the transplanted cells. Other technological needs for development include new methods of introducing cells; the creation of artificial niches to contain transplanted cells; and automated methods of growing cells.

Preclinical development, which is in general not funded by the federal government, occurs largely in pharmaceutical and biotechnology companies. In large, well-capitalized companies, preclinical development can be easily financed, but in small companies, the ability to carry out preclinical development for a promising treatment is often the difference between success and failure. If CIRM is to be successful in bringing therapies to the clinic that are based on stem cell research, we will need to develop new funding mechanisms to address the problems posed by preclinical development.

Clinical Research

Ultimately, any potential stem cell or stem cell derived cure or therapy must be rigorously tested in human subjects before it can be made broadly available to patients. Clinical trials are designed and conducted to address safety, dose, delivery, mechanism, regimen, and efficacy with the ultimate goal of developing a therapy that can benefit patients. They are conducted in three sequential phases. Each phase builds on the information gathered in the previous phase and is designed to generate additional information about the candidate therapy.



Phase	Outcomes	Numbers of Patients	Phase Duration (Years)
Phase I	Safety, dose, regimen, mechanism	Tens	1 - 2
Phase II	Dose, regimen, mechanism, efficacy signal; safety	Tens to hundreds	1 - 5
Phase III	Statistical proof of efficacy; safety	Hundreds or more	2 - 5

Because of their expense and because of the time required to reach this stage of clinical development, CIRM is unlikely to fund Phase III trials over the time span of the Strategic Plan. Although CIRM will likely fund some Phase II trials, most funded studies will be Phase I trials. Some of these trials will be conducted by investigative groups at academic medical centers (AMCs); others may be conducted by private companies, often in partnership with AMCs.

Clinical research is heavily regulated by the FDA in the U.S. The FDA requires that a therapeutic candidate to be tested in humans be produced by well-defined, documented procedures that result in lot-to-lot consistency of a product that meets standards of purity,

identity and potency and that there be a reasonable expectation of safety and benefit based on preclinical studies. Because the field is new and will be developing rapidly, FDA regulations may be expected to evolve. By maintaining communication with the FDA, CIRM and CIRM-funded investigators can play an important role in aiding the development of these standards.

Because it involves human subjects, clinical research is arguably the most difficult form of biological research. Subjects must freely and voluntarily consent to the trial; every precaution must be taken to minimize risk to subjects; and there must be potential benefit. To maintain these standards, clinical research is necessarily complex, particularly when it has the intent to register a therapeutic candidate for marketing approval.

Developing and Enabling Critical Resources

The progress from laboratory to the clinic will be accomplished through the deployment of a variety of resources.

Scientific Training and Development

There is a critical need for trained personnel in human embryonic stem cell research at all levels. Basic, translational, and clinical scientists in stem cell science, as well as trained technical staff, are all in short supply. CIRM will thus sponsor training programs in stem cell research at both the professional and technical levels.

Innovation Science

To fully exploit the creative energies of California scientists, we will need to have broad initiatives that allow scientists to obtain funding to explore new ideas or new techniques that we cannot now know or predict. Limited federal support for innovation science on stem cells makes it imperative that CIRM support open-ended, investigator-driven research related to stem cells.

Mission-Directed Science

Although scientific understanding provides the foundation, the main thrust of CIRM's research is to develop therapies. Thus, a substantial body of CIRM research will support research projects directed toward specific ends. CIRM will deploy both grants and contracts in the support of such mission-directed science.

CIRM Special Programs

CIRM Special Program Initiatives are those in which the Institute proposes to organize funding in new and unconventional ways in order to promote progress. The hallmarks of the first initiatives in the program will be an emphasis on:

- Collaborative teams
- Specific goals with a timeline and milestones
- Active management of the project
- Active CIRM participation in evaluation and project management

Teams will be organized to attain specific goals within a given time and the project will be actively managed. Progress will be evaluated and strategy modified as necessary by an advisory group that includes members of the team, outside scientists, and CIRM personnel.

Tools, Technologies and Infrastructure

Many of CIRM initiatives will be directed toward projects to develop specific tools, enabling technologies, or infrastructures that will support the basic, translational and clinical science needed to develop therapies. CIRM may set up one or more specialized centers that will develop technology and make it available for the scientific community. One example is a stem cell bank that would maintain, store and characterize stem cells lines. CIRM may also wish to provide infrastructure that will help investigators through consultation, service or training.

Facilities

An essential component to achieve the goals of CIRM will be adequate research space for hESC research. CIRM may use up to 10% of its funds, as specified in Proposition 71, to build and renovate both large- and small-scale facilities for human embryonic stem cell research.

Communities of Science

CIRM will engage in a variety of activities to create a vigorous, energetic and committed scientific community of stem cell research in California, including researchers in both non-profit research institutions and in the commercial sector. CIRM will also facilitate and support scientific cooperation between California scientists and those in other parts of the United States and abroad. These partnerships may be particularly useful in combining California's comparative advantage with that of potential collaborators to leverage our efforts in stem cell research to more rapidly move the field forward.

Responsibility to the Public

CIRM has a responsibility to explore the impact of stem cell research on the California public as well as to convey an accurate account of the benefits that arise from such research. CIRM also has a responsibility to fund scholarly studies on ethical and legal matters related to stem cell research and on the social, economic and health-related impact of that research on society.

For complex reasons, the diversity of California is not adequately reflected in the scientific community and CIRM will need to make special efforts to encourage the training and education of minority scientists. CIRM will also need to ensure that clinical trials of therapies resulting from stem cell research include minority populations. Finally, CIRM will make special efforts to maintain communication with its diverse public constituency.

In addition to our responsibility to the general public, CIRM has a special responsibility to patients and patient advocacy groups. They define our purpose and reason for being and it is important that we maintain strong lines of communication with them, both through our communications activities and as we continue to refine and develop our research program.

Initiatives to Address Needs and Aims

To support its mission and achieve its objectives, CIRM will launch a series of scientific initiatives. These initiatives, which are organized according to the categories defined in the "Developing and Enabling Critical Resources" section of the Scientific Strategic Plan, are discussed in detail in the body of the report. The following table outlines these initiatives and indicates which of the three broad categories defined in the "Charting the Path to Therapies" section of the plan they support:

"The only restraint that should be placed on funding is that it must support world-class science."
-Bill Rastetter,
SPAC Member

Specific Initiatives

CIRM will undertake the following initiatives:

Initiative	Laying the Foundation	Preparing for the Clinic	Clinical Research
Scientific Training and Development			
Scientist Training / Internships	●	●	●
Technical Staff Training	●		
Scientific Personnel Development	●	●	●
Innovation Science			
hESC Jump Start Initiative	●	●	●
Annual Innovation Grants	●	●	●
Biology of Stem Cells	●		
Egg and Embryo Research	●		
Mission-Directed Science			
New Methods for Development of Stem Cell Lines	●	●	
Stem Cell Based Tissue Engineering in Regenerative Medicine	●	●	
Translational Research	●	●	
Generation and Use of Disease Specific Cell Lines	●	●	
Immune Tolerance	●	●	●
Bio-process Engineering and Automation		●	
Preclinical Product Development		●	
Clinical Investigation			●
CIRM Special Programs			
Disease Teams	●	●	●
Interdisciplinary Research Teams	●	●	●
Tools / Technologies and Infrastructure			
Tools and Technologies	●	●	●
Cores	●	●	
Banks	●	●	
Facilities			
Laboratories / Research Facilities	●	●	
Communities of Science			
Journal / Web Portal	●	●	●
Responsibility to the Public			
Public Outreach	●	●	●
Stem Cell Research and Society: Implications and Impact	●	●	●
Economic Impact	●	●	●

Estimated Cost Projections

The development of the Scientific Strategic Plan was accompanied by the development of a financial model. CIRM's projections, while subject to change, are intended to reflect the amount of funding that will be allocated to each category of initiatives over the next ten years. The amounts (millions) assigned to each category vary according to many factors, including the number, size, and duration of the grants to be awarded as well as the nature of the work to be performed. The following table details the allocation of CIRM funding across the three segments of our framework.

Initiative	Laying the Foundation	Preparing for the Clinic	Clinical Research	Total
Research Activities				
Scientific Training and Development			**Total for Resource Category**	**$ 299.0**
Scientist Training / Internships	$ 94.2	$ 31.4	$ 31.4	$ 157.0
Technical Staff Training	$ 38.0	$ -	$ -	$ 38.0
Scientific Personnel Development	$ 34.7	$ 34.7	$ 34.7	$ 104.0
Innovation Science			**Total for Resource Category**	**$ 375.5**
hESC Jump Start Initiative	$ 80.4	$ 26.8	$ 26.8	$ 134.0
Annual Innovation Grants	$ 89.1	$ 29.7	$ 29.7	$ 148.5
Biology of Stem Cells	$ 75.3	$ -	$ -	$ 75.3
Egg and Embryo Research	$ 17.7	$ -	$ -	$ 17.7
Mission-Directed Science			**Total for Resource Category**	**$ 1,272.1**
New Methods for Development of Stem Cell Lines	$ 8.2	$ 4.1	$ -	$ 12.3
Stem Cell Based Tissue Engineering in Regenerative Medicine	$ 43.7	$ 43.7	$ -	$ 87.4
Translational Research	$ 138.8	$ 323.8	$ -	$ 462.6
Generation and Use of Disease Specific Cell Lines	$ 15.2	$ 15.2	$ -	$ 30.4
Immune Tolerance	$ 20.1	$ 30.2	$ 10.1	$ 60.4
Bio-process Engineering and Automation	$ -	$ 60.0	$ -	$ 60.0
Preclinical Product Development	$ -	$ 108.0	$ -	$ 108.0
Clinical Investigation	$ -	$ -	$ 451.0	$ 451.0
CIRM Special Programs			**Total for Resource Category**	**$ 182.0**
Disease Teams	$ 24.4	$ 48.8	$ 48.8	$ 122.0
Interdisciplinary Research Teams	$ 24.0	$ 24.0	$ 12.0	$ 60.0
Tools / Technologies and Infrastructure			**Total for Resource Category**	**$ 211.0**
Tools and Technologies	$ 41.6	$ 41.6	$ -	$ 83.2
Cores	$ 52.2	$ 52.2	$ -	$ 104.4
Banks	$ 11.7	$ 11.7	$ -	$ 23.4
Communities of Science			**Total for Resource Category**	**$ 5.6**
Journal / Web Portal	$ 1.9	$ 1.9	$ 1.9	$ 5.6
Responsibility to the Public			**Total for Resource Category**	**$ 32.3**
Public Outreach	$ 1.5	$ 1.5	$ 1.5	$ 4.5
Stem Cell Research and Society: Implications and Impact	$ 8.5	$ 8.5	$ 8.5	$ 25.5
Economic Impact	$ 0.8	$ 0.8	$ 0.8	$ 2.3
Totals	**$ 821.9**	**$ 898.5**	**$ 657.1**	**$ 2,377.5**

Facilities				
Facilities				
Laboratories / Research Facilities	$ 192.1	$ 82.3	$ -	$ 274.4
Totals	**$ 192.1**	**$ 82.3**	**$ -**	**$ 274.4**

The amount committed to early-stage research reflects the need to build fundamental knowledge, while funds for the preclinical stage reflect the high cost of such research and the growing number of therapies that will be developed with time. Although clinical research is very expensive, its long time course means that most of these costs will occur after the plan's ten-year time frame. The funding allocated to clinical research reflects this, as well as the fact that CIRM will support primarily Phase I trials, where costs are lower, and that CIRM expects to share the costs of later stage Phase II clinical trials with industry.