RECOMMENDATIONS FROM THE SYMPOSIUM

The field of stem cell research "needs more transformative thinking. …Think of Eric Lander and the genome project. … California is in a position to do something transformative." – George Daley

The goal of CIRM is to fund research on stem cells to develop therapies and treatments that will help prevent, detect, diagnose and treat disease and disability. Proposition 71 also mandates that priority be given to research that:

(i) Is not funded or underfunded by the NIH
(ii) Is risky and innovative
(iii) Is of the highest quality
(iv) Enables young researchers to enter the stem cell field

The recommendations presented at the symposium largely fall into four categories: Basic and Clinical Research Areas, Tools, Core Facilities, and Strategic Approaches. The proposed priority for implementing each recommendation is described as near-term (**NT**) if it is to be initiated in the first 3 years; intermediate term (**MT**) to begin in 3-6 years; and long-term (**LT**) to begin in 5 years or more.

I. Basic and Clinical Research Areas

Because the field of stem cell research is new, scientists lack a comprehensive understanding of the basic biology of ESCs. The molecular bases of many fundamental properties of stem cells are still unknown. The following 6 research projects are recommended to provide fundamental knowledge that is required for the design of meaningful preclinical and clinical applications of stem cells.

1) Creation of new embryonic stem cell lines **(NT)**
   The creation of new and novel cell lines is a high priority for the whole field. Because federal funds can only be used for work on a limited number of existing cell lines, U.S. scientists have extremely limited resources to create new lines such as those described below. Proposition 71 provides one of the few avenues for this effort in the U.S.
   a. More "normal" or wild-type lines are needed for genetic diversity and to obtain clinical grade lines free of exposure to animal cells or products.
   b. Disease-specific human ESC lines, produced either by homologous recombination, or with embryos from pre-implantation genetic diagnosis (PGD) or via somatic cell nuclear transfer (SCNT) are critical for studying disease mechanisms in familial disorders, for drug discovery and for the development of treatments and diagnostics.
   c. Development of robust cryopreservation techniques will enable stem cell researchers to ensure quality, viability and reliability of frozen stem cell lines and preparations for research and clinical applications.

2) Controlling self- renewal of human embryonic stem cells **(NT- MT)**
   A fundamental understanding of the processes that regulate ESC self-renewal is essential for basic and clinical research.
   a. Developing standard culture conditions that minimize or eliminate the use of animal cells and products while optimizing self-renewal, homogeneity and genetic stability will provide a basis for the development of clinical-grade cell lines.

b. Understanding the mechanisms and regulation of self-renewal will allow large scale production of stem cell populations - a prerequisite for therapeutic treatments and cell transplantation.
c. Determining methods for reversible blocking of differentiation by human ESCs may facilitate the maintenance of stem cells in a self-renewing state.

3) Lineage-specific differentiation by stem and progenitor cells **(NT-MT)**
A detailed molecular characterization of stem cell differentiation, especially human ESCs is required to generate appropriate and functional target cell preparations for cell replacement.
a. An understanding of, and control of, lineage commitment and maturation pathways pf different target populations will enable preclinical research and provide a basis for the reliable production of therapy-grade cells.
b. Development of methods to control self-renewal may allow the prevention of teratoma formation by transplanted cells.

4) Understanding of stem cell fate decisions **(MT-LT)**
The discovery that cancer stem cells may be the etiological cause of several cancers is a recent and potentially revolutionary finding with tremendous potential for drug discovery and novel treatment approaches. It also highlights the fact that stem cells may make fate decisions that lead them astray. Understanding the molecular mechanisms that allow such transformations of a stem cell is vitally important for preventing tumor formation when stem cells are used for therapy. Recommended areas of research are:
a. Identification of cancer stem cells and distinction from normal stem cells or tumor cells.
b. Identification of oncogenic changes as early biomarkers of disease and targets for study of basic mechanisms of renewal, differentiation, and proliferation.

5) Somatic cell nuclear reprogramming **(MT-LT)**
Understanding of mechanisms employed by oocytes to reprogram the nucleus from a somatic cell is needed for the long-term goal of reprogramming somatic cells for tissue repair. These studies include:
a. Mechanisms of somatic cell nuclear reprogramming using oocytes
b. Developing methods for reprogramming nuclear function without oocytes

6) Modulation of the immune system for recipients of cell transplants **(MT-LT)**
Graft rejection and graft-versus-host disease are significant obstacles to successful cell replacement. Research on inducing tolerance or reducing rejection of transplanted cells will address these obstacles. Recommended areas of research are:
a. Development of techniques to cross MHC barriers
b. Methods to re-educate the immune system to accept alloantigens on transplanted cells.

II. Tools

Numerous calls were made throughout the meeting for the development of a variety of research tools and essential reagents that are too labor-intensive and expensive for any single laboratory to shoulder. These include:

1) Bioinformatics tools for collecting, sharing, and analyzing large datasets **(NT-MT)**

2) Library of antibodies against stage-specific cell surface markers for identifying, sorting and purifying cells at different stages of differentiation **(NT-MT)**

3) Collection of DNA microarray profiles for stem cells and their differentiated progeny to "fingerprint" cells at various stages of differentiation **(NT-MT)**

4) Standardized and quality-controlled reagents and growth factors for cell culture to reproduce experimental conditions more effectively across different laboratories **(NT-MT)**

5) Imaging approaches and reagents to track the fate and function of transplanted cells, especially using non-invasive technologies **(MT)**

6) *In vivo* cell delivery methods and techniques that minimize immune rejection or reaction and promote therapeutic function such as encapsulation and scaffolds **(MT)**

7) Guidance and consulting on the application of federal regulations, including those of the FDA to assist investigators in the planning and implementation of preclinical research **(MT)**

III. Core Facilities

A consistent theme throughout the conference was a recommendation for the development of state-wide research core facilities that would decrease financial and labor burdens imposed on individual laboratories, and greatly facilitate stem cell progress through the provision of sophisticated tools and technologies. The availability of such shared regional facilities will be a tremendous advantage for Californian stem cell investigators, particularly those working in small institutions. These include:

1) Vector core **(NT-MT)** to develop molecular tools for:
    a. Conditional gene expression in stem cells
    b. Bioimaging markers to track cells and cell components
    c. RNAi vectors for regulating protein expression
    d. Facilitating homologous recombination in human cells

2) Small animal core **(NT-MT)** to assess cell preparations that are intended for transplants. Such a core will develop and run standardized assays to evaluate:
    a. Tumorigenicity (using immune-deficient mice and other models)
    b. Cellular function and stability
    c. Efficacy
    d. Toxicology

3) Pre-clinical core **(NT-MT)** to train and guide researchers on regulatory issues, good manufacturing practice and quality assurance in preparation for preclinical projects.

4) Embryonic stem cell bank **(MT)** for:
    a. Derivation of new ESC lines
    b. Analysis and characterization of ESC lines
    c. Maintenance/distribution of well-characterized human ESC lines to researchers in California

5) High-throughput screening core **(MT)** for:
    a. Basic studies such as screening for small molecule or other regulators of:
        i. Self-renewal
        ii. Differentiation
    b. Drug discovery studies using:
        i. "Normal" or wild-type cells for studying toxicology
        ii. Disease-specific cells for drug discovery

6) Large animal facility **(MT-LT)** for the use of large mammals to assess cell preparations that are being planned for application in clinical trials as transplants. The following will be assessed:
    a. Tumorigenicity
    b. Cellular function and stability
    c. Efficacy
    d. Toxicology

7) Good Manufacturing Practice (GMP) cores GMP facilities currently exist in California at UCLA, UCSF, Stanford University and the City of Hope Medical Center. The type of GMP facility needed however varies with the stage of development of a treatment. Recommendations for new GMP facilities include:
    a. Small GMP facilities **(NT)** — used in early stages of cell derivation in anticipation of obtaining clinical grade cells in the future
    b. Medium GMP facilities **(MT)** — to produce sufficient quantities of clinical grade cells for Phase I trials
    c. Large GMP facilities **(LT)** — for manufacturing quantities of cells for late phase clinical trials involving large numbers of patients.

    At present, few projects have yet to reach the preclinical or clinical stage; therefore, the requirement for large GMP facilities is not seen as an immediate need.

IV. Strategic Approaches

Four recommendations describe strategic approaches that will promote the growth of stem cell research in California and the integration of this field with other disciplines.

1) Organize a Strategic Planning Committee to provide the CIRM with advice on scientific and clinical matters ranging from basic research approaches to designing effective clinical trial networks. In order for the CIRM to benefit from a broad range of ideas and points of view, this group should not include members of the ICOC or of any of the CIRM Working Groups.

2) Encourage multidisciplinary and interdisciplinary collaborations between clinicians, engineers, physicists, computer scientists, chemists as well as biologists from other disciplines to work with stem cell scientists on complex problems and technologies.

3) Encourage partnerships between academic scientists and industry to accelerate the process of developing promising preclinical studies into actual treatments for patients.

4) Support a sabbatical program to encourage a global exchange of ideas, tools and reagents between Californian stem cell scientists and scientists in other parts of the country and the world.