MEETING NOTICE AND AGENDA
REGULAR MEETING OF THE
INDEPENDENT CITIZENS OVERSIGHT COMMITTEE
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
Organized Pursuant To The
CALIFORNIA STEM CELL RESEARCH AND CURES ACT

Wednesday, October 9, 2013
9:00 am – 5:00 pm

Main Location
Hilton SFO Bayfront Hotel
600 Airport Boulevard
Burlingame, CA 94010

[Members of the Public will be invited to provide testimony before or during consideration of each item. Makers of public comments are asked to limit their testimony to three (3) minutes.]

REPORTS & DISCUSSION ITEMS

1. Call to Order.

2. Pledge of Allegiance.

3. Roll Call.

4. Chairman's Report.

5. President's Report.

ACTION ITEMS

6. Consideration of appointment of new scientific members and reappointment of existing members to the Grants Working Group.

7. Consideration of appointment of a new ICOC patient advocate member to the Grants Working Group.

8. Request for consent to initiate rulemaking to amend conflict of interest regulations for non-ICOC members of the Grants Working Group.

9. Consideration of minutes from the May, July & August ICOC board meetings.

DISCUSSION ITEMS

10. Update on CIRM's translational program.

ACTION ITEMS

11. Consideration of presentation by CIRM staff regarding report from the Scientific Advisory Board.

CLOSED SESSION

12. Discussion of Personnel [Evaluation of President] (Government Code section 11126, subdivision (a); Health & Safety Code section 125290.30(f) (3) (D)).

DISCUSSION ITEMS

13. Public comment. The Committee will accept public testimony on any matter under its jurisdiction that is not on the agenda, but the Committee cannot act on any such matter at this meeting.

THE ORDER OF BUSINESS MAY BE CHANGED WITHOUT NOTICE.

NOTICE

The California Institute for Regenerative Medicine and its Independent Citizens Oversight Committee, and any subcommittees thereof, comply with the Americans with Disabilities Act (ADA) by ensuring that the meeting facilities are accessible to persons with disabilities, and providing that this notice and information given to the Members of the Committee is available to the public in appropriate alternative formats when requested. If you need further assistance, including disability-related modifications or accommodations, you may contact Maria Bonneville at the California Institute for Regenerative Medicine at 415-396-9100 no later than the day prior to the meeting.

Questions or requests for additional information prior to the Independent Citizens Oversight Committee meeting may be referred to Maria Bonneville at the California Institute for Regenerative Medicine at mbonneville@cirm.ca.gov or 415-396-9100.

This meeting agenda is also available on the website for the California Institute for Regenerative Medicine at http://www.cirm.ca.gov.

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The state stem cell agency

President's Report

Ellen Feigal, M.D.

ICOC Meeting — October 2013

Burlingame, CA

iPS Cells form organoids with multiple types of brain cells

J. Knoblich et al. Austrian Academy, *Nature,* Sept. 19

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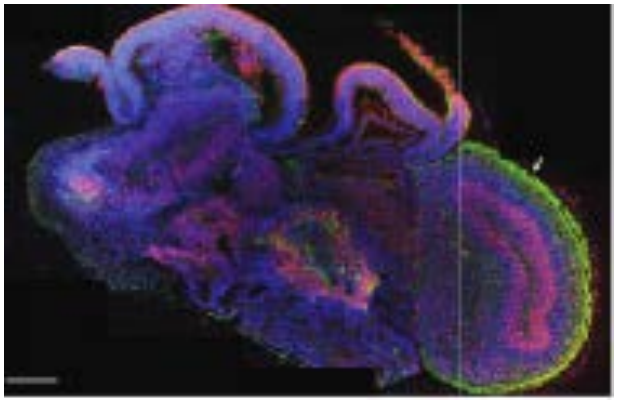
- Most complex neural tissue to date
- Assembled spontaneously in lab
- Key to assembly: gel that mimicked natural connective tissue
- Organization not like normal brain
- Immediate impact, researching neurologic disease



- i.e. iPS cells created from patient with microcephaly resulted in smaller clumps of cells
  - neural stem cells seemed to mature too quickly

Down Syndrome Cognitive Deficits Linked to Stem Cell Regulation

Michael Clark, Stanford, *Nature,* Sept. 11

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- Gene found studying cancer is on Chromosome 21
- Usp16 determines rate stem cells are depleted
- Down patients' third copy results in stem cell loss as in aging
- Lowering expression of Usp16 causes cells to behave more normally
- This gene and its protein

  are now therapeutic targets

- *Unlikely only culprit gene*

Genetic Manipulation Gets Mouse Hearts to Repair Themselves

Kenneth Chien et al. Harvard, *Nature Biotech,* Sept. 8

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- VEGF a logical gene, it promotes new blood vessels

— Prior studies of direct injection of raw DNA not good results

- Synthetic mRNA provided brief pulsed expression
- Reduced infarct size, improved survival
- Seems to mobilize native progenitor stem cells

- Parallel study in *Cell Research* Sept. 10 showed similar effect in human cells

Pancreatic stem cells isolated in mice and shown able to produce two key tissues Hans Clevers, Hubrecht Inst, Netherlands, *EMBO,* Sept. 17

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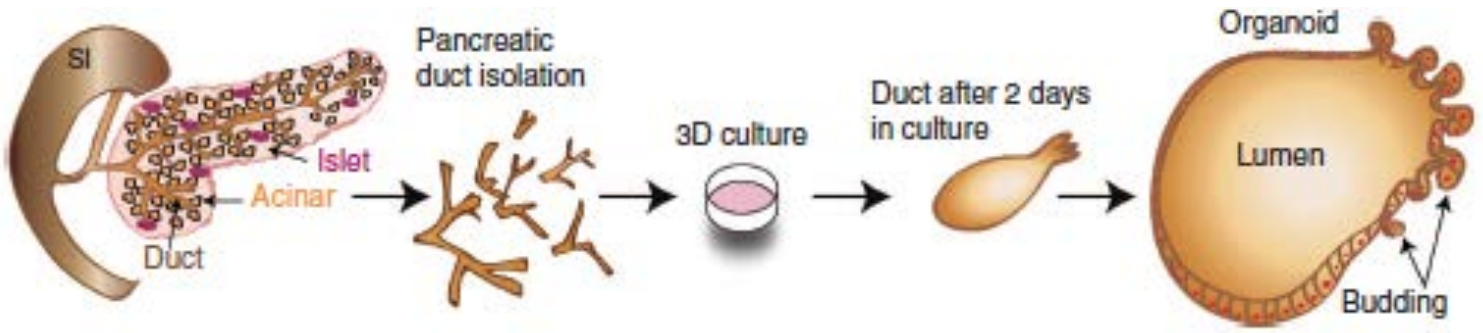
- Activated progenitor cells by turning on key genes
- 3-D culture system allowed organoids to form
- Organoids could expand many fold
- Organoids could create Beta cells and duct cells



RFA Program

- Disease Team III
  - ICOC Funding Decision – December 2013
- Basic Biology V
  - ICOC Funding Decision – January 2013
- Genomics
  - GWG Review of Applications – November 2013
- Strategic Partnership III
  - GWG Review of Applications – February 2014
- Research Leadership Extension
  - GWG Review of Applications – March 2014

RFA Program

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- Tools and Technologies III
  - RFA Posting – October 2013
- Alpha Clinics
  - RFA Posting – October 2013

Public Outreach and Engagement

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- October 2nd Stem Cell Awareness Day
  - — 20 events in 4 countries and 4 U.S. states
  - — reached more than 4,500 high school students in CA
- Patient advocate day in LA
  - — 25 joined in a roundtable discussion
- Town Hall: HIV Cure Research
  - — @ 150 attended in SF





CIRM mini symposium: Breaking the Bottleneck: Deriving Definitive HSC from hPSC Aug 29,2013

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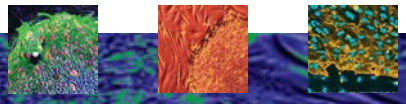
- Goal to define and discuss key scientific and technical bottlenecks prevent ing successful derivation of fully functional HSC from hPSC, and how CIRM might act to address these challenges
- Overcoming bottleneck would have significant impact not only on basic and developmental biology, but also on translation of stem cell science from bench to bedside for many hematological and non-hematological diseases, including inborn errors of metabolism and genetic diseases
- Presentations from 6 external thought leaders, including 4 CIRM investigators and panel discussion with CIRM scientific staff
- White paper to be produced by end of year: examples of recommendations include: consider as priorities in upcoming RFAs; allowing co-PIs in basic research grants and promoting collaborations with investigators external to California



CIRM works with FDA on regulatory pathway for cell therapy

- Regulatory Pathways: International Workshop on Cell Therapies, September 17, 2013 Bethesda, MD
  - CIRM-led international regulatory workshop, focus on N. American, European, and Japanese regulatory frameworks for developing cell-based therapies

CIRM works with FDA on regulatory pathway for cell therapy

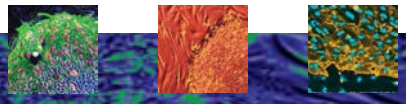
- CIRM webinar on Moving cell based therapies to the clinic for Parkinson's Disease speakers from FDA, academia, industry November 14, 2013 10 am to 12 noon Pacific http://www.cirm.ca.gov/our-funding/regenerative-medicine-consortium

Speakers

- Wilson Bryan, M.D., Director, Division of Clinical Evaluation and Pharmacology/Toxicology, OCTGT, CBER, FDA
- Jeffrey Kordower, Ph.D., Professor of Neurological Sciences and Neurology, Rush University Medical Center
- Karl Johe, Ph.D., Chief Scientific Officer, Neuralstem
- White paper from CIRM sponsored PD workshop as reference

Business Development Update

- Stem Cell Meeting on the Mesa:
  - October 14 – 16th
  - Partnering Forum: Representatives from regenerative medicine companies; pharma and investment community and CIRM Funded programs
  - CIRM Funded Team participated in “pitch practice” with two VC’s providing input
  - Roundtable Meeting (Oct. 16th): follow up to the June Workshop on technology hurdle. Topics to include:
    - Building a Stem Cell Tool Kit
    - Suspension Culture for increasing titer



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The state stem cell agency

Finance Report

October 9, 2013

Financial Highlights for 13/14 FY

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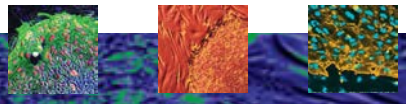
- Current Year OpEx 13/14 FY: $2.0M
  - Prior FY OpEx 12/13 FY: $1.8M

- Grant disbursements 13/14 FY: $59.3M
  - Prior period 12/13 FY: $39.1mm



Operating Expense Detail

Dollars in 000	Jul 2013-Aug 2013	Jul 2012 - Aug 2012
Employee Expenses	1,857	1,622
External Services	42	139
Reviews, Meetings, Workshops	86	28
Memberships/Training	3	2
Travel	30	14
Equip/Supplies/Telecom/Software	17	8
TOTAL	2,034	1,813

Major drivers of OpEx variance vs. prior period:

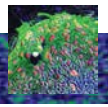
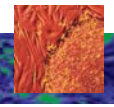
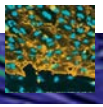
- Employees: Increase from 53 to 56 FTEs

Audit/Cash Update

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- 2012/13 Annual Financial Audit
  - Completed
  - Report by MGO

- Available cash as of Sept 30, 2013
  - $61.4M

Donations

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- $1,000
  - Amalgamated Transit Union Local 1277
    Los Angeles

CIRM Scientific and Medical Research Funding Working Group
Biographical information of candidates nominated to serve as Scientific Members of the Working Group

Bradley E. Bernstein, MD, PhD

Dr.. Bernstein is Associate Pathologist at Massachusetts General Hospital, Associate Professor of Pathology at Harvard Medical School, and Senior Associate Member at the Broad Institute. He is also an Early Career Scientist of the Howard Hughes Medical Institute. He co-directs the Epigenomics Program at the Broad Institute, and serves as a principal investigator in the Broad's Klarman Cell Observatory and is affiliated with Massachusetts General Hospital's Center for Systems Biology and Center for Cancer Research and the Harvard Stem Cell Institute. Dr. Bernstein received his BS from Yale University in physics and his MD and PhD from the University of Washington School of Medicine. After receiving his MD and PhD, Dr. Bernstein completed a residency in clinical pathology at Brigham and Women's Hospital. He carried out postdoctoral research at Harvard University with Stuart Schreiber and also collaborated extensively with Eric Lander. He joined the faculty of Massachusetts General Hospital and Harvard Medical School in 2005.

Dr. Bernstein's research focuses on epigenetics - changes in gene activity governed by influences outside the genes themselves - and specifically how modifications to the protein scaffold called chromatin contribute to mammalian development and human cancer. His laboratory is characterizing epigenetic mechanisms that underlie stem cells' ability to give rise to almost any kind of cell, while also exploring how epigenetic mechanisms contribute to malignant transformation and therapeutic resistance.

Dr. Bernstein oversees two major NIH projects at the Broad Institute. These include the NHGRI-sponsored ENCODE project, which seeks to catalog all of the working parts of the genome, and the Epigenomics Project, which produces reference epigenomes for human tissues and stem cells. This work benefits from an outstanding team of production-oriented scientists in the Epigenomics Program and extensive collaborations with the sequencing center, computational scientists, and disease researchers at the Broad Institute.

Dr. Bernstein's honors and awards include a Howard Hughes Postdoctoral Research Fellowship for Physicians, a Young Investigator Award from the Academy of Clinical Laboratory Physicians, a Career Award in the Biomedical Sciences from the Burroughs Wellcome Fund, a junior faculty award from the Culpeper Foundation, a Howard Goodman fellowship, and the Martin Prize in Basic Research from Massachusetts General Hospital.

Richard A. Gibbs, PhD

Dr. Gibbs is the Wofford Cain Chair in Molecular and Human Genetics, Professor in the Department of Molecular and Human Genetics, and Director of the Human Genome Sequencing Center at Baylor College of Medicine. He earned his BSc (Hons)

and his PhD in Genetics and Radiation Biology at the University of Melbourne and completed a postdoctoral fellowship at Baylor College of Medicine studying the molecular basis of human X-linked diseases and development of technologies for rapid genetic analysis. In 1991, Dr. Gibbs joined the faculty at BCM and played a key role in the early planning and development phases of the Human Genome Project (HGP). In 1996, he established the Human Genome Sequencing Center (HGSC) that subsequently was chosen to be one of five worldwide sites to complete the final phase of the project. The HGSC contributed approximately ten percent of the HGP and it was completed in 2004.

The HGSC now occupies more than 36,000 square feet, employs over 200 staff including eighteen faculty. The group collaborated to sequence the first species of fruit fly, Drosophila melanogaster, the Brown Norway rat and rhesus macaque. The group independently completed the second species of fruit fly, Drosophila pseudoobscura, the honeybee, wasp, flour beetle, the bovine genome, the sea urchin, Dictyostelium discoideum and innumerable bacteria. The BCM-HGSC also engaged in a program to sequence all human cDNAs, create the human and bovine haplotype maps and more recently, the cancer genome project. In 2007, the group produced the first sequence of a diploid human, James Watson. In that year a new method for capture and analysis of human DNA was developed.

Current research within the HGSC is focused upon the genomics of cancer, heart disease and autism. To achieve this the group is sequencing single human genomes at an increasing rate. New molecular technologies are being developed for the mapping and sequencing, for exploring novel chemistries for DNA tagging, and to enable development of instrumentation for DNA manipulation. The HGSC is also part of the Human Microbiome Project and has an active bioinformatics program, with research projects involving biologists and computer scientists. Problems under study focus on developing tools for generating, manipulating, and analyzing genome data.

Dr. Gibbs has received many awards and honors including election to membership in the Institute of Medicine (IOM), receipt of LSU Chancellor's Distinguished Lectureship, and the Michael E. DeBakey, MD Excellence in Research Award.

Martin F. Pera, PhD

Dr. Pera is Professor of Stem Cell Sciences at the University of Melbourne, the Florey Neuroscience Institute, and the Walter and Eliza Hall Institute for Medical Research. He serves as Program Leader for Stem Cells Australia, the Australian Research Council Special Research Initiative in Stem Cell Sciences (www.stemcellsaustralia.edu.au). He received his BA degree in English Language and Literature from the College of William and Mary and his PhD in Pharmacology from George Washington University. Dr. Pera carried out postdoctoral research at the Institute of Cancer Research and the Imperial Cancer Research Fund in London, and was a Research Fellow at the Department of Zoology at Oxford University. Thereafter he moved to Australia where he became Research Professor at the

Monash Institute of Medical Research at Monash University and the Director of Embryonic Stem Cell Research at the Australian Stem Cell Centre. He served as Professor and Founding Director of the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at the Keck School of Medicine of the University of Southern California from 2006 before returning to Melbourne in 2011.

Dr. Pera's research interests include the cell biology of human pluripotent stem cells (PSCs), early human development, and germ cell tumors. Dr. Pera was among a small number of researchers who pioneered the isolation and characterization of PSCs from human germ cell tumors of the testis, work that provided an important framework for the development of human embryonic stem cells (ESCs). His laboratory at Monash University was the second in the world to isolate ESCs from the human blastocyst, and the first to describe their differentiation into somatic cells in vitro. He has provided extensive advice to state, national and international regulatory authorities on the scientific background to human ESC research.

Dr. Pera's research group focuses on the extrinsic factors (signals from outside the cell) involved in maintenance of the pluripotent state in human ESCs, and those factors that drive stem cell commitment into progenitor cells representative of the three embryonic germ layers (the precursors of the primordia that form the tissues of the body). A major hypothesis behind this work is that PSC cultures represent an interactive hierarchy of different cell types, similar to those found in the embryo around the time of implantation into the womb, and that just as communication between different cell populations in the embryo acts to specify cell fate during development, similar conversations control stem cell maintenance and early lineage choice in vitro. This work has fundamental importance for our understanding of stem cell biology, but it also addresses practical questions that must be solved before human ESCs can achieve their full potential in research and medicine. Recently the Pera laboratory has focused on specification PSCs to the neural lineage and their differentiation into the cells that form the cerebral cortex. The cerebral cortex is that part of the brain that is uniquely human, and PSCs provide us for the first time with insights into how the cortex is formed, and into many important disorders, including epilepsy, schizophrenia and autism, that are thought to arise during this stage of brain development.

Dr. Pera serves on the Steering Group of the International Stem Cell Initiative, was on the advisory board of the National Stem Cell Bank (US), ES Tools (European Union), the Canadian Stem Cell Network, and many other initiatives, and he chairs the Membership Committee of the International Society for Stem Cell Research and is a member of its Finance Committee. He is on the Editorial Boards of *Cell Stem Cell*, *Stem Cells*, *Stem Cell Research*, and *PLoS1*. He is author of over 100 peer-reviewed publications and inventor on 14 issued patents and published patent applications.

Barry Rosen, PhD
Dr. Rosen is at the Wellcome Trust Sanger Institute (WTSI) in Cambridge, UK, an institute focused on engaging researchers in projects that seek to further

understanding of gene function in health and disease and to generate data and resources of lasting value to biomedical research. His Ph.D. work was with Dr. Bruce Spielgeman of Harvard University on the molecular biology of adipocytes and his post-doctoral work on mouse embryology with the late Dr. Rosa Beddington in Edinburgh. He then went on to work on gene trap mutagenesis strategies and mouse embryology in INSERM in Nice, France. In 2003 he joined the Sanger focusing on the development of high throughput approaches for the systematic mutagenesis of all genes in mouse embryonic stem cells as part of the EUCOMM and KOMP programs, which formed a major part of the International Knockout Mouse Consortium. He has been a Group Leader/Senior Scientific Manager in the ES Cell Mutagenesis Team for the past 7 years and one of the key scientists developing both wet lab and informatics based approaches to functional annotation of the mouse genome. These efforts have continued as part of the EU's EUCOMMTOOLs program where Dr. Rosen has managed a program to make 250 new strains of Cre driver mice. He also runs a laboratory that develops bespoke mouse models for the Sanger Faculty.

For the past several years he has also been involved in genome engineering and differentiation of human stem cells both at the Sanger and in collaboration with the Centre for Regenerative Medicine at Cambridge University (with Prof. Roger Pedersen) and the differentiation of human stem cells to adipocyte lineages (with Prof. Toni Vidal). Presently he is involved at the Sanger in the development of approaches to use designer nucleases (TALENS/CRISPRS) for large scale genome engineering of human stem cells.

Dr. Rosen is also active as an educator at the WTSI, serving as chief instructor for the past five years on an intensive course on Genome Manipulation of Mammalian Stem Cells and is well published on topics related to his areas of expertise and speaks at various international conferences on large scale mutagenesis strategies.

Steven Jon Russell, MD, PhD
Dr. Russell is Assistant Professor of Medicine at Harvard Medical School and an Attending Physician at Massachusetts General Hospital. Dr. Russell earned his MD and PhD at University of Texas Southwestern Medical School and did his Residency and Fellowship at Massachusetts General Hospital. He is certified by the American Board of Internal Medicine in Internal Medicine and Endocrinology, Diabetes & Metabolism.

Dr. Russell is a principal investigator in a collaborative group of investigators from Massachusetts General Hospital and Boston University who are working to make automated blood glucose control a reality. In order to reduce the impact of diabetes on those who live with this disorder, the group is developing a closed-loop artificial pancreas blood glucose control system capable of monitoring blood glucose levels every five minutes and utilizing a computer algorithm to deliver rapid-acting insulin and glucagon as needed to avoid hyper- and hypoglycemia. They have recently completed the first outpatient trial of this device. Other projects are focused on automated management of glucose in the hospital, insulin pharmacokinetics, and

real-time insulin sensing. Dr. Russell's clinical interests include diabetes mellitus, hyperglycemia of critical illness, intensive insulin therapy, and new technology in the management of diabetes.

Dr. Russell is active in a number of professional societies and is a reviewer for several journals including *The New England Journal of Medicine, Diabetes, Diabetes Care*, *Aging Cell, The FASEB Journal*, and *Molecular and Cellular Endocrinology*. His research is supported by the National Institutes of Health (NIH), the Leona M. and Harry B. Helmsley Charitable Trust, the American Diabetes Association, and the Juvenile Diabetes Research Foundation.

Reappointment of Scientific Members to the Grants Working Group

Grants Working Group Members originally appointed in late 2006 and early 2007 have terms that are now expiring or just expired. We are seeking the reappointment of the individuals listed in the table below. Their updated biographies follow. In accordance with the rules set forth by Proposition 71, reappointments should be staggered into thirds, each with a 2, 4, or 6-year term. We propose 2 and 6-year reappointment terms for this cohort as indicated in table below.

Proposed Reappointments to GWG

Last	First	Term (Yrs.)	Expertise
Heimfeld	Shelly	6	Cellular Therapy; Hematology; GMP Cell Production
Lemischka	Ihor	2	Cell Fate; Hematopoietic Stem Cells; Systems Biology; Stem Cell Biology
Zwaka	Thomas	6	Pluripotent Stem Cell Biology; Molecular Genetics

Shelly Heimfeld, Ph.D.
Dr. Heimfeld is a Full Faculty Member at the Fred Hutchinson Cancer Research Center in Seattle, Washington and serves as Scientific Laboratory Director for the Cellular Therapy Laboratory and cGMP Therapeutic Manufacturing Facilities. These facilities are responsible for all minimally and more extensively manipulated cell components used for treatment of patients at the Center. His primary responsibilities are to ensure the safety, quality, and effectiveness of each product, but also include implementation of new technologies, translation of basic science procedures into appropriate clinical protocols, product development, process improvement, and regulatory compliance.

Dr. Heimfeld received his Ph.D. in Cell Differentiation from the University of California, Irvine and completed postdoctoral studies with Dr. Irv Weissman at Stanford before going into industry to work as a founding scientist at SyStemix and later at CellPro, Inc, the first company to develop an FDA approved device for $CD34^+$ cell enrichment.

Dr. Heimfeld is internationally recognized for his research in hematopoietic-derived stem cells and the development of cell processing technologies for improved cancer therapy. His long-term goals for this area are to identify better markers for characterization of stem and progenitor cells, to improve isolation technologies, and to develop *ex vivo* manipulation strategies that can enhance the therapeutic potential of these cells. He has also been involved in the clinical development of T-cell based immunotherapy for various diseases.

Dr. Heimfeld is a Past-President and Past-Chair of the Executive Advisory Board for ISCT (International Society of Cellular Therapy). He is a leading authority in regulations and lab practices needed for cell therapies, including Good Laboratory Practice (GLP), Good Tissue Practice (GTP), and Good Manufacturing Practice (GMP). Dr. Heimfeld continues to work with the Food and Drug Administration (FDA) to facilitate exchange of ideas in the rapidly evolving area of Cell Therapy.

Ihor R. Lemischka, PhD

Dr. Lemischka is the Director of The Black Family Stem Cell Institute, the Lillian and Henry M. Stratton Professor of Developmental and Regenerative Biology, and Professor of Pharmacology and Systems Therapeutics at Mount Sinai. Dr. Lemischka earned his PhD at Massachusetts Institute of Technology (MIT). There, he served as a postdoctoral research associate and also completed a fellowship at MIT's Center for Cancer Research. Dr. Lemischka then went to the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts where he completed his postdoctoral training. In 1986, he joined the faculty at Princeton University where he rose from Assistant Professor to Professor of Molecular Biology. He remained on the Princeton faculty for 21 years before coming to Mount Sinai.

An internationally renowned stem cell biologist, Dr. Lemischka has patented techniques to isolate stem cells and has significantly advanced the study of stem cell activity and behavior. Dr. Lemischka is working to establish Mount Sinai as the leading stem cell institute in the United States, which he hopes will serve as a model worldwide.

Stem cell research has clinical implications for many diseases. The first step is to understand what makes the stem cell "decide" what type of cell it will become and how it communicates with neighboring cells. Dr. Lemischka hopes to characterize the stem cell's decision-making process and regulatory network, which will then help scientists manipulate stem cell decisions and develop therapies that could treat diseases.

A vocal advocate of stem cell research, Dr. Lemischka believes the latest findings about stem cells are just the tip of the iceberg of all the medical advances that will come from stem cell research. Dr. Lemischka stands by the notion that scientific freedom is key to resolving some of the biggest mysteries in medicine.

A member of the International Society for Stem Cell Research, he has traveled the world to educate the public about stem cell behavior and has delivered countless lectures about stem cell differentiation.

Thomas P. Zwaka, MD, PhD

Dr. Thomas Zwaka, an Assistant Professor in the Department of Molecular and Cellular Biology and the Center for Cell and Gene Therapy at the Baylor College of Medicine also serves as Director of the Baylor Embryonic Stem Cell Core, and was one of the founders of the Stem Cells and Regenerative Medicine Center. After receiving his M.D. Ph.D. degrees from the University of Ulm, Germany, Dr. Zwaka completed postdoctoral fellowships in molecular cardiology at the University of Ulm, and in human and mouse embryonic stem cell biology at the National Primate Research Center at the University of Wisconsin, Madison with Dr. James Thompson. He has received numerous awards and honors, including the Gillson Longenbaugh Foundation Junior Investigator award and the Lance Armstrong Foundation Junior Investigator Award. He has served on a number review panels for the National Institutes of Health (NIH), including the NIGMS Special Emphasis Panel for human embryonic stem cell research, and he sits on the Scientific Advisory Board of the Genetics Policy Institute and Stem Cells Source, Inc.

Dr. Zwaka's research currently focuses on fundamental questions surrounding human embryonic stem cell biology, including how to reverse the process of differentiation and "re-program" any given cell type into a pluripotent stem cell. Dr. Zwaka has authored fundamental publications on the genetic modification of human embryonic stem cells, and has filed patents on embryonic stem cell differentiation and modification both in the US and internationally.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

MEMORANDUM

To: Independent Citizen's Oversight Committee

Fr: Paul Stein; Scott Tocher; James Harrison

Re: Amendments to Conflict-of-Interest Rules for Non-ICOC Members of the Grants Working Group

Date: September 27, 2013

I. SUMMARY AND REQUESTED ACTION:

In April 2013, CIRM reported to the Legislature that it intended to modify its conflict-of-interest rules for non-ICOC members of the Grants Working Group to clarify certain provisions in an effort to prevent future conflicts from arising. To that end, CIRM has prepared a set of proposed amendments to the regulations, and now seeks the Board's consent to initiate a formal rulemaking process.

CIRM aims to clarify the circumstances which may give rise to a personal, professional, or financial conflict. By doing so, CIRM intends to: (1) reduce the risk that conflicts will occur in the future; (2) make our conflict-of-interest rules more objective, understandable, and easier to apply for Grants Working Group members, CIRM staff, and the public; (3) streamline the conflict screening process CIRM undertakes in advance of each meeting of the Grants Working Group; and (4) only screen reviewers for personal, professional, or financial interests that could genuinely be deemed material.

The proposed amendments drafted by CIRM are shown in red-line on Attachment A to this memo. *We are not asking the Board to approve these amendments at this time.* Rather, Staff drafted these amendments to initiate the process of obtaining public comment, and shaping a final recommendation to the Board. As part of the rulemaking process, the amendments will be posted for public review and comment and refined as needed before Staff returns to the Board to request final approval.

II. BACKGROUND:

The Grants Working Group (GWG) is an advisory body composed of expert scientific members, patient advocate members of CIRM's Board, and the chairperson of CIRM's Board. The GWG reviews applications for research funding based on scientific

merit and makes recommendations to the Board, which has final decision-making authority. In addition to making funding recommendations, the GWG is charged by Proposition 71 with: (1) recommending criteria, standards, and requirements for considering funding applications and for awarding grants and loans; (2) recommending standards for the scientific and medical oversight of awards; (3) conducting peer group reviews of grantees to ensure compliance with the terms of CIRM awards; and (4) recommending standards and requirements governing the conduct of CIRM awards, including but not limited to reporting requirements.

Non-ICOC members of the GWG are subject to conflict-of-interest and economic disclosure requirements adopted by the ICOC.[1] Because the state's chief conflict-of-interest law, the Political Reform Act, would not otherwise apply to the GWG, Proposition 71 required CIRM to adopt its own conflict of interest rules for scientific members of the GWG. Indeed, the ICOC's conflict rules for the GWG go beyond, and are more restrictive than, the Political Reform Act in that they prohibit not only financial conflicts, but also personal and professional conflicts. A GWG member is prohibited from participating in the review of any application for CIRM funding in which the member has a personal, professional, or financial conflict, as defined in the regulations.

Prior to each meeting of the GWG, CIRM staff work extensively with grant reviewers to identify potential conflicts and ensure that any reviewer with a conflict is recused from the application in question. If, during or after the review, CIRM discovers that a violation of the rules has occurred, it is required to provide a report to the Legislature, together with a review of corrective actions taken to prevent future occurrences.

A confirmed conflict under the rules has occurred on only two occasions, most recently in April 2013. In each of these cases, the reviewer had a personal or professional relationship with someone involved in the applicant's research team who stood to receive a very small amount of salary from the grant – so small as to be immaterial. The violations were both inadvertent and highly technical. Although CIRM applied its rules strictly in each case, we believe situations such as these were not intended to trigger a conflict. We are also concerned that, by causing prospective reviewers to be flagged for a technical conflict, when in fact they have no financial or other interest that could realistically compromise the quality or integrity of the review process, strict application of the rules could hamstring the GWG's ability to attract the nation's leading scientific and medical experts. In order to prevent both the reality and appearance of a conflict,

[1] GWG members who also sit on the ICOC are subject to separate conflict-of-interest rules found in Proposition 71 (Health and Safety Code § 125290.30(g)) and the ICOC's bylaws. We are not proposing changes to the ICOC's bylaws.

while preserving CIRM's ability to attract the best reviewers available, the rules should flag only those interests that could genuinely be deemed material.

The amendments address this by establishing a monetary threshold for personal and professional conflicts of $5,000 per year in salary or consulting fees. Under this approach, GWG members who have personal or professional ties to specified members of the applicant's research team who stand to receive less than $5,000 per year in salary or consulting fees from the grant being reviewed would not be required to report a conflict.

This new monetary threshold for personal and professional conflicts is consistent with the way the rules presently address "financial benefits" which a GWG member may receive from the applicant institution, but which are unrelated to the proposal in question. Under the current rules, a financial benefit unrelated to the proposal of $5,000 or more per year triggers a conflict. The proposed amendments would leave this $5,000 threshold intact, but substitute the term "financial interest" for financial benefit, and clarify when such a financial interest exists.
A more detailed summary of the proposed amendments follows.

III. SUMMARY OF PROPOSED AMENDMENTS:

CIRM proposes to modify the definition of each type of conflict under the rules: financial, professional, and personal.

A. Financial Conflicts.

Presently, a non-ICOC member of the GWG has a financial conflict if s/he is an employee of the applicant institution; is under active consideration for a position at the applicant institution; stands to receive a financial benefit of any amount from the application under review; or has received or "could receive" a financial benefit of any type from the applicant institution that is "unrelated to the proposal" being reviewed. Further, a financial conflict exists not only if the GWG member has a prohibited financial interest in his her or her own right, but also if "his or her spouse, or any other person *with whom the member has a common financial interest*," has such an interest. Some aspects of these requirements may be subject to different interpretations by reviewers, as well as CIRM staff.

For example, the rules do not explicitly define whether a member has a "common financial interest" with someone sufficient to trigger a conflict. CIRM proposes to clarify the regulation by providing that a financial conflict exists where either: (1) a member has a prohibited interest in his or her own right; or (2) someone in the GWG member's "immediate family" has a prohibited interest. (See Att. A, § 100003(b)(1).) Consistent with state conflict-of-interest laws, "immediate family" means spouse, domestic partner, or dependent children.

CIRM also proposes to broaden the "employment" trigger for a financial conflict such that a conflict would exist where a GWG member or someone in the member's immediate family is either an employee of the applicant institution, the Principal Investigator, or Co-Principal Investigator, or "has received, or has been promised, income of $5,000 or more, or gifts of $500 or more, in the past year" from the applicant institution, the Principal Investigator, or Co-Principal Investigator. (See Att. A, § 100003(b)(1).)

CIRM also proposes to clarify the circumstances in which an investment or other financial interest in the applicant institution triggers a conflict. Presently, a conflict exists if a GWG member has received or "could receive" a financial benefit of any type of over $5,000 per year from the applicant institution that is "unrelated to the proposal" being reviewed. To clarify this provision, CIRM proposes to prohibit reviewers from having a "financial interest in the applicant institution of $5,000 or more," including but not limited to "current stock holdings, equity interest, [and] intellectual or real property interest . . . ." (See Att. A., § 100003(b)(4).)
Finally, it should be noted that: (1) the rules presently ban GWG members from participating where they stand to receive a financial benefit of *any* amount from the application under review; and (2) that prohibition is not affected by the proposed amendments.

B. Professional Conflicts.

Presently, a conflict exists where a GWG member and a "primary member of the applicant's research team" are engaged in, or are planning to be engaged in, collaboration. CIRM proposes a more objective screen to determine which people on the applicant's research team must be checked for present or future collaborations. Specifically, a conflict would arise where a GWG member is collaborating or plans to collaborate with any "person listed on the grant application as Principal Investigator or Co-Principal Investigator or someone who will receive salary or consulting fees of $5,000 or more per year from the grant." (See Att. A, § 100003(c)(2).)
The same $5,000 per year threshold would also apply to conflicts based on professional ties between a GWG member and certain members of the applicant's research team. In addition, in order to clarify the rule, the term "professional associate" has been defined more precisely to mean someone who has been a "research collaborator, a former student, post-doctoral fellow, or someone with whom the member has co-authored a publication, within the past three years." (See Att. A, § 100003(c)(1).)

CIRM proposes similar changes to the rule prohibiting professional conflicts based on "long-standing scientific differences or disagreements or disagreements that are known to the professional community and could be perceived as affecting the member's objectivity." Presently, this prohibition is triggered where a GWG member and the "applicant" are determined to have such differences or disagreements. CIRM proposes to screen not the "applicant," which is typically an academic institution or a company, but

rather those persons "listed on the grant application as Principal Investigator or Co-Principal Investigator or someone who will receive salary or consulting fees of $5,000 or more per year from the grant." (See Att. A, § 100003(c)(3).)

C. Personal Conflicts.

CIRM proposes similar changes to the regulatory language governing "personal" conflicts. Instead of screening members to determine whether any close family member or personal friend is an "applicant," the rule would require a check into whether any such person is "listed on the grant application as Principal Investigator or Co-Principal Investigator or someone who will receive salary or consulting fees of $5,000 or more per year from the grant." (See Att. A, § 100003(d)(1)-(2).)

D. Economic Disclosures.

The regulations presently require disclosures of specified economic interests that GWG members may have in their own right, as well as any interests held by their "spouses, or others with whom the member has a common financial interest." As above, in order to provide greater clarity and ease of administration, CIRM proposes to require disclosure of specified economic interests held by the member and anyone in the member's immediate family, rather than anyone with whom the member may have an undefined "common financial interest." (See Att. A, § 100003(e)(1)-(6).)

ATTACHMENT A

Adopt 17 Cal. Code of Regs. section 100003 to read:

§ 100003. Conflicts of Interest – Non-ICOC Members of the Scientific and Medical Research Funding Working Group.

(a) Prohibition: Except as provided otherwise in this regulation, a non-ICOC Grants Review Working Group member may not participate in a decision of the working group in which the individual has a conflict of interest. A conflict of interest exists when a non-ICOC Grants Review Working Group member has a real or apparent interest in the outcome of an application such that the member is in a position to gain financially, professionally or personally from either a positive or negative evaluation of the grant proposal.

(b) "Financial: Conflict of Interest - Defined: A non-ICOC member has a financial conflict of interest if:

(1) The member~~, his or her spouse, or any other person with whom the member has a common financial interest,~~ or a member of his or her immediate family is an employee of either the applicant institution~~, or~~ the Principal Investigator, or the Co-Principal Investigator on an application, or has received, or has been promised, income of $5,000 or more, or gifts worth $500 or more, in the past year from the applicant institution, the Principal Investigator, or the Co-Principal Investigator.

(2) The member or a member of his or her immediate family~~, his or her spouse, or any other person with whom the member has a common financial interest,~~ is under active consideration for a faculty or administrative position at an applicant institution.

(3) A member or a member of his or her immediate family~~, his or her spouse, or any other person with whom the member has a common financial interest,~~ stands to receive a financial benefit of any amount from an application under review.

(4) A member or a member of his or her immediate family has a financial interest in the applicant institution of $5,000 or more. A "financial interest" includes~~, his or her spouse, or any other person with whom the member has a common financial interest, has received or could receive a financial benefit of any type from an applicant institution or organization unrelated to the proposal, of over $5,000 per year. This total includes honoraria, fees, stock and other benefits. It also includes~~ current stock holdings, equity interest, intellectual property or real property interest, but does not include an interest held through a ~~-~~diversified mutual funds.

(c) "Professional" Conflict of Interest - Defined: A non-ICOC member has a professional conflict of interest if:

(1) A person listed on the grant application as Principal Investigator or Co-Principal Investigator, or someone who will receive~~s~~ salary or consulting fees of $5,000 or more per year from the grant, has been a research collaborator~~is a professional associate, such~~

~~as,~~ a former student, ~~or~~ post-doctoral fellow, or someone with whom the member has co-authored a publication, within the last three years.

(2) The member and a person listed on the grant application as Principal Investigator or Co-Principal Investigator, or someone who will receive salary or consulting fees of $5,000 or more per year from the grant, ~~primary member of the applicant's research team~~ are engaged in, or are planning to be engaged in, collaboration.

(3) A person listed on the grant application as Principal Investigator or Co-Principal Investigator, or someone who will receive salary or consulting fees of $5,000 or more per year from the grant, ~~An applicant~~ is ~~someone~~ a person with whom the member has had long-standing scientific differences or disagreements that are known to the professional community and could be perceived as affecting the member's objectivity.

(d) "Personal" Conflict of Interest - Defined: A non-ICOC member has a personal conflict of interest if:

(1) A close family member or close personal friend is a person listed on the grant application as Principal Investigator or someone who will receive salary or consulting fees of $5,000 or more per year from the grant~~an applicant~~.

(2) A person listed on the grant application as Principal Investigator or someone who will receive salary or consulting fees of $5,000 or more per year from the grant~~An applicant~~ is ~~someone~~ a person with whom the member has had long-standing personal differences.

(e) Disclosure: A non-ICOC working group member shall disclose confidentially and under penalty of perjury the following financial interests: 10/01/06 3 100003

(1) Income of $5,000 or more, or gifts worth $500 or more, received by the member or a member of his or her immediate family from a~~All~~ California-based academic or non profit research institution in the past years ~~from which members, their spouses, or others with whom the member has a common financial interest, receive income or other benefit of $5,000 or more.~~

(2) Income of $5,000 or more received by the member or a member of his or her immediate family from ~~All~~ a publicly-held biotechnology ~~and~~ or pharmaceutical company~~ies from which members, their spouses, or others with whom a member has a common financial interest, receive current income or other benefit, or hold an investment, of $5,000 or more~~.

(3) An investment worth $5,000 or more held by the member or a member of his or her immediate family in a publicly-held biotechnology or pharmaceutical company.

(~~3~~4) Income received by the member or a member of his or her immediate family in a~~All~~ privately held biotechnology company~~ies in which reviewers, their spouses, or others with whom a member has a common financial interest, have an equity interest~~.

(5) An investment held by the member or a member of his or her immediate family in a privately held biotechnology company.

(46) An interest worth $2,000 or more~~Real property interests in California held~~ held by the members or a member of his or her immediate family in real property in California~~, their spouses, or others with whom a member has a common financial interest~~.

(f) Disqualification: A non-ICOC member is required to report to the CIRM staff any conflict of interest of which he or she is aware, including, but not limited to, those described in subdivisions (b) through (e) of this regulation. Any member of the Grants Review Working Group who has a real or apparent conflict of interest with respect to an application may not review or vote on the application and must leave the room when that application is discussed. In exceptional cases, the President of the CIRM may decide that the need for special expertise of the reviewer outweighs any possible bias posed by a real or apparent conflict of interest. Under these circumstances, the CIRM staff shall publicly disclose the working group member's interest before the meeting and the working group member shall be permitted to participate in the discussion but will not be permitted to vote on the application or participate in the scientific scoring.

(g) All non-ICOC members must ~~sign a pre-review statement~~ indicate~~ing~~ any possible conflicts of interest that they have in advance of a review, and must ~~also sign a post-review statement~~certify that they did not participate in the discussion or review of any application for which they might have a conflict of interest, or ~~shall~~ indicate permission to participate was granted by the President pursuant to subdivision (f) of this regulation.

(h) Record-Keeping: All financial disclosure documents shall be kept confidential by the CIRM staff and preserved for purposes of review by the State Auditor or another independent auditor and any other audit as required by law. Records of the working group indicating those members who participated in or voted on particular recommendations shall be maintained by the CIRM staff. If the CIRM or an auditor discovers a violation of these conflict of interest provisions, a report will be made to the Legislature along with a review of corrective actions taken by the CIRM to prevent future occurrences.

(i) For purposes of this section, "immediate family" means spouse, domestic partner, and dependent children.

Note: Authority cited: California Constitution, article XXXV; Section 125290.40, subd.(j), Health and Safety Code.
Reference: Sections 125290.50, subd. (e), 125290.60, Health and Safety Code.

CALIFORNIA'S STEM CELL AGENCY

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Translation Program Update

Ellen G. Feigal, M.D.
Senior Vice President, Research and Development

Patricia Olson, Ph.D.
Executive Director, Scientific Activities

Presentation to the ICOC October 9, 2013

CIRM's Vision and Strategy

Mission

"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"

Explore (2004-2010)

- Fund broad number of diseases and projects
- Establish foundation for leadership in stem cell research

Focus (2011-2016)

- Prioritize projects and investments
- Drive clinical trials for patients to generate preliminary evidence of therapeutic benefit
- Develop partnerships

Deliver (2016+)

- Facilitate commercialization of therapies
- Advance therapies to patients
- Enable business model for stem cell-based therapies

Translational Portfolio RFAs cover product development spectrum

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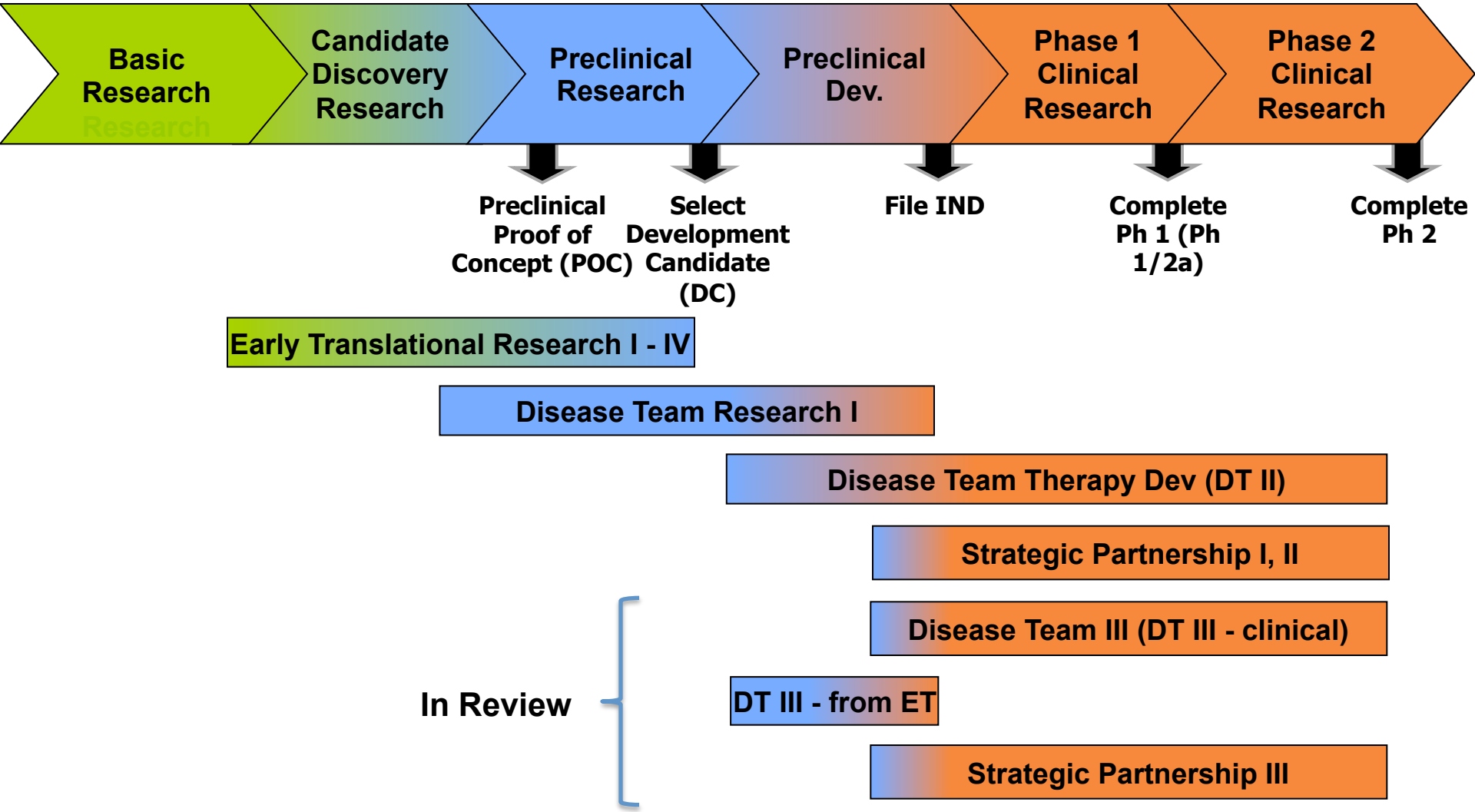
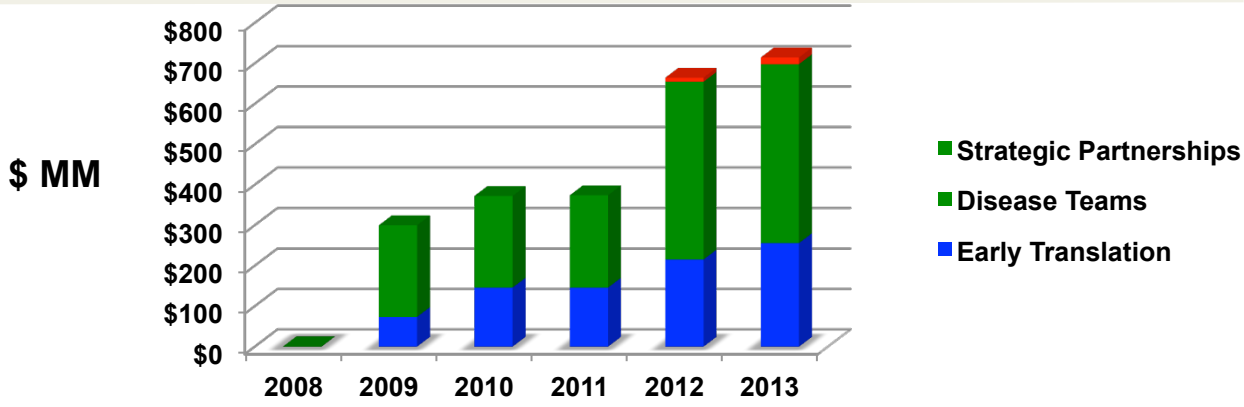
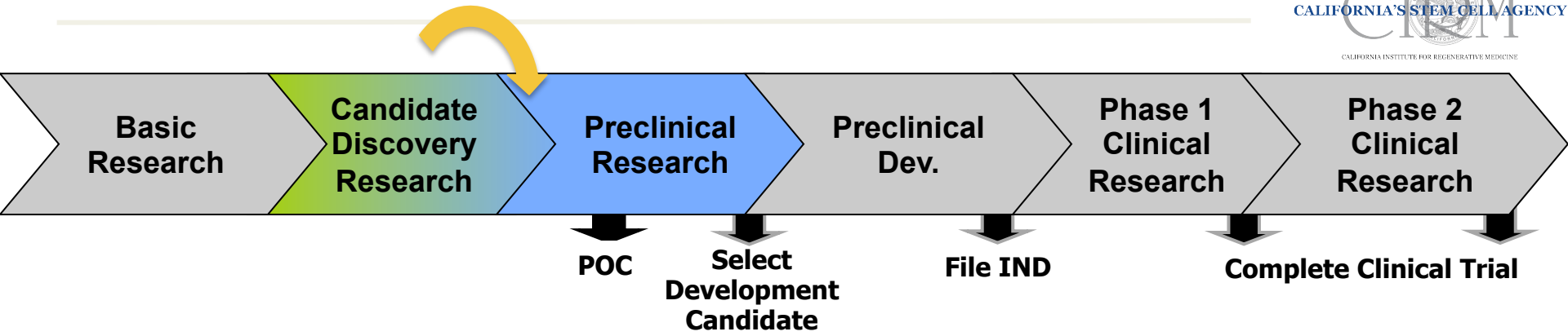


Annual Cumulative CIRM Translation Program-ICOC Awarded Funds *(as of Aug '13)*



		2008	2009	2010	2011	2012	2013
# Awards, Cumulative		***0***	***30***	***51***	***51***	***84***	***98***
	Early Translation	0	16	37	37	58	71
	Disease Teams	0	14	14	14	25	25
	Strategic Partnerships	0	---	---	---	1	2
$ MM, Cumulative		***$1.1***	***$300.0***	***$372.3***	***$374.1***	***$664.6***	***$714.6***
	Early Translation	---	$73.4	$145.7	$145.7	$215.1	$255.7
	Disease Teams	$1.1	$226.6	$226.6	$228.4	$439.5	$442.5
	Strategic Partnerships	---	---	---	---	$10.0	$16.4

Early Translational Program



Program Goal: Enable the early steps in the translation of promising, innovative stem cell discoveries

Rationale: Therapeutic hypothesis testing

Objective: Within project period,

- Achieve *in vitro* or *in vivo* proof of concept (DCF award), or
- Achieve a development candidate ready to move into IND-enabling preclinical development (DC award), or
- Address a translational bottleneck (Bottleneck award)

Early Translation Program: Summary

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RFA	Program Period	Grants Awarded, #				Funds Committed, $ MM				Funds, Awarded $ MM
		B*	DCF	DC	Total	B	DCF	DC	Total	
ET I	2009 - 2012*	8	-	8	***16***	34.7	-	38.7	***73.4***	***72.0***
ET II	2011 - 2014	-	9	12	***21***	-	16.7	55.6	***72.3***	***64.1***
ET III	2012 - 2015	-	11	10	***21***	-	19.6	49.8	***69.4***	***65.0***
ET IV	2013 - 2016		8	5	***13***		15.4	25.2	***40.6***	***≤ 40.6***
	Total	***8***	***28***	***35***	**71**	***34.7***	***51.7***	***169.3***	***255.7***	***≤ 241.7***

* 13 of the 16 ET I are closed or are being closed

Early Translation Program: Goal

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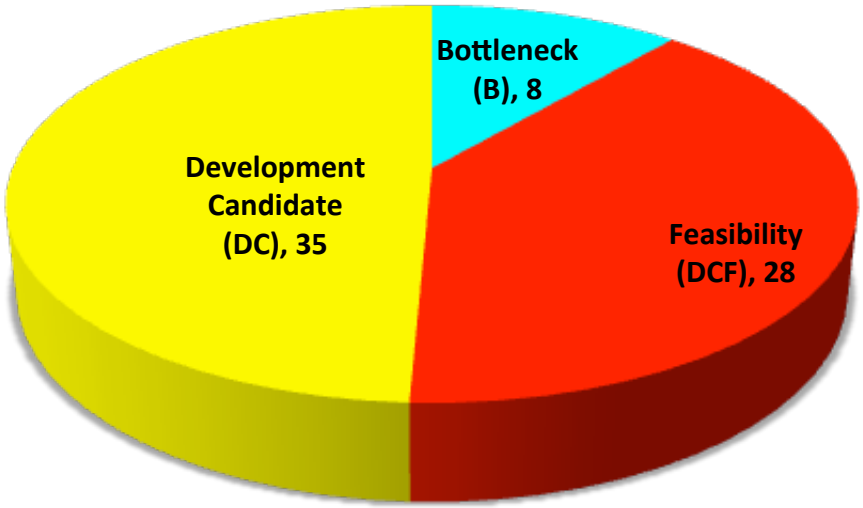
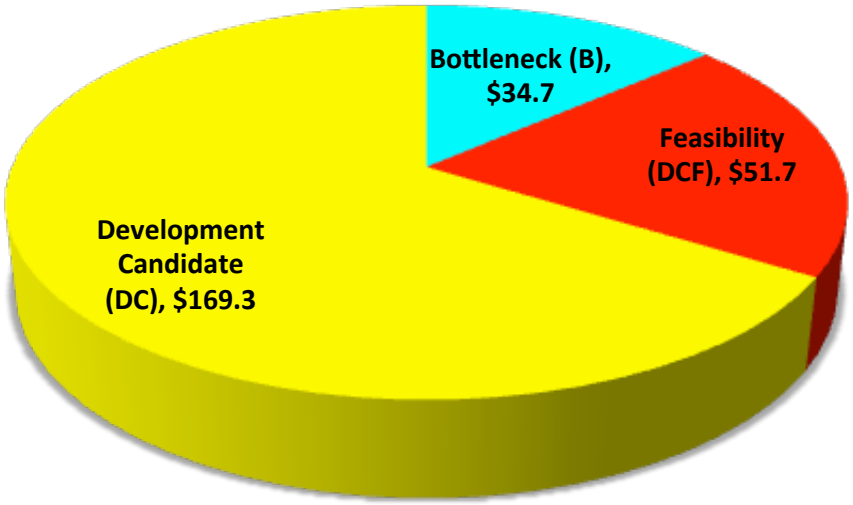
71 Awards *



$255.7 MM Committed^



* Excludes conversions
^ $241.7 actual

Early Translation Program: Priorities

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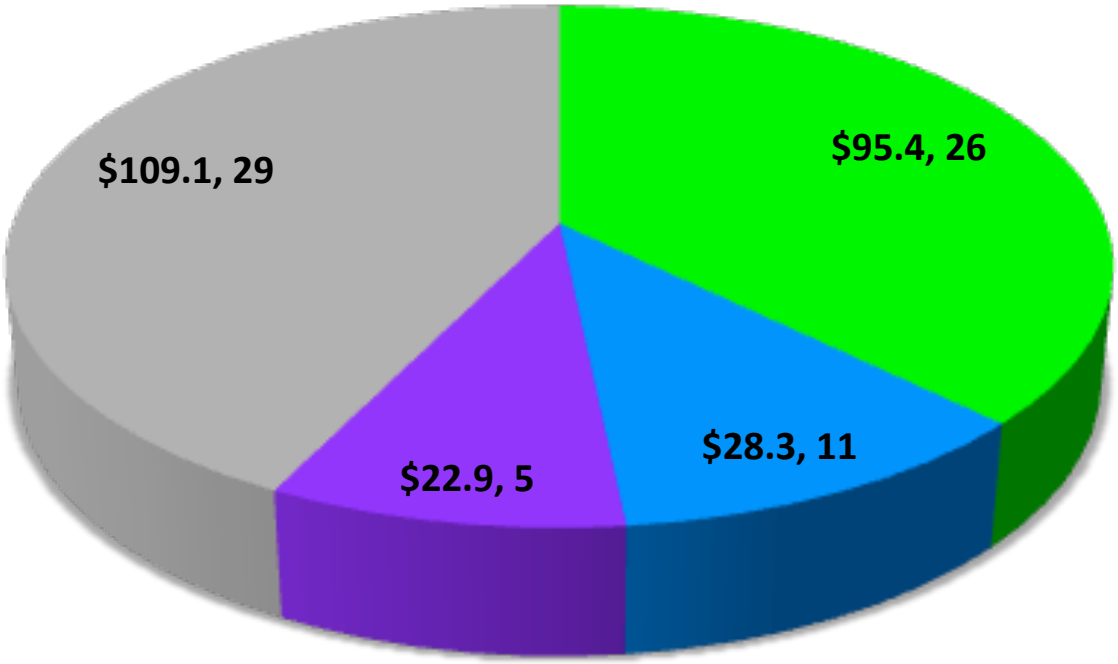
- Advance cell therapies derived from pluripotent stem cells
- Advance therapeutic candidates using cells derived from human pluripotent stem cells
- Address bottlenecks to advancement to the clinic of effective, novel cell therapies; particularly cell therapies derived from human pluripotent stem cells.

Early Translation Program: PSC Priority



Pie slices are
$ MM or # awards

PSC – Cell Therapy
PSC – DC Discovery
PSC – Translational Bottlenecks
Other

Early Translation Program: PSC Priority, Detail

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		ET 1	ET2	ET3	ET4	All ET	%, All ET
# Awards		**16**	**21**	**21**	**13**	***71***	
	PSC-derived Cell Therapy	6	8	7	5	26	37%
	PSC Derivitive for Therapeutic Candidate Discovery	-	3	4	4	11	15%
	Bottlenecks to PSC-derived Cell Therapy	5	-	-	-	5	7%
	Other	5	10	10	4	29	41%
$ MM		**$73.4**	**$72.3**	**$69.4**	**$40.6**	***$255.7***	
	PSC-derived Cell Therapy	$30.2	$24.1	$28.5	$12.4	**$95.4**	37%
	PSC Derivitive for Therapeutic Candidate Discovery	-	$9.6	$6.9	$11.8	**$28.3**	11%
	Bottlenecks to PSC-derived Cell Therapy	$22.9	-	-	-	**$22.9**	9%
	Other	$20.3	$38.5	$34.0	$16.4	**$109.1**	43%

Early Translation Program: Outcomes ET I, II to Date

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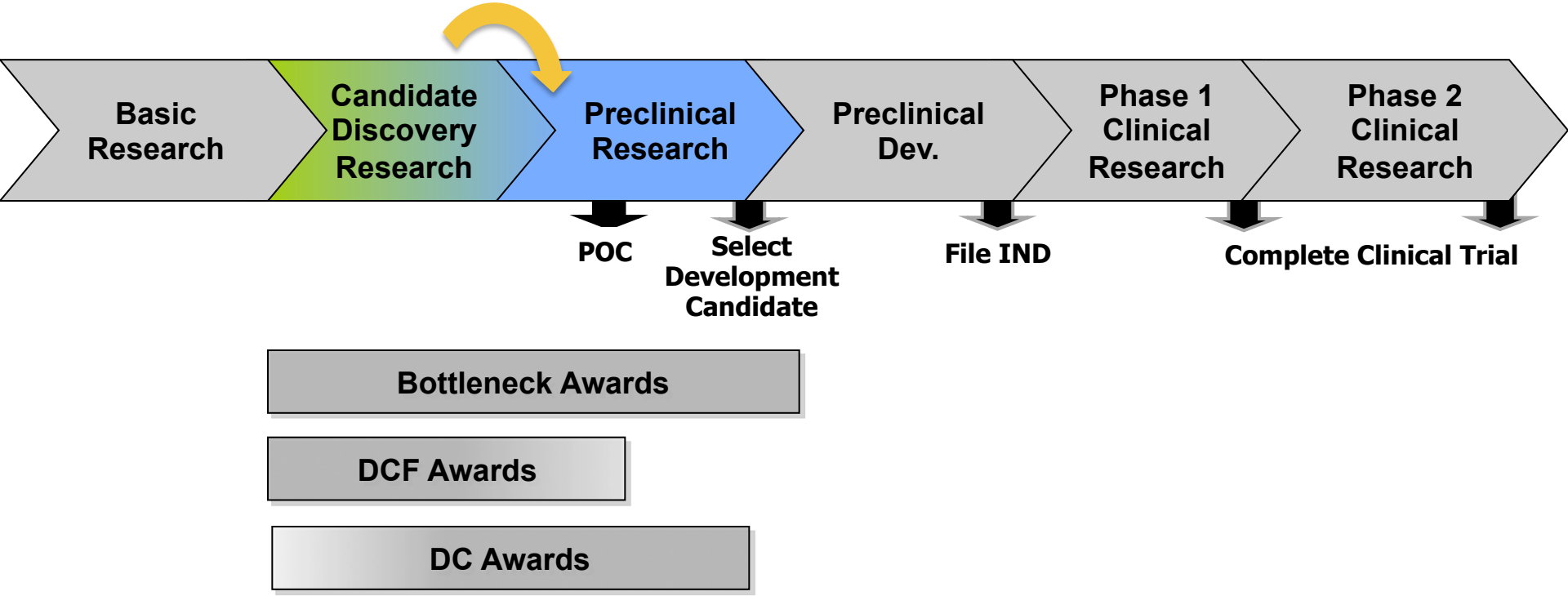
- 123 scientific publications; 31 in "high impact" scientific journals
- 23 invention disclosures, 14 active/pending patent applications
- Attracted co-funding – 5 Collaborative funding partners contributed $14.3 million to 14 funded ET projects, leveraging $55 million of CIRM funding

Early Translation Awards



Early Translational I: Bottleneck Awards

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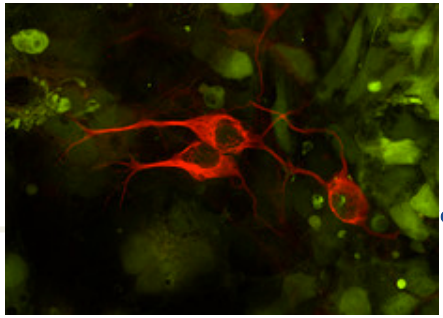
8 Awards focused on:

- Better models for developing/testing candidate therapies, 3 awards
- Characterizing, mitigating risks of PSC-derived cell therapies (teratoma/tumorgenicity, genetic instability, immunogenicity), 5 awards

Better models for developing/ testing candidate therapies

- TR1- 01232, Hall/Kaur, Jackson Laboratory West
  - Developed and released standardized mouse models for Type 1 diabetes, Multiple sclerosis, Parkinson's disease; models near release for myocardial infarction, stroke, spinal cord injury and traumatic brain injury
- TR1- 01246, Langston, Parkinson's Institute:
  - Derived over 50 iPSC lines from PD patients with causative mutations; defined phenotypic readout
  - Led to multiple new collaborations and new funding from both public and private (~$700,000)
- TR1- 01269, Tarantal, UC, Davis:
  - With a long term goal of treating inherited pediatric hematologic disorders, showed in a relevant preclinical model long term high levels of cord blood engraftment in in utero models with no adverse events. Showed imaging could be used for longitudinal monitoring of cell fate

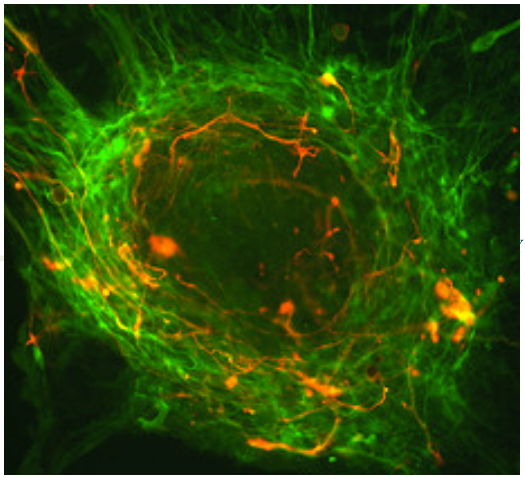
Mitigating risk of PSC-derived candidate therapies



- TR1-01227, Greene, Gladstone Institute
  - Developed assays and technologies to look at role of retro-element transposition in genomic stability during iPSC generation and maintenance. Published that reprogramming may be associated with increased endogenous retro-transposition
- TR1- 01277, Xu, UCSD
  - Developed and published an improved method for episomal (non-integrative) iPSC generation. Tested a suicide gene approach for residual PSC purging - may not be as effective as claimed by others; conducted and published the work that initiated useful debate on immunogenicity of autologous iPSC, further addressed in manuscript under review
- TR1- 01250, Loring, Scripps
  - In collaboration with Partner PI Laslett (CFP – State of Victoria), successfully generated and characterized novel live PSC reactive, antibodies at least one of which is better than the standard antibody used to detect residual PSC

Image courtesy of A. Ghosh lab, UCSD

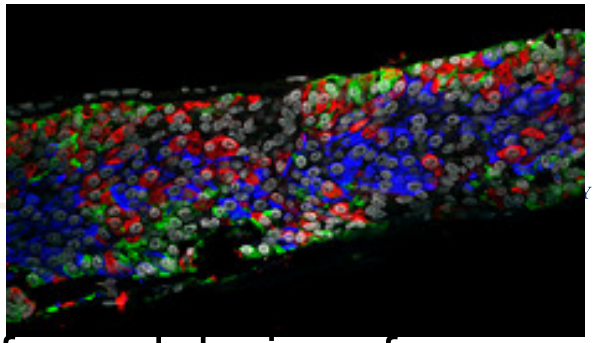
Mitigating risk of PSC-derived candidate therapies



- TR1-01276, West, BioTime
  - Characterized clonal embryonic progenitor lines (EPC) derived from hESC for differentiation to cartilage, bone and vascular endothelial cells. Identified and tested in a model of cartilage repair a chondrogenitor EPC line that showed articular cartilage formation. (publication)
  - Used EPC and phage display to identify peptides and antibodies specific for subsets of differentiating cell populations that can be used for monitoring hPSC differentiation and for purification of specific progenitor lineages (publication, patent application filed)

Image courtesy of G. Fan, UCLA

Mitigating risk of PSC-derived candidate therapies



- TR1-01215, Kelly, Viacyte
  - Developed and conducted in vivo studies that informed design of definitive IND enabling teratoma/tumorigenicity studies; functional and histological data were published in a paper describing scalable system for differentiation of pancreatic progenitors from hESC
  - Developed and established feasibility of an automated system and associated software for the in vitro immunocytochemical detection of residual hESC in the manufacture of the pancreatic progenitor cell component of combination product candidate VC-01. Reporter lines generated by Partner PI Ed Stanley (CFP – State of Victoria) have provided important corroborative data in the development of the this assay
  - Defined and establishing feasibility of assays for encapsulation device integrity.
  - Contributed to product development continuing in CIRM DT1 and newly initiated SP1 awards

Image courtesy of K. Kadoya. Viacyte

Early Translation I, II: DC, DCF Research Awards

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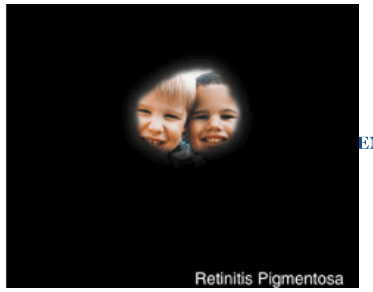
- 20 projects with a goal of achieving a therapeutic development candidate (DC awards) ready for IND-enabling development
- 9 projects with a goal of achieving proof of concept for a development candidate (DCF awards)
- Outcomes to date
  - 2 awarded DT II funding
  - 1 reviewed, recommended and approved for Bridge funding
  - 5 submitted eligible Letters of Intent for Disease Team III

Early Translation I, II Research Awards: Eye Disease

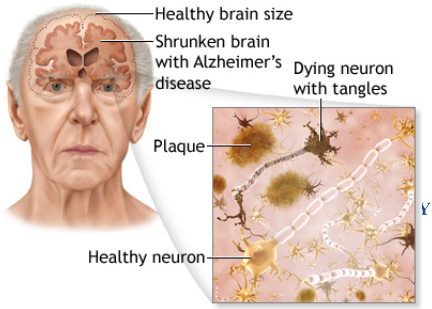


- TR2-01794, Klassen, UCI
  - Allogeneic tissue-derived retinal progenitor cells for retiniitis pigmentosa, DC award
  - Awarded DT funding (DR2A-05739)
- TR1-01219, Freidlander, Scripps
  - Autologous iPSC-derived RPE for atrophic AMD, DC award
  - Developed novel iPSC derivation method where replaced 3 out 4 Yamanaka factors with small molecules to generate 1-factor iPSC (1F-iPSC). Following extensive comparative in vitro and in vivo characterization, concludes that 1F-iPSC-RPE may be superior for clinical use. Published.
  - Conducting studies of technology with skin biopsies from AMD patients, the target population for therapy

Early Translation I, II Research Awards: Eye Disease

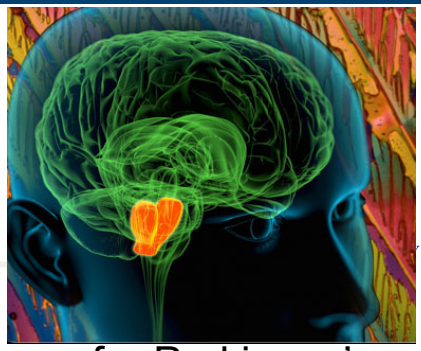
- TR1-01272, Travis, UCLA
  - PSC-derived RPE ± genetic modification to express negative regulators of complement for atrophic AMD. DC award
  - Defined a molecular signature for evaluating the fidelity of hPSC conversion to RPE; demonstrated that functional RPE cells can be derived from multiple lines of hESC and hiPSC with varying efficiencies (published).
  - Continued work to optimize iPSC-derived RPE
- TR2-01768, Deng, UCLA
  - Autologous tissue-derived limbal stem cells for corneal injury, DCF award
  - Developed xenobiotic-free culture conditions for the effective expansion of LSC based on markers and criteria previously demonstrated to be clinically relevant.

Early Translation I, II Research Awards: Neurodegenerative Disease – AD, HD



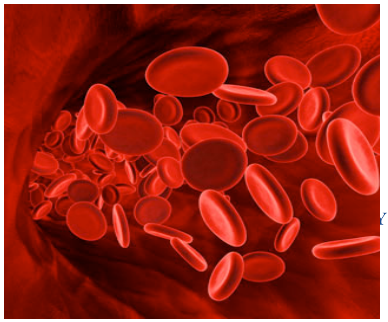
- TR1-01245, LaFerla, UCI
  - Allogeneic ESC or tissue-derived NSC for Alzheimer's Disease. DC award
  - Disease team funding awarded (DR2A-05416)
- TR1-01257, Nolta, UCD
  - Allogeneic hMSC engineered ex vivo to deliver siRNA to silence expression of mutant huntingtin mRNA for treatment Huntington's Disease. DC award
  - Showed, in an in vitro model system, reduction of mHTT protein in recipient cell population due to transfer of anti-HTT siRNA from NSC. Publication, patent application filed.
- TR2 -01841, Thompson, UCI
  - Allogeneic hESC-derived NSC, APC or NPC for Huntington's Disease. DC award
  - Selected NSC, successfully differentiated from GMP-compatible hESC line. Showed neurological and behavioral improvement in mouse model of HD. Full characterization, dosing studies in progress

Early Translation I, II Research Awards: Neurodegenerative Disease – PD



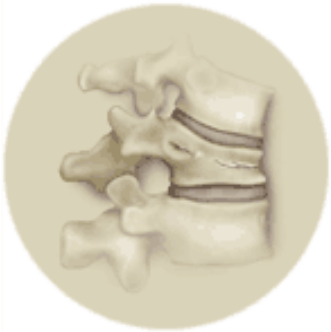
- TR1- 01267, Snyder, Sanford Burnham
  - Allogeneic committed neural progenitors derived from ESC, iPSC or tissue for Parkinson's Disease. DC award
  - Selected genetically modified hESC line based on comparative studies in a relevant preclinical disease model of differentiated committed neural progenitors from several PSC or tissue derived NSC. Made a research working cell bank; developing optimal cell preparation strategies
- TR2- 01856, Zeng, Buck Institute
  - Allogeneic hPSC-derived dopaminergic neural precursor cells (NPC) for Parkinson's Disease. DC award
  - Selected hESC line and a back-up hESC line as source for NPC. Made research working cell banks. Developed scalable GMP compatible process, and showed comparability to research process derived NPC
- TR2- 01778, Gage, Salk Institute
  - Patient iPSC-derived in vitro neurons + astrocytes co-culture model to identify anti-inflammatory small molecules against a proposed target that could be neuroprotective and correlate activity in assay with patient data from Partner PI, J. Winkler (CFP, BMBF). DCF
  - Fibroblasts received from clinically well characterized PD patients, iPSC lines derived, co-culture system under development, optimizing astrocyte differentiation

Early Translation I, II Research Awards: Blood Disorders



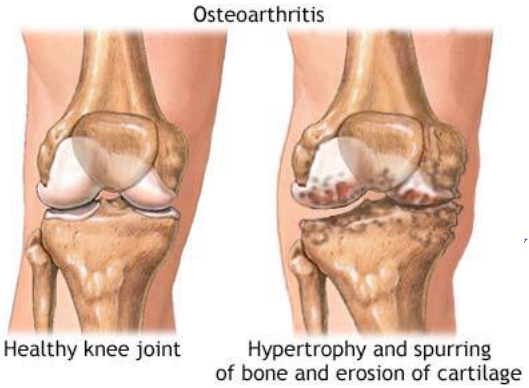
- TR1-01272, Verma, Salk Institute
  - Autologous iPSC-derived HSC genetically corrected ex vivo by homologous recombination to treat Fanconi Anemia, X-SCID
  - Derived iPSC lines from skin samples from patients with Fanconi Anemia and X-SCID; generated preclinical mouse models of X-SCID and Fanconi Anemia (SCID-X1 and FANCA-mutant mice with NOD-SCID backgrounds)
  - Developed and demonstrated a robust and reproducible method for efficient generation of multipotent hematopoietic progenitor cells from ESCs and iPSC in short term engraftment studies (published).

Early Translation I, II Research Awards: Bone Disorders



- TR1- 01249, Longaker, Helms, Stanford
  - Stable formulation of recombinant Wnt3A for ex vivo use, in combination aspirate/bone graft material (BMA/BGM), for autologous bone repair. DC award
  - Developed a cell line, methods and assays for research production and purification; demonstrated that treatment with stable recombinant Wnt3a was sufficient to stimulate osteogenic gene expression, to generate significantly more new bone in severalpreclinical models compared to available treatment option(s) and was not associated with any adverse reactions. Patent applications filed, publications
  - Reviewed, recommended and approved for Bridging funding
- TR2- 01821, Peault, Soo, UCLA
  - Autologous adult perivascular stem cells (aPSC) and an osteo-inductive protein on a FDA-approved acellular scaffold for bone repair. DC award
  - In preclinical model, showed improved capacity of combination product for high quality bone formation over controls. Developed process for reproducible isolation of aPSC and cell line and process for scalable GMP compatible isolation of osteoinductive protein.
- TR2- 01780, Gazit, Cedars-Sinai
  - Allogeneic MSC ± PTH for bone repair to treat osteoporosis- related vertebral compression fractures. DCF award
  - Developed bone defect models and systems to monitor homing and activity of MSC ± PTH in vivo. MSC + PTH showed enhanced homing and fracture repair compared to controls

Early Translation I, II Research Awards: Cartilage Disorders



- TR1-01216, D'Lima, Scripps
  - Chrondrocyte progenitors embedded in a scaffold implanted into chrondral defect or injected into OA joint
  - Optimized differentiation conditions, characterization assays, and scaffold components to enhance chrondrogenic potential and improved tissue quality. Selected ESC cell line source for chondroprogenitors based on histological criteria and function in in vitro and in vivo models. Conducted pilot safety assessment.
- TR2-01829, Schultz, Scripps
  - Optimized small molecule of lead molecule PRO1 that induces chrondrocyte differentiation of resident hMSC for osteoarthritis. DC award
  - Developed assays, performed SAR, made many Pro1 analogs, identified molecules with improved activity in cell culture and in relevant preclinical in vivo models. Synthesizing a final series of molecules to profile with respect to in vitro and in vivo chondrogenesis activity, pharmacokinetics and safety prior to candidate selection

Disease Team Program
Strategic Partnership Program

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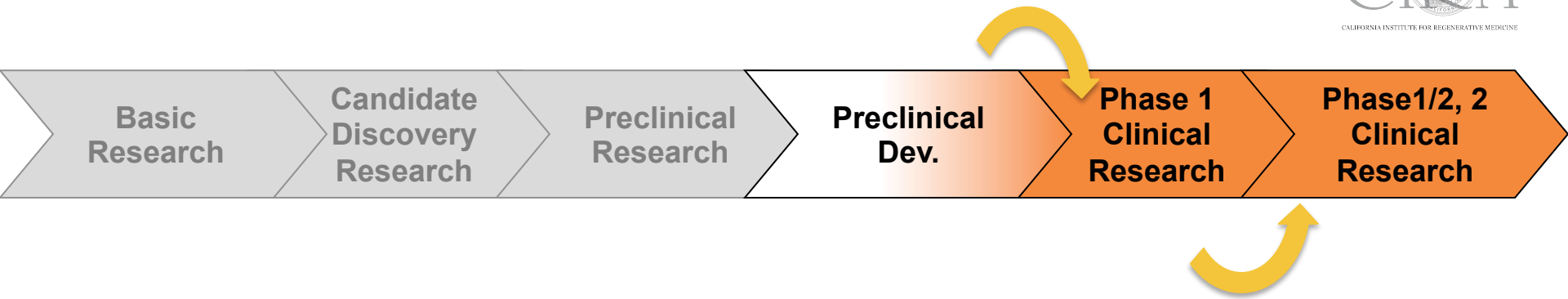

Program Goal: Enable preclinical dev to file IND to enter FIH and/or to complete clinical trial; for Strategic Partnership to attract industry engagement and investment

Outcomes: Within 4 years,

- Complete IND enabling studies to file IND to enter FIH and/or
- Complete clinical trial to establish feasible dose, delivery that is safe with evidence of biologic activity and/or clinical parameters of preliminary efficacy

Translational programs advancing to next stage

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Early translation preclinical research developing potential therapeutic candidates

ET Yr funded	#	DT awarded 2012	DT 2013 LOIs
2009	8	1	2
2011	21	1	3
2012	21		

Development teams successfully advancing through pre-IND FDA meetings, entering clinical trials

Year funded	#	Pre-IND	IND 2012	IND expected 2013/14	Clin Trials 2013
2010 DT	14	>50%	2	6	2
2012 DT	10				
2012/13 SP	2				

Outcomes of disease teams and strategic partnership programs

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- Disease Team 1 (DT1)
  - 14 projects funded with a goal of filing an approvable IND by the end of the project period (2014)
  - 2 DT1 projects filed INDs and are conducting CIRM-funded clinical trials in 2013 through continued DT1 (HIV) and awarded DT2 (recent heart attack and congestive heart failure)
  - Over half of DT1 projects successfully advanced through their pre-IND meeting with FDA
  - 1 approved for Strategic Partnership 1 funding
  - 1 received supplemental external funding
  - 2 were recommended and approved for CIRM Major Supplement Funding ($3 million each)
  - 6 submitted eligible Letters of Intent for DT3
- Disease Teams 2 and Strategic Partnerships starting

PI	Outcomes of Disease Teams – Heart Disease
Marban Cedars-Sinai Smith Capricor	**DT1** team completed IND-enabling preclinical safety/efficacy studies and **successfully filed IND** for their **allogeneic cardiac-derived stem cell** (CDCs) product **in 2012**. Capricor, a spin-out company obtained NIH funding to initiate a first-in-human phase 1 clinical trial (ALLSTAR) in **patients with heart failure following a heart attack.** CIRM **DT2** awarded to Rachel Smith, Capricor, will **fund the randomized phase 2 portion of the Phase 1/ 2 trial pending review of phase 1 data**. Phase 1 portion is designed to test 2 different doses of CDCs in 2 different patient cohorts, comprised of either recent or chronic heart failure patients after their heart attack, and is **on track to complete phase 1 component in 2013**, and after assessment of data, to enter phase 2 portion. To date, the trial has progressed smoothly. *ClinicalTrials.gov Identifier: NCT01458405*
Wu Stanford	**DT2** team in its first year, developing **hESC derived cardiomyocytes** for **end stage congestive heart failure**. After 3 months, **all activities for milestones are on target**. Stanford and Gladstone (Srivastava) labs are standardizing methods for preclinical surgical models, process development is ongoing to select manufacturing parameters to demonstrate preclinical proof of concept comparability of hESC-derived cardiomyocytes differentiated with improved manufacturing methods to cardiomyocytes differentiated using growth factors. Goal is to complete IND enabling studies to successfully file IND for FIH trial.

PI	Outcomes of Disease Teams – Vascular Dis
Laird UCDavis	**DT2** team in its first year, developing **allogeneic MSC engineered to express VEGF** delivered by intramuscular injection for patients with **critical limb ischemia**. Preclinical studies in progress; goal is to complete IND enabling studies to successfully file IND and complete phase 1 clinical trial.

PI	Outcomes of Disease Teams- HIV
Symonds Calimmune	**DT1** Filed/Approved IND to conduct first-in-human clinical trial with autologous cell therapy **attacking HIV entry/fusion**. The investigational product is LVsh5/C46(Cal-1) **modified CD34+ hematopoietic stem/ progenitor cells and CD4+ T lymphocytes**; IRB, RAC approved and **enrolling patients at California sites in 2013**, and no reports of serious safety events; share trial design & data from a second, planned future ex-US trial with same product in a different subgroup of HIV patients.*ClinicalTrials.gov Identifier: NCT01734850*.
Zaia CityofHope Sangamo	**DT1** team identified lead candidate autologous CD34+ hematopoietic stem cells gene modified at CCR5 locus with zinc finger nuclease-mRNA technology, to **disrupt expression of HIV co-receptor**; achieved preclinical proof of concept and disease-modifying activity in preclinical studies; completed pre-IND meeting earlier this year, and RAC review unanimously approved clinical protocol Sept 2013, and targeting 2014 for IND filing, with plan to enter FIH clinical trial for HIV patients

PI	Outcomes of Disease Teams - Cancer
Slamon UCLA Tak Mak Canada	**DT1** 1st **kinase (PLK4)** program completed CTA with Canada and cleared to do a clinical trial. FDA requested Certificate of Analysis (CoA) before approving the IND submission. Drug product manufacturing completed and CoA expected in October. Project is moving very well, has clinical supply (PLK4). 2nd kinase program has selected a development candidate, determined maximum tolerated dose in pilot toxicology studies and contracted to manufacture GMP batches for GLP tox studies. Team anticipates selection of backup to 2nd kinase program by end of 2013. Received CFP $ with Canada; planning FIH for **patients with solid cancers**
Aboody CityofHope	**DT1** Pre-IND meeting completed; IND enabling tox protocol vetted; passed RAC review Sept 2013; Preclinical POC prelim results show decreased tumor volume, prolonged survival in xenogeneic brain tumor model with human glioblastoma cell line, and studies with primary brain tumor pending;**IND filing** on track of **clinical trial for patients with brain cancer**. Developed in vivo iron-based cell labeling protocol, first 3 patients received it and images being analyzed; **founded company TheraBiologics** for dev of neural stem cell based treatments that home to brain cancer and deliver enzyme to enhance chemotherapy delivery; 6 publications acknowledge CIRM DT1 funding; awarded NIH-NINDS funds for preclinical studies of same product in another indication

PI	Outcomes of Disease Teams - Cancer
Weissman Stanford Vyas UK	Identified novel therapeutic candidate, an **inhibitor to CD47 a "don't eat me" signal on cancer stem cells**; achieved preclinical POC; pre-IND discussions completed and IND-enabling plan has been vetted; pilot safety studies competed; GLP/GMP manufacturing completed; pivotal safety studies initiated; IND filing planned for 2014; patent filed for the therapeutic candidate Mab which was characterized under the **DT1** award. CFP funding with UK; **planning FIH clinical trial(s) for patients with leukemia and other cancers**
Carson UCSD John Dick Canada	**DT1** Identified lead candidate, an **inhibitor to ROR-1 on cancer stem cells**; achieved preclinical POC;continuing work on GMP production of UC-961 (antiROR1 Mab), developing potency assays, formulation and continuing stability studies. In vivo dose response studies in preclinical models implanted with patient cancer stem cells are continuing; performing formal pharmacokinetic studies and tissue array studies in preparation for IND enabling studies. On track for IND-enabling studies to be completed by end of grant period; CFP funding with Canada; **planning FIH clinical trial for patients with leukemia**

PI	Outcomes of Disease Teams – blood dis.
Kohn UCLA	**DT1**, using **autologous bone marrow hematopoietic stem cells genetically modified to re-engineer** (**encodes anti-sickling beta-globin**) production of normal red blood cells **for patients with sickle cell disease (SCD)**; achieved preclinical POC, disease modifying activity, published in Journal Clinical Investigation July 2013; completed pre-IND meeting; cleared protocol from RAC; established clinical scale manufacturing process; GLP preclinical safety studies in progress;clinical protocol reviewed,approved by UCLA IRB, IBC and scientific protocol review committee; **on schedule to file an IND in 2014 for first-in-human clinical trial.**
Urnov Sangamo	**SP2,** in first year of award (currently in PFAR), developing **autologous hematopoietic cells that have been genetically modified with zinc finger nucleases (ZFNs) to re-activate the gamma globin gene**. During infancy, gamma-globin-containing fetal hemoglobin protects Beta-thalassemia patients from developing disease symptoms until gamma globin is replaced by adult-type beta-globin chains. **Completed pre-pre IND April 2013** in which preclinical, CMC,outline of clinical dev plan was discussed.
Shizuru Stanford	**DT2**, in first year of award to develop **monoclonal Ab** that **depletes blood stem cells and enables chemotherapy free transplants**. Assess safety, tolerability, pharmacokinetics and pharmacodynamics of humanized mAb as conditioning for purified hematopoietic stem cell transplants **in patients with severe combined immune deficiency**. Executed contract with company for rights to utilize the humanized mAb; **pre pre IND held in May 2013**.

PI	Outcomes of Disease Teams – Eye diseases
Humayun USC Coffey UK	**DT1** completed pre-IND meeting for product, **hESC derived retinal pigment epithelium (RPE) on a scaffold for patients with age-related macular degeneration**; pivotal safety/efficacy studies ongoing; **IND filing planned for 2014**; Regenerative Patch Technologies spin-out established; 5 publications referencing DTI award – describing the approach, methodology, differentiation to RPE and the matrix; **major novel advance is the design and composition of the matrix that supports the RPE monolayer**. Matrix designed to mimic permeability characteristics of the natural Bruch's membrane (which is defective in AMD) while being strong enough to enable surgical handling and transplantation; cells on a matrix approach allows transplantation of cells in their natural state as a polarized monolayer with top surface facing the photoreceptors as required for correct functioning of the RPE. **Developed a customized surgical tool to perform the transplant.** Multiple patent filings (IP licensed to RPT) cover the matrix and surgical tool. CFP funding with UK
Klassen UCI	**DT2** in first year of award, developing **retinal progenitor cells** to treat patients with **genetic disorder leading to blindness, retinitis pigmentosa**. Conducted activities required for initiation of IND enabling toxicology and POC studies; had pre-IND meeting; plan IND filing in 2014 to subsequently enter clinical trial. Published review in Clinical Investigation: Stem cell clinical trials: towards cell-based therapy for retinal degeneration. Spin-out company Jcyte

disease

Steinberg Stanford	**DT1** Preclinical studies to develop **allogeneic hESC-derived NSC therapy for stroke**. On-going studies to demonstrate: reproducibility of production process, efficacy in both an acute and chronic model of stroke, and preliminary toxicity in a model that supports cell persistence. Anticipated review of this data in Nov 2013; goal is to complete studies for successful filing of IND.
Svendsen Cedars-Sinai	**DT2** in first year of award, working on their manufacturing process, preclinical studies and device delivery for **allogeneic neural progenitor cells genetically modified with GDNF**; goal is to complete studies for successful filing of IND and completion of phase 1 clinical trial **for patients with ALS.**
Capela Stem Cells, Inc	**DT2** in first year of award developing **neural stem cell transplantation for neuroprotection in Alzheimer's disease**. After 3 months, all activities for milestones are on target, goal is to complete preclinical studies for successful filing of an IND.

PI	Outcomes of Disease Teams – Bone, Skin Diseases
N.Lane UCDavis	**DT2** in first year, **developing a synthetic molecule**, LLP2A-Ale, to **enhance homing of endogenous bone marrow MSCs to bone surface for patients with osteoporosis.** Working on a detailed plan to conduct IND enabling studies that includes a GMP, manufacturing program and a preclinical program to assess stability, toxicology and efficacy of the proposed drug. Manufacturing, and dev. of analytical assays to characterize and qualify the drug product in progress and subsequently will release material for toxicology, pharmacology and stability studies.They plan to successfully submit IND in 2014, followed by conducting a Phase 1 clinical study.
A.Lane Stanford	**DT1** developing therapeutic approach of **epidermal sheets** from **expanded autologous genetically corrected** (to express wild type COL7A1**) iPSC-derived keratinocytes for patients with rare genetic skin disorder lacking collagen type 7**, epidermolysis dystrophic bullosa; achieved preclinical POC; generated patient-derived gene corrected lines; **fostering regulatory path for patient-specific iPSC-derived therapies** for patients with rare skin dis; goal is to complete IND enabling studies to successfully file IND to enter clinical study.

PI	Outcomes of Disease Teams – Diabetes
Robins/Foyt ViaCyte	**DT1→SP1** Developing **allogeneic hESC-derived pancreatic cell progenitors in a device implanted subcutaneously for patients with insulin-requiring diabetes.** Completed pre-IND meeting; pivotal IND-enabling preclinical GLP studies in progress; **IND filing on track for 2014**; completed **$10.6M in private financing from investors, including J&J Development Corporation, for clinical development**; collaborative funding with JDRF; **SP1 award launched**, with goal to complete early phase clinical trial.

Disease Team 1 Status

Grant/PI	Disease	Award	Current Status
DR1-01461/Marban	Heart fail	5.6M	IND approved 6/2012; clinical trial PI Smith (Capricor) DR2-05735
DR1-01431/Chen DR1-06893/Symonds	HIV	20M	Chen converted to ET; Calimmune IND approved, clinical trial PI Symonds
DR1-01490/Zaia	HIV	14.6M	Continue
DR1-01477/Slamon	Solid ca	20M	Continue
DR1-01421/Aboody	Brain ca	18 M	Continue
DR1-01426/Berger	Brain ca	19.2M	Terminated NoGo milestone
DR1-01485/Weissman	leukemia	19.3M	Continue
DR1-01430/Carson	leukemia	20M	Continue
DR1-01452/Kohn	Sickle	9.2M	Continue
DR1-01454/A.Lane	Skin dis	11.7M	Continue
DR1-01444/Humayun	Eye dis	16M	Continue ICOC approved $3M supp
DR1-01423/Robins	Diabetes	20M	Continue ICOC approved $3M supp;SP1 with PI Foyt
DR1-01480/Steinberg	Stroke	20M	Continue
DR1-01471/Goldstein	ALS	11.5M	Converted to ET

Disease Team 2 and Strategic Partnership 1,2 Status

Grant/PI	Disease	Award	Current Status
DR2-05302/N.Lane	osteoporosis	20 M	Starting
DR2-05320/Svendsen	ALS	17M	Starting
DR2-05415/Wheelock	Huntington's	17.8M	Starting
DR2-05423/Laird	Limb ischemia	14.2M	Starting
DR2-05739/Klassen	Eye dis	17M	Starting
DR2-05735/Smith	Heart failure	19.8M	Starting
DR2-05394/Wu	Heart failure	20M	Starting
DR2-05365/Shizuru	immunodef	20M	Starting
DR2-05416/Capela	Alzheimer's Dis	20M	Starting
SP1-06513/Foyt	Diabetes	10M	Starting
SP2-06902/Urnov	Thalassemia	6.37M	Pre-funding admin review

CIRM works with investigators to avoid “bumps” in the development pathway

AP / Damian Dovarganes

CIRM science officer helps teams build product development experience in California

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Programs driven by science and evidence, and regulatory considerations needed on development pathway

- Prior to award
  - Set mutually agreed upon Go, no go, progress milestones, and success criteria
- During conduct of research
  - Discussions at least quarterly e.g., updates on interval and annual progress, review preclinical/clinical protocols, regulatory strategy, prep for interactions with FDA, attend team meetings
- Education and training of teams through CIRM/FDA webinars, roundtables, conferences, seminars

CIRM resources to guide product development for investigators

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http://www.cirm.ca.gov/sites/default/files/files/RFA13-01_DiseaseTeamIII_AMENDED11Feb2013.pdf

- CIRM Major Milestones Template
- CIRM Clinical Protocol Synopsis Template
- CIRM Manufacturing Plan Synopsis Template
- CIRM Target Product Profile (TPP) Template
  - CIRM workshop on preparing a TPP: http://youtu.be/QK_zPmarkws
- Communications with the FDA on the Development Pathway for a Cell-based Therapy: Why, What, When and How? Stem Cells Translational Medicine Vol 1, #11, November 2012
- www.fda.gov
- www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation
- www.fda.gov/ohrms/dockets/ac
- drugs@fda.gov

CIRM works with FDA on regulatory pathway for cell therapy

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- Webinars, roundtables and workshops
  - cell characterization, preclinical animal studies, imaging technology, immune response, scaffolding, clinical trials http://www.cirm.ca.gov/our-funding/regenerative-medicine-consortium

Regulatory Pathways: International Workshop on Cell Therapies

CIRM-led international regulatory workshop Sept 2013, focus on N. American, European, and Japanese regulatory frameworks for developing cell-based therapies

CIRM works with external Advisors on individual development projects at key milestones

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- Clinical Development Advisory Panel (CDAP) complements CIRM's interactions with development teams
  - Experts in product development, e.g., preclinical and clinical, cell process and manufacturing, regulatory, stem cell/disease-specific biology, disease-specific clinical expertise and commercial relevance
- Yearly meetings with each Development team to assess key milestones
- Advice helps informs CIRM decisions
  - Continue forward progress; refine approach e.g., modify milestones, timelines, budgets; convert the project to an earlier phase with reduced scope and budget, or terminate the project

Where to focus and prioritize to meet our strategic goals?

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- CIRM has a translational portfolio that is broad, often deep
- CIRM is advancing projects through the pipeline
  - What are the key criteria (characteristics, attributes) to consider for identifying which projects to select for more focused attention and funding?
  - Considerations for which types of platforms?
    - Within cell therapy, balance of autologous relative to allogeneic? pluripotent relative to tissue (adult) stem cells? Cell therapy relative to more standard e.g., biologics, small molecules?
  - Rare or common diseases?
  - High risk high impact vs nearer term?
  - Endogenous pipeline vs continued investment in external opps?
  - Continued early preclinical vs clinical trials?
  - In the early preclinical, which attributes to consider investing?

CIRM works with external Advisors on strategy for translational portfolio

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- CIRM convened meeting with external advisors in July 2013
- Identify attributes of what would constitute a competitive translational portfolio for developing effective therapies, and advice on strategies to get there
- Discussion on critical attributes separated by target diseases (therapeutic areas) and product characteristics; early endpoints and POC issues in clinical trials, and issues in commercialization
- CIRM in process of deliberating on recommendations

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Scientific Advisory Board Recommendations and Preliminary Management Response

Ellen G. Feigal, M.D.
Senior Vice President, Research and Development

Presentation to the ICOC October 9, 2013

Purpose of SAB review

- SAB was established in response to 2012 recommendation of IOM panel charged by CIRM with reviewing the Institute's operations.
- 13-member IOM panel, made up of experts in stem cell research, business and finance, law and bioethics, and research administration produced a set of recommendations aimed at ensuring that "all aspects of CIRM's operations are functioning at peak performance".
- One recommendation was for CIRM to establish an external SAB, made up of experts in the "scientific, clinical ethical, industry, and regulatory aspects of stem cell biology" to be appointed by and report to the president. The IOM panel believed that a single SAB as opposed to multiple advisory boards would be best positioned to provide integrated advice to the president on strategic priorities for future RFAs, innovation projects, and the research portfolio.

SAB members – see appendix for details

- **Sir John Bell**, Oxford University, UK (Chair for August 2013 meeting)
- **Dr. Corey Goodman**, VenBio Corp. USA
- **Dr. Maria Grazia Roncarolo** Hospital San Raffaele, Italy (not attending)
- **Dr. Sean Morrison**, Children's Research Institute at UTSW, USA
- **Dr. Christine Mummery**, Leiden University Medical Center, The Netherlands
- **Dr. Stuart Orkin**, Harvard Medical School, Dana Farber Cancer Institute, USA
- **Dr. Fiona Watt**, *Centre for Stem Cells and Regenerative Medicine*, King's College, UK
- **Dr. John Wagner**, University of Minnesota Stem Cell Institute, USA

Plan is to conduct 3 to 4 SAB sessions per year, with at least one session in person

Meeting Agenda and Process

CIRM president convened the SAB on August 23rd , and asked them to consider the following high-level questions relating to CIRM's strategy during its next cycles of funding:

- CIRM is completing the allocation of funds provided by the California bond initiative and seeks advice on the best use of the remaining funds from this cycle of funding. How can we best maximize the impact of CIRM in regenerative medicine with the remaining funds, which at this time is approximately $600 million dollars, to be allocated in projects to be completed by approximately 2021?
- What unique priorities does the SAB recommend for CIRM for the next four years, consistent with the goals and objectives of the 2012 Strategic Plan?

Meeting Agenda and Process

On August 23, the SAB convened one-day meeting with CIRM staff and a closed session of the SAB to draw up a set of recommendations. The SAB also requested a closed-session, one-hour teleconference with several CIRM grantees (Irv Weissman, Rusty Gage, Owen Witte, and Larry Goldstein).

- Prior to the meeting, the SAB was provided with a document summarizing the following: 2012 Strategic Plan Update, Scientific Programs, Collaborative Funding Program, Industry Engagement, and other ancillary information.

Recommendations - overview

- SAB advises CIRM to identify, through a prioritization process, the top 6 to 8 projects, with clear relevance to the remit of CIRM's stem cell mission, and to setaside the funding to ensure the projects can proceed to phase 1 and 2a clinical trials as rapidly as possible, without financial impediments
  - Achieving clinical proof of concept is a key goal to achieve, to attract future potential investors and supporters of stem cell research, and has a strong chance of success, as long as CIRM advances the most promising clinical candidates "at speed"; this will require careful assessment / prioritization of portfolio

Recommendations - overview

Preliminary management response: Management accepts this recommendation and will need to identify a process for selection of these projects that would include representatives from GWG, CDAP, and other external expertise as needed, and the amount of funding that would need to be set aside by the ICOC. Recommendations will be developed for this priority group of projects as to where expertise and approach need to be modified to maximize the potential and to ensure rapid and effective progress. Management will provide separately a process to select these priority projects.

Recommendations - specific

CIRM Question : Training grants and shared laboratory funding build infrastructure and future capacity. Current training grants and shared laboratories will end in the next few years. However, there is strong support for these from California institutions and advice is sought on whether to continue or cease this program. Please advise whether there are particular opportunities or areas of unmet need in training that could be accomplished in the next 4 yrs

Recommendations - specific

- SAB recommends continued funding of training programs at all levels to develop a work force of trained individuals, which will be valuable as cell therapies burgeon; the SAB does not recommend continued funding of the 17 shared labs; these should operate on a revenue-neutral basis; although essential as a safe haven during NIH funding ban, the importance of these resources to CIRM's mission and achieving sustainability of earlier investments is not as compelling.

Recommendations - specific

CALIFORNIA'S STEM CELL AGENCY

Preliminary management response: Management supports the continued support of training programs; in addition, management supports the recommendation of not extending support for the shared labs, recognizing that some institutions may have problems in maintaining these facilities; need for these facilities has declined with political changes and time, and where possible, these facilities could be absorbed into general institutional facilities

Recommendations - specific

CIRM Question: The 2012 Strategic Plan Update emphasizes movement from the bench to bedside, which, in fact, is how CIRM's scientific programs have evolved, with increased emphasis on funding research in the clinic as opposed to basic and early translational research. Nonetheless, CIRM is still strongly supporting the engine of discovery, so please discuss whether there are particularly important areas of opportunity in the next four years for a) basic discovery and b) early translational research.

Recommendations - specific

- Basic: SAB recommends continued support for basic research, but felt restriction of CIRM funding in some RFAs to projects using only human cells was too prescriptive, and doesn't take into account the benefits that model organism research can offer.

Recommendations - specific

- Translation: SAB noted clinical projects should be carefully selected so they are strong in terms of their mechanistic basis, and have a strong chance of success. There was no consensus on particular areas of research - some felt a focus on ES cells, where California has already shown leadership and accumulated expertise, one suggested CIRM not focus on iPSCs given Japan's strong push in this area , whereas others thought a broader approach would be most effective in terms of maximizing successes and taking advantage of the broad range of projects and expertise in the state.
- Grant reviewers: SAB noted CIRM should continue to obtain the very best external reviewers, and could consider enhancing funding for its chairs, and schedule review mtgs 1-2 yrs ahead, if there are difficulties in recruitment.

Recommendations - specific

Preliminary management response

- Basic: Management supports continued funding of basic science. Priority of supporting “transforming” basic research is a feature of more recent RFAs. Human cells rather than cells of model systems have been a CIRM priority from the beginning. Innovative ideas that could be demonstrated with research on model systems has been included in Basic Science RFAs in recent years. Management believes we should continue to emphasize study of human cell systems, but will ensure any likely transforming work in other organisms be supported in selection of grants for review.

Recommendations - specific

Preliminary management response

- Translational Research: Management agrees that translational studies should have a strong mechanistic basis. There was no SAB consensus on particular cell types to pursue, and management thinks it is in the best interest of CIRM to pursue broad range of scientifically compelling stem cell platforms.
- Grant Reviewers: Management agrees that the best available reviewers should continue to be chosen for assessing grants, and CIRM's remuneration to reviewers already compares favorably to NIH and other foundations. It is available time, not dollars, that is a rate limiting step for reviewers.

Recommendations - specific

CIRM Question: What is your advice on how to better engage the private sector to partner with CIRM, to enable the translational and clinical development programs further opportunities to continue towards clinical proof of concept, and if successful, towards FDA approval and commercialization? Should CIRM funding support California cell manufacturing capacity for large-scale phase 3 studies to begin in 2-5 years? What types of costs and facilities would be necessary and is it reasonable to fund these without private-public partnerships?

Recommendations - specific

- SAB had a very positive view of interactions between CIRM and the commercial sector. They noted an advantage of leveraged funding from the commercial sector of externally validating the quality of science and the likelihood of success. They also recommended for the top prioritized set of projects, that it is important to ensure they can be funded without requiring matched leverage funding until after phase 2a when successful programs should readily obtain external support.

Recommendations - specific

Preliminary management response: Management agrees that where appropriate, translational and development studies can be driven inside academia. Management believes that preclinical and early clinical trials need expertise that generally resides in industry and that consultants and partnerships should be integrated into academic teams. Industry needs to be encouraged to participate in clinical trials with teams working across the portfolio and particularly for studies involving small molecules and biologics. However, it is important not to adversely penalize teams with sound competitive projects where industry does not buy in.

Recommendations - specific

CIRM Question: Should we engage our collaborating partners in a major project as a flagship to set the field in motion as we wind down?

Recommendations - specific

- SAB considered this option around a “straw man” in one therapeutic area, but felt the uncertainty of science in any one therapeutic area would make this a very high risk strategy and the SAB was against consolidating programs in this way. If an opportunity arose to participate in a major project in a single therapeutic area in a partnership that provided significant financial leverage to CIRM, it might be an effective use of resources provided it did not constrain progression of the prioritized portfolio.

Recommendations - specific

Preliminary management response: Management agrees that a major flagship project that would commit a large quantum of CIRM funds is not appropriate at this stage of CIRM's life. However, if significant national or international projects evolve in time, it may be appropriate for the ICOC to consider some involvement together with other relevant agencies.

Recommendations - specific

CIRM Question: Looking to the future, how would you best make the case that CIRM was a great innovation in public funding of cutting edge science and whether it has delivered, and could continue to deliver in the future, value to the citizens of California and to the field of regenerative medicine?

Recommendations - specific

- Advancing a project to the stage of clinical proof of concept will be important to making this case to the public. Care must be taken to ensure that the most promising projects are supported through to this stage by CIRM funding.

- The case that CIRM has been transformative in this exciting emerging field of biomedical science seems self-evident to the SAB. The level of activity in this field in California is extraordinarily high and there are many excellent programs being supported by the CIRM that would have failed to be supported given the limited amounts of funding available for this field when CIRM was established. The program has yielded a large number of extremely well trained students and investigators supported directly or indirectly by the CIRM, there is a critical mass in a number of the major academic centers around California that has allowed it to compete internationally in this field, and the commercial environment for regenerative medicine in California has thrived as a result of CIRM intervention.

Recommendations - other

SAB noted that CIRM, despite its considerable achievements, had not received the attention and attribution that many equivalent funding bodies would have had for their contribution to successful science. SAB strongly suggests that CIRM ramps up its outreach activities, both to improve the California public's awareness of CIRM's uniqueness in the world, its successes so far, and the potential of stem cell research to advance treatment of diseases and injuries. Its brand recognition internationally and even nationally is limited and this should be corrected.

Recommendations - other

Preliminary management response: Management recognizes that CIRM should continue to elevate recognition in leading global developments in stem cell research and medical applications, and will work on ways to more effectively ensure that advances and developments arising from CIRM supported activities are effectively transmitted to scientific community and the public. Management will work with CIRM communications particularly relating to communication to the public.

CIRM staff attending SAB review

- **Ms. Elona Baum**, General Counsel & Vice President for Business Development
- **Dr. Natalie DeWitt**, Special Projects Officer to President
- **Dr. Ellen Feigal**, Senior Vice President of Research and Development
- **Dr. Patricia Olson**, Executive Director of Scientific Activities
- **Dr. Bettina Steffen**, Associate Director of Development Activities
- **Mr. Ian Sweedler**, Senior Counsel for International Programs
- **Dr. Jonathan Thomas**, Chair, ICOC
- **Dr. Alan Trounson**, President
- **Dr Michael Yaffe**, Associate Director, Research Activities

Meeting agenda

August 22, 2013	
6:00-9:00	Dinner and Discussion
August 23, 2013	
8:30-9:00	Breakfast: election of meeting Chair
9:00-Noon	CIRM staff presentations and discussion (15 min presentations)
Alan Trounson	CIRM
Pat Olson	Funding: awarded, approved and allocated
Michael Yaffe	Basic Science, shared facilities, and training programs
Ellen Feigal	Translation/Development and Clinical Programs
Elona Baum	Business development programs
Natalie DeWitt	Innovation programs
Jonathan Thomas	New financing opportunities
Noon-1:00	Lunch and Discussion with Californian Stem Cell Leaders (Irv Weissman, Owen Witte, Rusty Gage and Larry Goldstein)
1:00-5:00	SAB closed session
5:00-5:30	SAB and Alan Trounson