CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

President's Report

Alan Trounson
June 2008

Agenda Item 7


Stanford


SDCRM


UCSF


USC


UC Berkeley


BUCK Institute


UC Santa Cruz

New Developments in Stem Cells

Using genetic tricks to improve the odds on reprogramming adult cells.

Tarjei S. Mikkelsen, et al., *Nature* June 2008 (Alex Meissner/Jaenisch labs)
Broad Instit of MIT, Whitehead Instit, Harvard, MA General Hospital

What is “pluripotency”?

“Direct reprogramming to a pluripotent state (iPS) involves re-activation of endogenous pluripotency-related genes, establishment of an ‘open’ chromatin state, and comprehensive Polycomb-mediated repression of lineage-specifying genes”.

This remains a rare set of events because lineage specific transcription factor silencing is often incomplete or fails to activate hypermethylated pluripotency genes. Some progress was made to bias more complete reprogramming by DNA demethylation and RNAi inhibition of a number of transcription factors, especially Dnmt1.

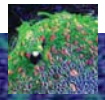
New Developments in Stem Cells

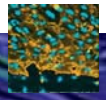
Location matters; reprogramming genes work together because they reside together.

Xi Chen, et al. *Cell* 133, 1106–1117 (2008) Singapore

Two networks of pluripotency. Pluripotency transcription factors bind DNA in clusters. Wei and Ng's analysis describes the transcription factors as "wired into the genome" in two clusters whose binding sites often overlap extensively. The first cluster contains an all-star cast including Nanog, Oct4, Sox2, Smad1 and Stat3. The second, smaller cluster consists of c-Myc (an oncogene that boosts reprogramming efficiency), n-Myc, Zfx and E2f1. (M Baker NRSC)

This can explain the characteristic cooperative function of pluripotency genes and the need to have a number of the key genes unregulated in iPS cells. Position of transcription factors in clusters appears to be functionally important. This could be important to partial reprogramming, e.g., for work such as that described by Doug Melton (Harvard) - "pancreatic exocrine cells" that secrete digestive enzymes and make up to 95 per cent of the pancreas, may be converted directly into insulin secreting beta cells.





New Developments in Stem Cells

Progenitor cells can both remyelinate neurons and rescue the otherwise lethally hypomyelinated shiverer mouse.

Martha S. Windrem, et al., *Cell Stem Cell* June 2008 (Steve Goldman's lab)
University of Rochester, NY, Baylor University, Cornell University, UCLA

Human fetal glial progenitor cells rescued the lethal Shiverer mice that fail to generate compact myelin by transplantation (bilateral hemispheric and cerebellum injections) - the mice survived and progressively improved their neurological deficits because of substantial remyelination throughout the neuraxis.

Indicates that glial progenitors (A2B5 +/PSA-NCAM-) given as multifocal perinatal transplants could rescue human conditions of lethal hypomyelination, e.g., Pelizeaus-Merzbacher disease (PMD) - an X linked misexpression of a proteolipid protein.
ES Cell glial progenitors could likewise be useful clinically.

New Developments in Stem Cells

The governor of muscle power as we age. **Imbalance between two cell signals induce inhibitors in old muscle stem cells.**

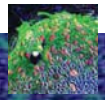
Morgan E. Carlson, Michael Hsu & Irina M. Conboy *Nature advance online publication* (15 June 2008) - UC Berkeley, CIRM funded

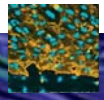
It is more difficult to maintain muscle mass as we age - not because there are fewer muscle stem cells (satellite cells) but that the balance in the meta-switches involving the gene *Notch* activates the cell division of adult muscle stem cells and TGFbeta induced - *pSmad3* that compete for the same promoters of Cyclin-dependent kinase (CDK) inhibitors which regulate cell division. With ageing *Notch* declines and TGFbeta increases, consequently tilting the balance towards less muscle made for regenerative purposes.

These observations are important in strategies designed to combat muscle wasting diseases, Alzheimer's and Parkinson's diseases cancer and ageing.

President's Priorities

- Staff morale and dedication to the same mission - structure and guidance (open discussion of CIRM staff composition and structure)
- 2008/2009 Budget
- Revision of the CIRM Strategic Plan
- Staff position descriptions and appraisal processes
- Introducing a program for compliance internally and with grantee organizations





President's Priorities

- International and national linkages
- CIRM grantee productivity (publications and presentations - ISSCR)
- Linking with Biotech and Pharma (meetings and BIO)
- Education and CIRM stem cell leadership recognition
- Responding to needs expressed by stakeholders
- Grantium – Implementation of Grants Management System

President's Priorities

Stem Cell Awareness Day
September 15th

Linking Victoria and California

Personnel

Margaret Ferguson
Finance Officer
(State Controller's Office)

Amy Adams
Communications Manager
(Stanford)

Science Program Funding Commitment FY 08/09

	$ (mil)
New Faculty II	44
Tools & Technologies	20
Training II	48
Bridges/Internship	18
Translational I	60 *
Disease Teams & Others	150 *
*Estimate	~$**340**

Grant Reviews Completed

CIRM New Faculty Awards II

ICOC Review - August 12 & 13

Tools & Technologies

140 Letters of Intent

* For-Profit – 50
* Not For-Profit – 90

Double program review will be necessary - stress point for reviewers

Upcoming RFAs

- Training Grants II (CIRM Scholars)
- Bridges to Stem Cell Research (Internship Program)
- Translational Research I (seeking concept clearance at June ICOC)

Proposed Workshops

- Predictive Toxicology - July 7 & 8
- Cancer Stem Cells – August 26
- Immunology Tools – tbd
- IP Policy Public Sessions –
  Sept 10-SF; Sept 12-San Diego
- Cell Production Facilities (for therapeutic and research purposes) - tbd
- Integrating Outcomes (for enhancing productivity) - an ongoing program

Science Meetings

- CIRM 2008 Grantee Conference
  September 17- 19th, 2008
  San Francisco
- Press Briefing September 17th

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

National and International Collaborations in Research

PRESENTATION TO ICOC

JUNE 26 AND 27, 2008

Agenda Item 8

Goals and Agenda

- Potential for Broader Opportunities of Collaborative Funding
- Joint funding of collaborations focused on achieving enhanced outcomes of CIRM mission
- Provides Leadership and Leverage of CIRM Funds and Programs
  - CIRM Mission and Strategic Plan
  - Define the Opportunity to Complement CIRM Programs
  - Different Mechanisms

CIRM Mission and Values

- Proposition 71:
  - …to realize therapies, protocols, and/or medical procedures that will result in, ***as speedily as possible***, the cure for, and/or substantial mitigation of, major diseases, injuries, and orphan diseases."
  - advance the field "in California to ***world leadership***…"

- Scientific Strategic Plan
  - Guiding Values: "fostering joint intellectual efforts and establishing partnerships"
  - Strategic Principles: "CIRM will seek partnerships with other organizations…to increase support for stem cell research"

Discussions of Collaborative Funding To Date: Overview

- Communication with key leverage organizations concerning possible joint funding
  - Canadian Consortium/Genome Canada
  - Victoria (Australia)
  - UK MRC
  - JDRF
  - Foundation for Fighting Blindness
  - Muscular Dystrophy Association
  - Michael J. Fox Foundation
  - (Israel, Singapore)

Collaborative Funding: Canadian Consortium and Victoria as Models

- Memoranda of Understanding with Canadian Consortium and Victoria
  - "Purpose…is to confirm the Parties' mutual interest in exploring opportunities for collaborative evaluation, funding and monitoring of applications for stem cell research" (Sec. I.2)
  - Subject to compliance with CIRM statutory and policy framework
  - No specific commitment of funds by either Party
  - CIRM funds stay in California
  - Anticipate Canadian Consortium involvement in CIRM Disease Team Awards

Next Steps

- Two Basic Approaches

1. Offer Joint Funding Opportunity as Part of CIRM Existing Processes

2. New Initiatives with Joint Funding Partners

Next Steps

- Recommended First
  - Small, incremental process folding collaborators into existing CIRM RFA program
  - Canadian Consortium involvement in Disease Team Grants model
    - They review RFA draft prepared by CIRM on Concept approved by ICOC
    - They promote existence of collaboration funds
    - They participate as observers in GWG

Next Steps

- Second Stage
  - Concepts and RFAs focused on jointly identified concept/target
  - Establish a network of funding partners across disease and research areas