CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

Presidents Report

Alan Trounson

December 2008

Agenda Item #6

New Developments in Stem Cells

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Induction of pluripotent stem cells from primary human fibroblasts with only Oct4 and Sox2.

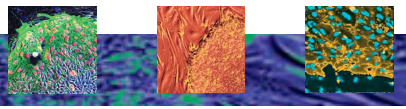
Huangfu et al, Melton Lab Harvard SCC Nature Biotech, Nov 2008

Showed valproic acid (VPA), a histone deacetylase inhibitor, enables the derivation of human iPS cells without the need for Klf4 and c-Myc oncogenes.

Induced pluripotent stem cells generated without viral integration.

Stadfeld et al, Hochedlinger Lab Mass Gen Science, Nov 2008

Showed mouse and human cells can be reprogrammed to iPS cells using nonintegrating adenoviruses transiently expressing Oct4, Sox2, Klf4, and c-Myc genes.



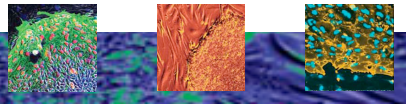
New Developments in Stem Cells

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Generation of mouse induced pluripotent stem cells without viral vectors

Okita et al, Yamanaka Lab, Kyoto. Science, Nov 2008

Possible to generate mouse iPS cells from embryonic fibroblasts without viral vectors by using repeated transfection of somatic cells with two expression plasmids, one containing the complementary DNAs (cDNAs) of Oct3/4, Sox2, and Klf4 and the other containing the c-Myc cDNA. This resulted in iPS cells without any evidence of plasmid integration.



New Developments in Stem Cells

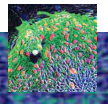
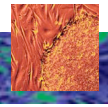
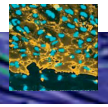
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Clinical transplantation of a tissue-engineered airway

Macchiarani et al, The Lancet Nov 2008

A 30 yr old patient with severe airway stenosis due to tuberculous infiltration was transplanted a decellularized cadaveric tracheal implant that had been seeded with the patient's own chrondrocytes (of bone marrow MSC origin) and airway epithelial cells biopsied from the patient's own airways.

The graft has provided the patient with a functional trachea to the lung lobe with the stenosis, > 2 months post-operation. There were no signs of rejection and the patient has much improved lung capacity. This has implications for bioengineering tissues.

New Developments in Stem Cells

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Micro RNAs to Nanog, Oct4 and Sox2 coding regions modulate embryonic stem cell differentiation

Tay et al, Singapore Nature 445:1124-8 Oct 2008

miRNAs direct mRNA degradation or disrupt mRNA translation in a sequence dependent manner. Because Nanog, Oct4 and Sox2 have many amino acid coding sequence-locating miRNA targets (some of which are species specific).

This is a new model where miRNAs exercise control over mRNAs through targets that can reside beyond the 3' untranslated regions of genes critical for pluripotency and differentiation.

New Developments in Stem Cells

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Derivation and characterization of canine embryonic stem cell lines with in vitro and in vivo differentiation potential.

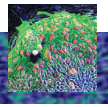
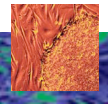
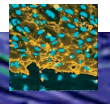
Vaags et al, Uni Toronto Stem Cells Nov 2008

First report of dog ESCs that form teratomas withy all 3 primary germ lineages

Generation of induced pluripotential stem cells from adult Rhesus monkey fibroblasts.

Liu et al, Peking Univ. Cell Stem Cell 3: 587-590 Dec 2008

Produced monkey iPS cells by viral mediated Oct4, Sox2, Klf4, c-Myc transductiion.

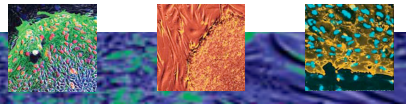
New Developments in Stem Cells

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

A pluripotency and self-renewal program controls the expansion of genetically unstable cancer stem cells in pluripotent stem cell derived tumors.

Conway et al, A Clark's Lab USC, Stem Cells Oct 2, 2008

Using mouse EGCs from testicular teratomas, they showed that acquisition of metastatic behavior is activated in a cellular background of genetic instability – non-clonal genomic rearrangements – and the inherent ability to self renew (treatment with the inhibitor for self renewal – RA – prevented tumor formation) in cancer stem cell populations derived from EGCs.



Personnel

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Lila Collins, Ph.D.
Science Officer (Geron)

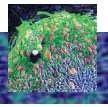
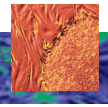
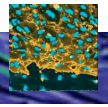
Stephanie Titus
Grants Management Specialist (UCSF)

Todd Dubincoff, Ph.D.
Science Writer/Multi-Media Editor
(Journal of Visual Experimentation)

President's Priorities

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- Little Hoover Commission
- 2008 Strategic Plan Revisions
- Grantium Computerized Grant Management System
- Loan Program Implementation Plan
- Visits with CIRM Funded Institutions
- Annual Staff Appraisals
- Modeling for CIRM Productivity

International Agreements

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Japan

Dr Kitazawa President JST
Dr Shinya Yamanaka

Spain

Cristina Garmendia Mendizabal
Minister Science & Innovation

Update on International & National Linkages

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Signed MOUs

- Canadian Cancer Stem Cell Consortium
- Victoria Government (Australia)
- UK/Medical Research Council (MRC)
- Juvenile Diabetes Research Foundation
- Japan Science and Technology (JST)
- Spanish Ministry of Science and Innovation

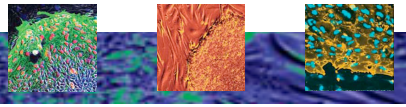
Initiated Talks

- Alliance for Gene Therapy
- Bi-National Science Foundation - Israel
- Germany
- The Netherlands
- Sweden

Grant Reviews

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- **COMPLETED GRANT REVIEWS**
  - **Tools & Technologies**
  - **Training Grants II (CIRM Scholars)**
  - **Bridges to Stem Cell Research**

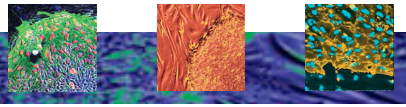


Upcoming Grant Review

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Early Translational Research

- 71 Applications
- 20 For Profits/ 51 Not for Profits
- 37 Development Candidates
- 34 Bottlenecks
- 9 International Collaborations
  - GWG Review – February 09
  - ICOC Approval – April 09

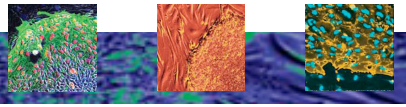


Upcoming RFAs

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- **Basic Research Initiative I**
  - RFA Released – December 08
  - GWG Review – June 09
  - ICOC Approval – August 09

- **Disease Team Research Awards**
  - RFA Released - February 08
  - GWG Review - Sept 09
  - ICOC Approval - Fall 09



Cell Production – GMP Workshop

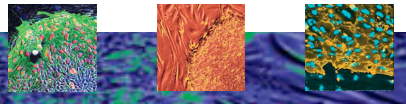
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- Interactive program of academic, industry, regulatory experts
- Establish a consortium network of present GMP organizations to advise on GMP priorities
- Research needs for GMP identified
- CIRM should not own or operate GMP facilities
- Optimizing CIRM grantee access to GMP

  -Capacity analysis ongoing to Phase III

  -Options for contract models reviewed

  -Grants budget adjustments as needed



Cell Production – GMP Workshop

CIRM should fund research in this area, as no other research dollars are available for optimizing processes, especially for hESC therapies.

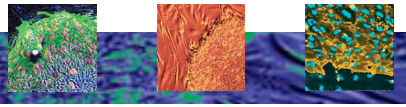
- undergraduate level Bridges-type program focused on GMP to build work force
- methods to expand hESC in suspension
- qualification and optimization of culture reagents to meet safety requirements
- methods to scale-up AND reduce costs
- derivation of hESC/iPS lines under GMP conditions
- methods for product development in the context of academic labs

Provide funding for scale-up from lab to GMP compliant production and for GMP production

Proposed Workshops

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- **UK-MRC/CIRM – Jan 09 (tentative)**
- **Immunology Tools – Feb 09**
- **Stem Cells, Autism and Mental Health**
- **Japan/CIRM**



Strategic Plan Update

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- Revision of the 2006 Strategic Plan
- Increased emphasis on translational and clinical research
- Repeating Basic, Translational, Disease Teams and Training Grant RFAs as core components
  - Supplemented with specific foci, e.g., Immunology Tolerance; Tools & Technologies
- Increased linkages with the biotechnology and pharmaceutical industries
- Increase global and national collaborations to enhance delivery of outcomes
- Increase education and public understanding of regenerative medicine based on stem cell research

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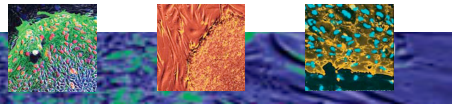
GRANTIUM UPDATE

John Robson

December 2008

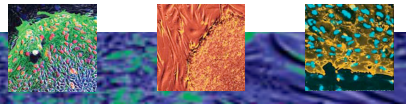


Grantium Implementation Update

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

CIRM Grant Activity

	2005/6	2008/9 (estimate)
Applications received	26	≈ 400
Grants awarded	16	≈ 120
Grants active	16	≈ 250
Total grant $	$38.5M	≈ $760



Grantium Implementation Update

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Finalized contract – April, 2008

- Significant activities:
  - Finalizing workflow processes
  - Moving existing (legacy data) to Grantium
  - Installing initial, operational software
  - Conducting user acceptance tests
- Current Strategy:
  - Select Roll-out Project Manger: 6-9 months
  - Engage replacement Director for Grants Management Systems: 1 year
  - Recruit new Director of Information Technology
  - Recruit Configuration Specialist to run Grantium
- Scheduled First RFA to run in Grantium – August, 2009