CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

President's Report

Alan O. Trounson

ICOC Meeting – June 2011

Los Angeles, CA

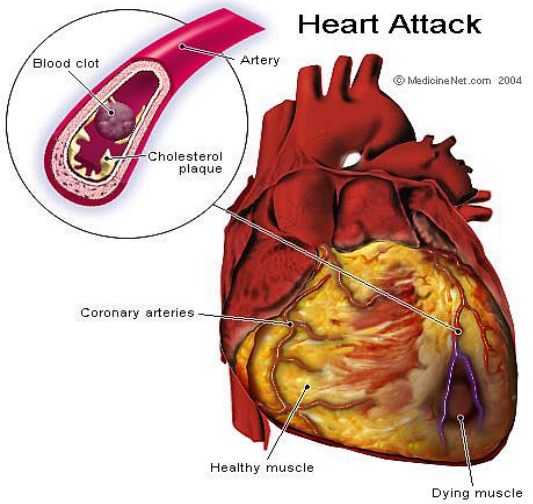
CIRM Cardiac Portfolio Pipeline

Current as of May 27, 2011

Enabling Technology

3 SEED

1 Tools & Technology



Basic Science

7 Basic Biology

2 New Faculty

2 SEED

1 Comprehensive

1 New Cell Lines

Candidate Discovery

4 Comprehensive

2 New Faculty

2 SEED

Pre-clinical & Clinical Development

1 Disease Team

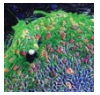
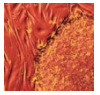
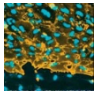
US attitudes toward human embryonic stem cell research.

Evans and Kelley, Nature Biotech 29: June 29

The American public has five distinct attitudes toward (i) cloning animals, (ii) cloning humans, (iii) curing serious diseases by therapeutic cloning or by using stem cells from an IVF embryo, (iv) curing serious diseases using adult stem cells and (v) using any of these for cosmetic purposes. They are strongly opposed to some, have mixed feelings about others and strongly support all that offer hope of curing serious diseases.

US federal government policy largely conforms to public opinion, but with a striking exception. Funding for research on therapeutic cloning has long been banned. Nonetheless, public opinion strongly supports it. In a democratic society, deferring to objections from a small (mainly religious) minority and limiting research that has so much therapeutic promise may well be unethical.

Public support is high, supporters out numbering opponents by 6 to 1 for treating cancer and almost that for heart disease. But the average level of support is not appreciably higher than for other stem cell sources, 73 points out of 100, despite the fact that no embryos are destroyed, a matter of great concern to the Catholic Church and many ethicists (difference not statistically significant at $P < 0.01$). Thus, for the public, iPSCs do not offer any substantial ethical advantage.

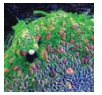
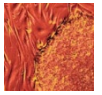
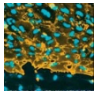




ISSCR Highlights

- **Sean Morrison** from University of Michigan (soon to move to UT Southwestern) gave a plenary session talk describing unpublished, elegant and thorough work to characterize the hematopoietic stem cell (HSC) niche using mouse genetic models. Defining and understanding the HSC niche could lead to improved in vitro methods for HSC culture and expansion and eventually, improved treatments for blood and immune diseases.

- **Ernesto Lujan** (a predoctoral CIRM trainee) in Marius Wernig's lab at Stanford presented a poster describing the direct reprogramming of mouse fibroblasts into clonogenic, multipotent neural progenitor cells (NPCs) that could be passaged >10 times. While the data are preliminary and unpublished, they may represent a major breakthrough in direct reprogramming by allowing the expansion of directly reprogrammed cells into therapeutically relevant numbers as well as their application to neurological diseases which might be better treated by immature cells.

- **Laura Niklason** – Yale University; spoke about her work in pulmonary tissue engineering. Specifically, she gave a synopsis of her work in decellularizing a lung to provide scaffolding to re-engineering lung tissue. She emphasized that in tissue engineering the most important consideration is design criteria [as in any sort of engineering]. She established a design criteria for lungs [mechanical properties, adequate gas exchange surface area, adequate barrier to prevent flooding of airways with blood, autologous cells]. She has begun in vivo procedures with her engineered lung in adult rats.

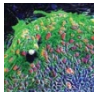
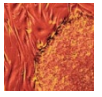
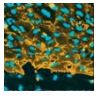




ISSCR Highlights

Michele De Luca: Limbal Stem Cell Therapy and Long term Corneal Regeneration. Impressive demonstration that a small biopsy containing 10-20 stem cells can regenerate a functional cornea and restore sight to patients blinded by chemical burns; 112 patients have been treated with 70% success rate and with long term follow up out to several (up to 10) years. This is a clear demonstration that stem cell therapy really can work . (Translational for the clinic.)

Hans Clevers: Hubrecht Laboratory, Utrecht The Netherlands. LGR5 Stem Cells in Self-renewal. Beautiful talk on the stem cells responsible for turnover of intestinal epithelium. LRG5 marks the stem cells in the crypts. They are found in a 1:1 ratio with Paneth cells, which are the niche cells and provide all the essential GFs for the SC.

Christine Mummery: (Leiden University Medical Center; Leiden, Netherlands). "Cardiomyocytes from pluripotent stem cells in genetic cardiac disease and drug safety pharmacology". Pluripotent cells were used to derive cardiomyocytes in culture and characterize their functional behavior. This stem cell based culture model was used to test in blinded fashion 20 different drugs, some of which had been pulled from the market for adverse cardiovascular effects. The system successfully classified 19 of the 20 compounds for those which would have adverse effects, presenting the possibility of a new drug screening tool to improve patient safety and cutting drug development costs by early identification of potential toxicities . (Translational for drug development.)

ISSCR Highlights

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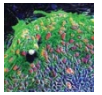
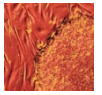
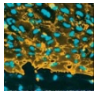
Thea Tlsty: (UCSF) reported on isolation and rigorous characterization of a minor population or mammary ductal epithelial cells which can self renew, form all three mammary lineages but surprisingly can also get other cells of the ectodermal lineage (form neurospheres) as well as the mesoderm (beating cardiomyocytes) and endoderm(pancreatic progenitors). Identical results were obtained with sorted cell populations and with single cells. These cells, which she is calling endogenous provisional pluripotent cells (ePPS) can form teratomas in vivo that contain three lineages but unlike pluripotent cells identified to date are mortal (i.e. expand 60 doublings and then arrest)

ISSCR Highlights

Christopher Breuer: Yale. - Vascular engineering using a biodegradable engineered tube seeded with autologous cells; -Seed with Bone Marrow mononuclear cells (BM-MNC), 2 hr cell attachment, 25 patients, 6-7 year follow up, no graft failures; -Analysis of mechanism of action in animal models: macrophages arrive in vascular transplant, causing inflammation-mediated vascular remodeling, transplanted cells disappear quickly, endogenous endothelial migrate from neighboring blood vessel into engineered vascular construct and form neotissue. Next step is to create a biomimetic scaffold, in which molecules will replace the seeded cells to trigger neotissue formation.

Robert Langer: MIT: working on overcoming an important clinical problem:
Problem: materials currently used to encapsulate cells in a way that protects them from the immune system – to allow allogeneic transplants and to protect from autoimmune response – become covered with fibrous material after transplantation. The transplanted encapsulated cells, e.g. beta cells, thereby lose effectiveness, as they can no longer communicate with the remainder of the organism.
Approach: Dr. Langer is using a high throughput method to produce polymer variants that are tested in a medium throughput mouse system to screen for new materials with improved biocompatibility, with the goal of identifying a material for encapsulation of beta cells without scarring around the material.

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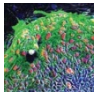
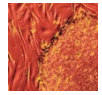
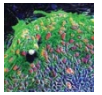
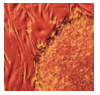
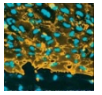




ISSCR Highlights

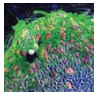
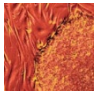
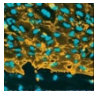
Rudolph Jaenisch: hESC vs. iPS - There has been discussion over last several months about the recent observations by Hochedliner that a certain region of iPS is aberrantly silenced, leading to decreased potential of cells compared to ESC. Now others have looked more closely at this region, and find that this is only the case in some iPS lines, whereas others express from that region similarly to ESC. They found subtle differences, perhaps just changing the order in which the Yamanaka factors are cloned into the expression plasmid (OSK vs. OKS, use of slightly different version of internal ribosome entry site) can affect the quality and potential of the reprogrammed cells. The reprogramming process, though very robust, is exquisitely sensitive to the dosing /timing of the master regulators.

Charles Sabine: A former NBC reporter gave inspirational presentation. Charles is a patient advocate that lost his father through Huntington's disease and was recently diagnosed with a mutation in the Huntington gene. As a war reporter he covered the two wars in Iraq and Kosovo and witnessed death, brutal killings, and tragedies, but was struck by the humanity that he saw during these wars. With interactive videos he shared these rare moments with a clear message; that without dignity and hope there is no humanity. Similarly, he witnessed how his brilliant father slowly lost his mind and dignity as the Huntington's disease progressed. His message was that while we have hope for cures this will keep us going. Science and technology provides the hope we will be able to introduce new therapies and preserve the dignity to humanity.

Achieved in Toronto

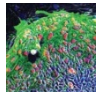
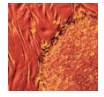
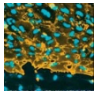
- CFPs: Scotland to sign MOU, NYSCF to bolt on to CIRM awards, The Netherlands to sign MOU, Connecticut to explore CFP relationship, Link proposed to Harvard Stem Cell Institute, Canada to broaden CFP relationship
- Major Pharma and CIRM approaching joint funding agreement
- Potential application opportunity to CIRM for entry to Phase IIb clinical trials
- ISSCR offers regional translational meeting in California in 2014
- Discussions progressing with major Stem Cell Biotech industry joint funding agreement
- Stem Cells Translational Journal launched – very strong interest from ISSCR members to contribute
- Several potential CIRM Leadership candidates expressing interest in moving to California
- Identified several new areas of new fast moving research that could be connected to Californian partners – Opportunity Fund candidates

President's Priority Opportunities

- **CIRM Stem Cells and Genomics Centers of Excellence:**

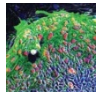
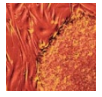
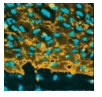
  Significant recent advances in DNA sequencing and genomics technology hold tremendous potential for accelerating the pace and expanding the scope of stem cell research. Dramatic decreases in costs for genomic analysis, including the impending "$1000 genome", will soon make genome-scale characterization and deep sequencing a practical tool for analysis of stem cells. Additionally, the development of technologies for high-throughput characterization of the transcriptome and epigenome (including microRNAs and retrotransposon activity), together with sensitive new methods for single cell genomic analysis that is essential to properly understand stem cell variety and heterogeneity, provide a host of innovative approaches for exploring stem cell biology and the cell differentiation processes, cell stability, genomic integrity and cell and tissue manufacturing. To fully exploit and apply these powerful and rapidly evolving technologies, stem cell scientists need ready access to genomics expertise and opportunities close collaboration with experts in genomics experimental design and the bioinformatic analysis of masses of data produced by such studies. This may be achieved by co-location of stem cell and genomic expertise in several Centers of Excellence in Stem Cells and Genomics. Considerable leverage may exist for CIRM investments in these Centers.

President's Priority Opportunities

- **CIRM Alpha Stem Cell Clinics:**

  Not all stem cell therapies can be delivered in the model of a drug therapy. Particularly in cases requiring manipulation of the patients own cells, or the delivery of cells to specific sites in the body may be more amenable to delivery through tertiary clinical centers in a model that is more akin to the bone marrow transplant units, cancer centers or IVF clinics. The presence of committed clinical expertise, cell and molecular biologists, experienced nursing staff and patient counselors will be necessary for clinical applications of cell therapies. The approach which we term the Alpha Stem Cell Clinic model, could be established in major cities and involve the presently FDA approved adult stem cell therapies studies. While the presently evolving strategies may in the future provide effective therapies or cures, there are already a number of adult cell based treatments presently used for regenerative medicine (e.g.. limbal stem cell transplants, immune and gene therapy using hematopoietic stem cells, MSCs in bone repair etc.). These Alpha Clinics could also be sites for the evolving cell therapy trials for newer and more effective cell therapies. The Clinics may have specialties that distinguish one another (e.g. Eye Diseases, Cancer Stem Cells and Genomics, Blood Diseases, Cardiovascular, Neurodegeneration, etc.). The infrastructure and capacity to closely monitor patients for extended periods, to provide patients with the full information on what is genuinely available in terms of treatment and expected outcome, and to provide the necessary good manufacturing procedures (GMP) facilities, surgeries and expertise to handle and manipulate cells, is absolutely critical. CIRM will explore the concept of seeding Alpha Clinics in California to initiate the cell therapy practices that are moving through the clinical pipeline for patients.

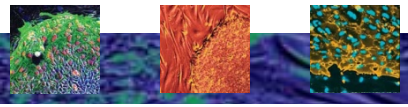




Upcoming RFAs

- **Disease Team Therapy Development**
  - RFA Posted -- November 2010
  - ICOC Review of Planning Applications –August 2011
  - Funding period begins September 1
  - Part 2 Research Award to be Posted – September 2011

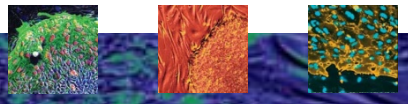
- **Early Translational III**
  - RFA Posted - June 13, 2011
  - Pre-Applications - due August 10, 2011

- **CIRM Stem Cell Biology IV**
  - Concept proposal -- October 2011



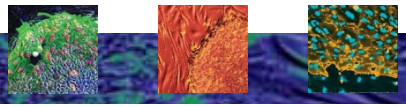
Workshop Report
CIRM-Japan (JST) Workshop

- Held May 16-17, 2011 in Kobe, Japan
- Attended by 9 California scientists and 20 scientists from Japan
  - Participation of Dr. Shinya Yamanaka and Dr. Shinichi Nishikawa
- Focus on Early Translation
- Activities:
  - Research Presentations
  - Networking and discussion of potential collaborations



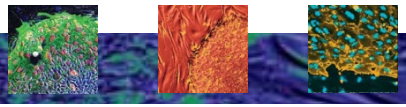
Workshop Report
CIRM-Cerebral Palsy Workshop

- Held June 7-8, 2011 in San Francisco, CA
- Attended by 30 California and International scientists
- Focus on Cerebral Palsy and Stem Cell Therapy
- Activities:
  - Research Presentations
  - Networking and discussion of potential collaborations
  - CIRM's Role in Pediatric Brain Developmental Disorders



CIRM 2011 Bridges to Stem Cells Annual Trainee Meeting - San Francisco, July 7-8, 2011

- 16 Bridges programs will participate
- Up to 160 trainees, mentors, and program directors
- Speakers, poster presentations, career panel
- The meeting will bring together trainees to present their research, meet peers and interact with scientists in the stem cell community.



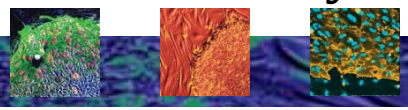
CIRM 2011 Grantee meeting - San Francisco September 14-16, 2011

Purpose:

- Bring together investigators and trainees funded by CIRM and CIRM's collaborative funding partners
- Highlight grantee work from basic through translational/clinical research
- Encourage scientific exchange and collaboration

Meeting Agenda:

- Plenary talks by CIRM Principal Investigators and other leaders in the field
- Posters and short talks by trainees
- Networking opportunities
- Training opportunity in public communication and advocacy



CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

2010-11 Budget Allocation and Expenditure Report

Recorded Through May 31, 2011

June 2011- ICOC Meeting

Chila Silva-Martin
Financial Services Officer

Fiscal Year 2010-11
Expenditures Posted Through May 2011