CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

Presidents Report

Alan Trounson

April, 2009

Agenda Item #7

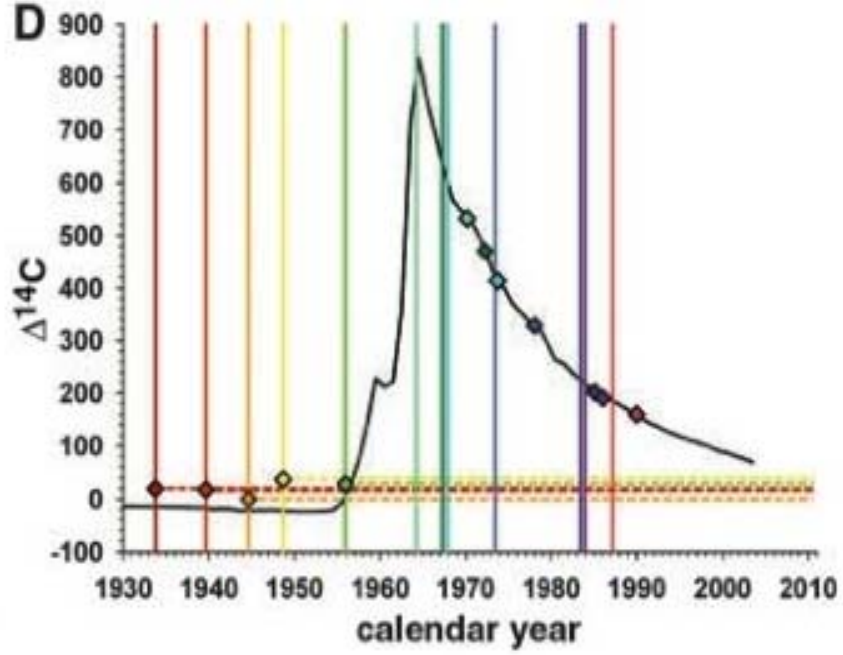
Evidence for Cardiomyocyte Renewal in Humans

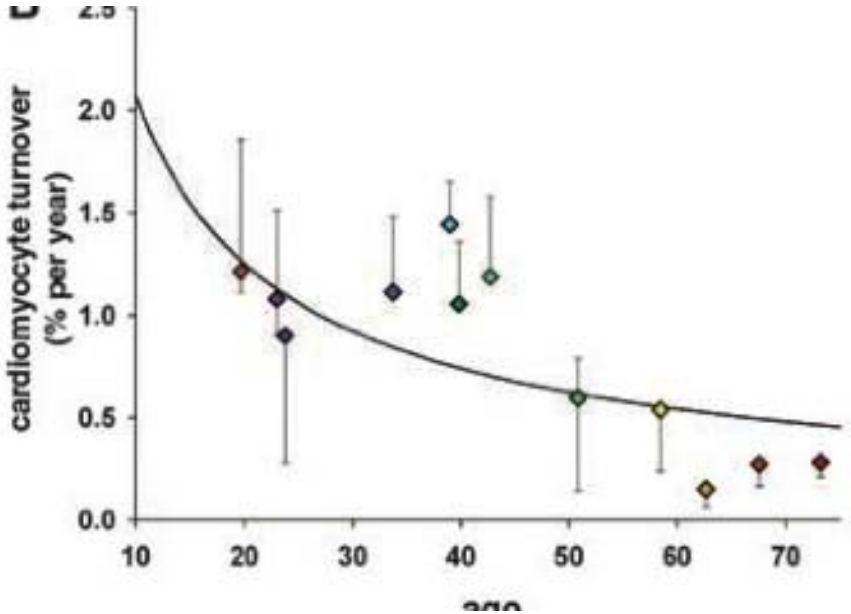
Berrgmann et al., Karolinska Institute Stockholm, Sweden

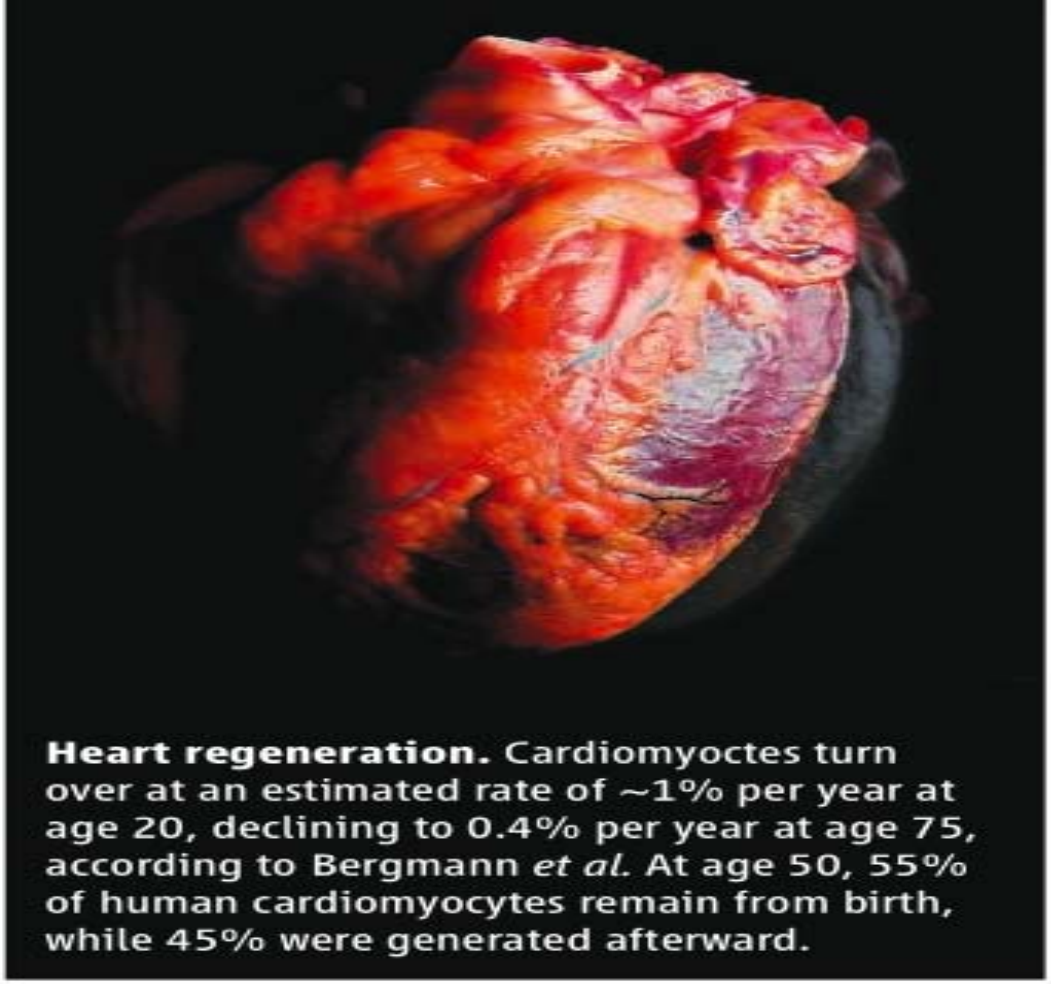
Science, April, 2009

It has been difficult to establish whether we are limited to the heart muscle cells we are born with or if cardiomyocytes are generated also later in life.

Took advantage of the integration of carbon-14, generated by nuclear bomb tests during the Cold War, into DNA to establish the age of cardiomyocytes in humans. Elevated amounts of 14C in the atmosphere rapidly equalized around the world as 14 CO2. After the Limited Nuclear Test Ban Treaty in 1963, the 14C concentrations dropped exponentially, not primarily because of radioactive decay (half-life of 5730 years), but by diffusion from the atmosphere



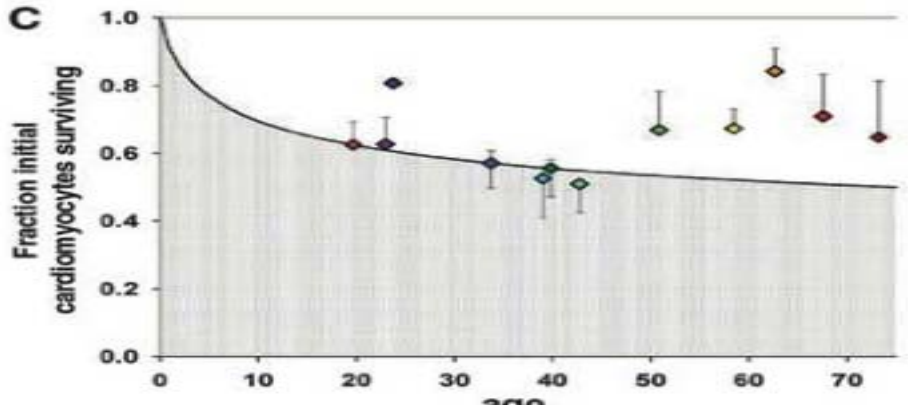


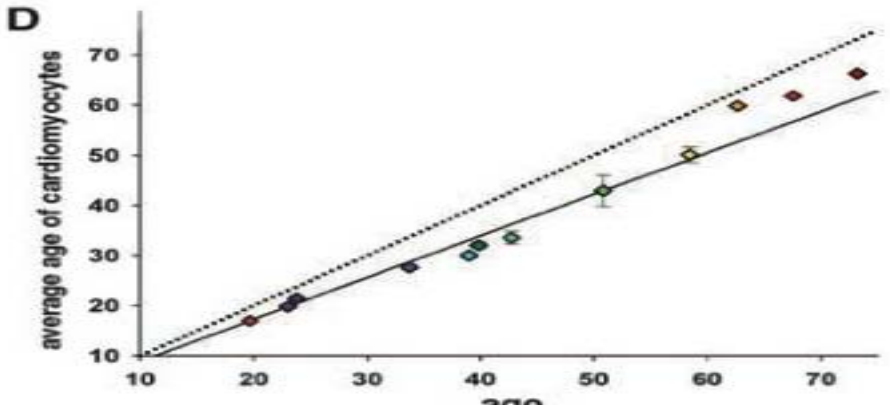


Heart regeneration. Cardiomyoctes turn over at an estimated rate of ~1% per year at age 20, declining to 0.4% per year at age 75, according to Bergmann *et al.* At age 50, 55% of human cardiomyocytes remain from birth, while 45% were generated afterward.

Showed that cardiomyocytes renew, with a gradual decrease from 1% turning over annually at the age of 25 to 0.45% at the age of 75. Fewer than 50% of cardiomyocytes are exchanged during a normal life span.

The capacity to generate cardiomyocytes in the adult human heart suggests that it may be rational to work toward the development of therapeutic strategies aimed at stimulating this process in cardiac pathologies.





Embryonic stem cell–specific microRNAs promote induced pluripotency

Robert L Judson, Joshua E Babiarz, Monica Venere & Robert Blelloch, UCSF
***Nature Biotechnology* April, 2009**

This report demonstrates that introduction of microRNAs (miRNAs) specific to embryonic stem cells enhances the production of mouse induced pluripotent stem (iPS) cells.

The miRNAs miR-291-3p, miR-294 and miR-295 increase the efficiency of reprogramming by Oct4, Sox2 and Klf4, but not by these factors plus cMyc.

cMyc binds the promoter of the miRNAs, suggesting that they are downstream effectors of cMyc during reprogramming. However, unlike cMyc, the miRNAs induce a homogeneous population of iPS cell colonies.

The study shows that miRNAs can replace cMyc and is a very interesting model for stem cell reprogramming dedifferentiation and developing cancer phenotype.

*Funded by CIRM (SEED Award and New Faculty Award)
*Video available at www.cirm.ca.gov or CIRM YouTube

Molecular stages of rapid and uniform neuralization of human embryonic stem cells

R Bajpai, G Coppola, M Kaul, M Talantova, F Cimadamore, M Nilbratt, DH Geschwind, SA Lipton and AV Terskikh, Burnham Institute, La Jolla

Cell Death & Differentiation March 2009

They characterized a new method for rapid and uniform differentiation of hESCs into committed neural precursor cells (C-NPCs).

The first wave of gene expression changes, corresponded to the transition through primitive ectoderm, started at day 3, preceding the formation of columnar neuroepithelial rosettes. The second wave started at day 5, coinciding with the formation of rosettes.

In culture, C-NPCs became electrophysiologically functional neurons; on transplantation into neonatal mouse brains, C-NPCs integrated into the cortex and olfactory bulb, acquiring appropriate neuronal morphologies and markers.

Never detected tumors or excessive neural proliferation after transplantation of C-NPCs into mouse brains

*CIRM Funded (Comprehensive Award)

Functional cardiomyocytes derived from human induced pluripotent stem cells.

Zhang J, Wilson GF, Soerens AG, Koonce CH, Yu J, Palecek SP, Thomson JA, Kamp TJ. , Department of Medicine, University of Wisconsin, WiCell Research Institute, Madison, WI 53792-3248, USA.

Circ Res. 2009 Feb 27;104(4):e30-41. Epub 2009 Feb 12

Human iPS cells were generated using OCT4, SOX2, NANOG, and LIN28 transgenes and compared to human embryonic stem (ES) cells.

The pluripotency genes OCT4 and NANOG were down regulated with cardiac differentiation, but the down regulation was blunted in the iPS cell lines because of residual transgene expression.

Proliferation of iPS and ES cell-derived cardiomyocytes based on 5-bromodeoxyuridine labeling was similar, and immunocytochemistry of isolated cardiomyocytes revealed indistinguishable sarcomeric organizations. Electrophysiology studies indicated that iPS cells have a capacity like ES cells for differentiation into nodal-, atrial-, and ventricular-like phenotypes based on action potential characteristics

Human iPS cells can differentiate into functional cardiomyocytes, and thus iPS cells are a viable option as an autologous cell source for cardiac repair and a powerful tool for cardiovascular research.

The reversal of hyperglycaemia in diabetic mice using PLGA scaffolds seeded with islet-like cells derived from human embryonic stem cells.

Mao GH, Chen GA, Bai HY, Song TR, Wang YX. Reproductive Medical Center, Peking University Third Hospital, Beijing, China.

Biomaterials. 2009 Mar;30(9):1706-14. Epub 2009 Jan 8.

They describe a five-stage protocol with adding exendin-4 instead of nicotinamide finally could generate islet-like cells from human embryonic stem (ES) cells.

Subcutaneous transplantation of scaffolds seeded with the islet-like cells or cell transplantation under kidney capsules for further differentiation in vivo could improve 6h fasted blood glucose levels and diabetic phenotypes in streptozotocin-induced diabetic SCID mice. More interestingly, blood vessels of host origin, characterized by mouse CD31 immunostaining, invaded the cell-scaffold complexes.

Shows scaffolds can serve as vehicles for islet-like cell transplantation.

Multifocal Lung Cancers Appear to Originate from Single Cancer Clone

Liang Cheng et al., Indiana University School of Medicine in Indianapolis

Journal of the National Cancer Institute April, 2009

They examined 70 lung cancer tumors from 23 female and seven male patients to determine whether multiple tumors from an individual patient shared a common genetic pattern. The investigators analyzed the tumors for chromosome loss at six loci previously associated with lung cancer and for mutations in the P53 gene. They also analyzed the X-chromosome inactivation pattern in tumors from female patients.

They found that multiple tumors in 23 of the 30 patients (77 percent) arose from a single cancer clone.

The human placenta is a hematopoietic organ during the embryonic and fetal periods of development

Bárcena A, Kapidzic M, Muench MO, Gormley M, Scott MA, Weier JF, Ferlatte C, Fisher SJ., Institute for Regeneration Med, Human Embryonic Stem Cell Program, UCSF

Dev Biol. 2009 Mar 1;327(1):24-33.

Studied human placenta for hematopoietic lineage progenitors and stem cells.

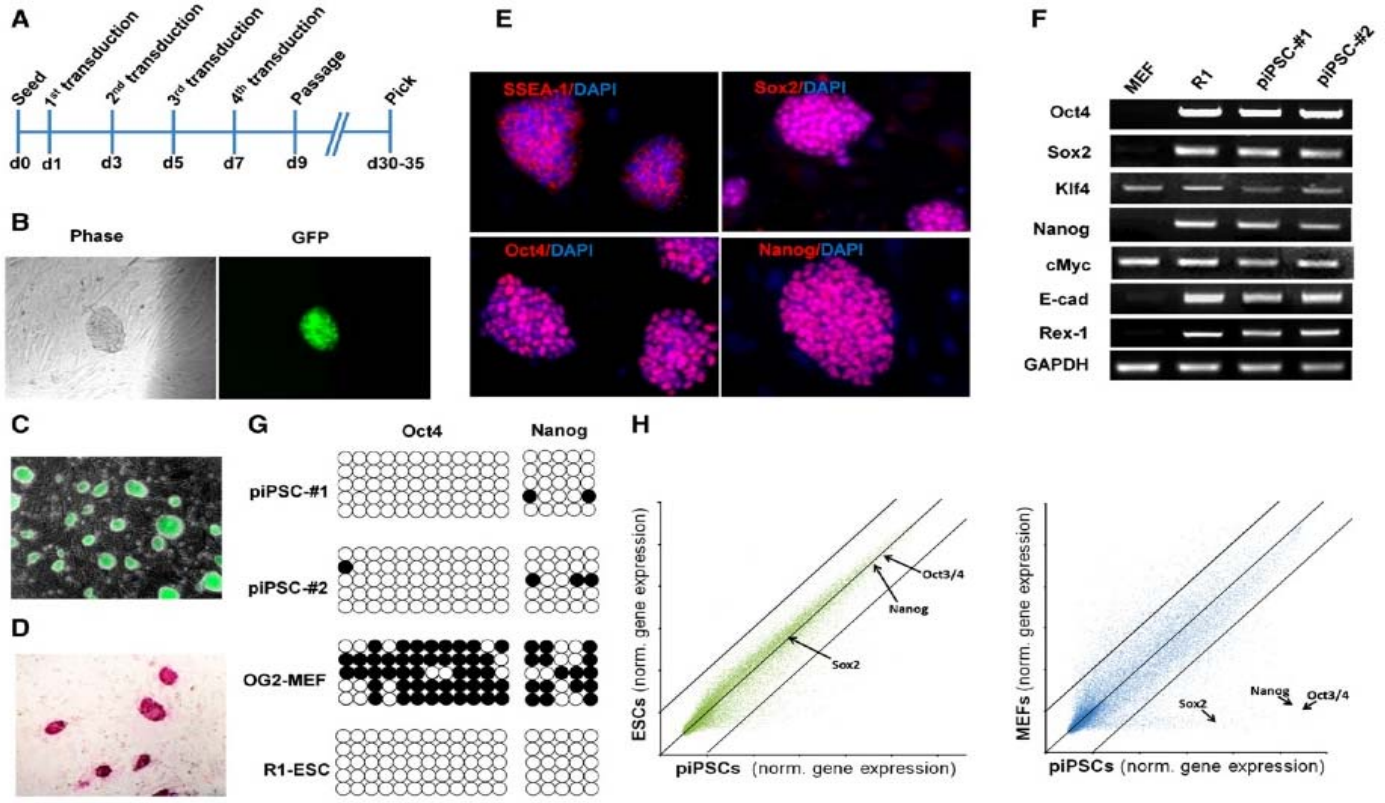
In addition to multipotent progenitors, the placenta contained myeloid- and erythroid-committed progenitors indicative of active in situ hematopoiesis. These data suggest that the human placenta is an important hematopoietic organ, and the hES cell derivatives of hematopoietic stem cells may be more likely placental than bone marrow.

Generation of Induced Pluripotent Stem Cells Using Recombinant Proteins

Zhou et al. Shen Ding's Lab, Scripps Institute, La Jolla

***Cell Stem Cell* April, 2009**

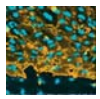
- Four proteins – Oct4, Sox2, Klf4, cMyc – fused with a poly-argi- nine (i.e., 11R) protein transduction domain to the C terminus.



President's Priorities

- President's senior researchers regular forums
- Preapplication for Basic Biology RFA (Apps. Due April 30)
- Major Facilities Programs – moving to completion of processes
- International agreements for collaborative research
  UK- Welcome Trust, Scottish Network,
  EU Framework collaborations, China
- Developing networks in US science and industry
- Planning financial and strategic adjustments to CIRM activities
- Defining the optimal CIRM staff profile
- Conceptual development of a program of CIRM Awards for Exceptional Scientists





President's Priorities

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- FDA meeting
- NIH meeting



Under Development – CIRM Investigator Awards

The purpose of this program would be threefold:

1. Recruitment - to attract some of the world's leading mid-career stem cell scientists to California;
2. Retention - to retain California's best mid-career stem cell scientists;
3. Excellence - to provide both groups the freedom to pursue creative, high-risk research.

The program would be very selective:

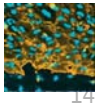
1. No more than 8 per year (4 recruitment; 4 retention)
2. Candidates must be truly outstanding.



Disease Team Research Award

- **73 Preliminary Applications (PreApps) eligible**
  - **15 For Profit (12 institutions) → CIRM Loan Program Candidates**
  - **58 Non-Profit (15 institutions)**
- **18 designate an International Collaborative Funding Partner**
- **Evidence of new partnerships/collaborations within California**
- **hESC, iPSC and adult SC well represented**
- **Diversity of therapeutic approaches**
  - **Approximately 2/3 are cell therapy (or cell and gene therapy)**
  - **1/3 are small molecule or biologic therapies (SC for discovery/development)**



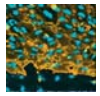


Disease Team Research Award

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- Autoimmune diseases
- Burns and skin wounds
- Cancer
- Cardiovascular disease
- Diabetes
- Eye diseases
- Hematopoietic disorders
- HIV / AIDS
- Infertility
- Kidney disease
- Liver disease
- Musculoskeletal diseases
- Neurological disorders and injury
- Peripheral vascular disease
- Tracheal stricture





Upcoming Workshops

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

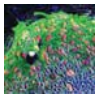
Autism

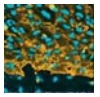
May 28-29

California/Japan Collaboration June 8-9

Ethics Workshop

June 30 – July 1

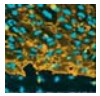




CIRM Autism Workshop: May 28-29

- Organizers: M. Csete & A. Nigh; Moderator: E. Penhoet
- Information gathering from multidisciplinary experts
  - -Not promoting any particular research agenda
- Interactive panels (Day 1)
  - -Update on pathophysiology
  - -Diverse animal models
  - -Disease in a dish (stem cell-based models)
  - -Current role of CNS stem cell transplants in brain disorders
    - -Animal studies
    - -Phase I studies in children with other CNS diseases
- Breakout sessions (Day 2)
  - -Define optimal research agendas
  - -Where can CIRM contribute to these agendas?





CIRM Workshop:
Advancing the Field: Institutional Approaches Supporting Ethics in Stem Cell Research

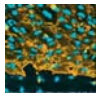
- **June 30 –July 1, 2009**

- This day and a half workshop, to be held in the San Francisco area, is designed to examine institutional approaches for addressing ethical, legal and policy issues related to stem cell research.

  - Contemporary issues related to regulatory compliance
  - New initiatives intended to support ethics in research
  - Challenges posed by translational research

- **WHO SHOULD ATTEND**: Institutions currently involved in human pluripotent stem cell research and those considering research in the future.





CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

2008-09 Budget Allocation and Expenditure Report

As of March 31, 2009

President's Report

April 28, 2009 - ICOC Meeting

Description	Budget Allocation	Expenditures Posted Thru Feb 2009	Expenditures Posted Thru Mar 2009	Changes Feb to Mar 2009	Available Budget Apr 2009 to Jun 2009	Percentage of Budget Allocation Posted
Personnel Services						
Salaries and Benefits	**7,045**	**3,418**	**3,935**	**517**	**3,111**	**56%**
Operating Expenses and Equipment						
Interagency Agreements	491	174	178	4	313	36%
External Contracts	2,716	1,371	1,584	214	1,132	58%
ICOC, Science, Work Group Meetings	1,574	403	567	164	1,007	36%
Other Travel	558	100	104	4	454	19%
Furniture and Equipment (Non-IT)	38	2	2		36	4%
Information Technology	53	27	34	7	18	65%
Other O.E.&E.	900	223	263	41	636	29%
Total O.E.&E.	**6,329**	**2,299**	**2,732**	**433**	**3,597**	**43%**
Total CIRM Support Expenditures	**13,375**	**5,717**	**6,667**	**950**	**6,708**	**50%**

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

Future Funding Programs

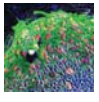
John Robson

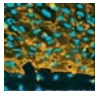
April 28, 2009 - ICOC Meeting

CIRM Future Funding Programs

Programs with ICOC Concept Approval

Program	Budget	Expenditure (thru 12/31/10)
Early Translation	$60.0M	$30.0M
Basic Biology 1	$30.0M	$11.7M
Disease Team	$210.0M	$59.0M
Basic Biology 2	$30.0M	$5.0M
Total	**$330.0 M**	**$105.7M**



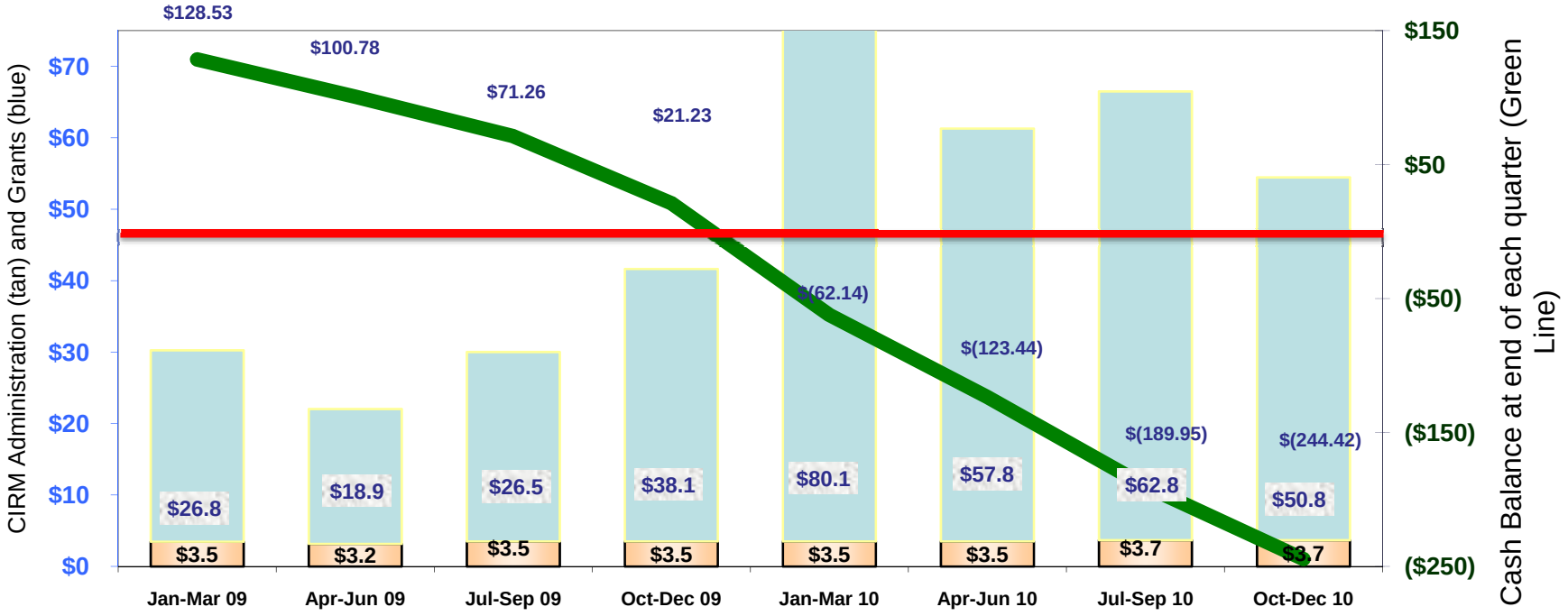


CIRM Funding

Financial Projections to 12/31/10

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Concept-approved Programs



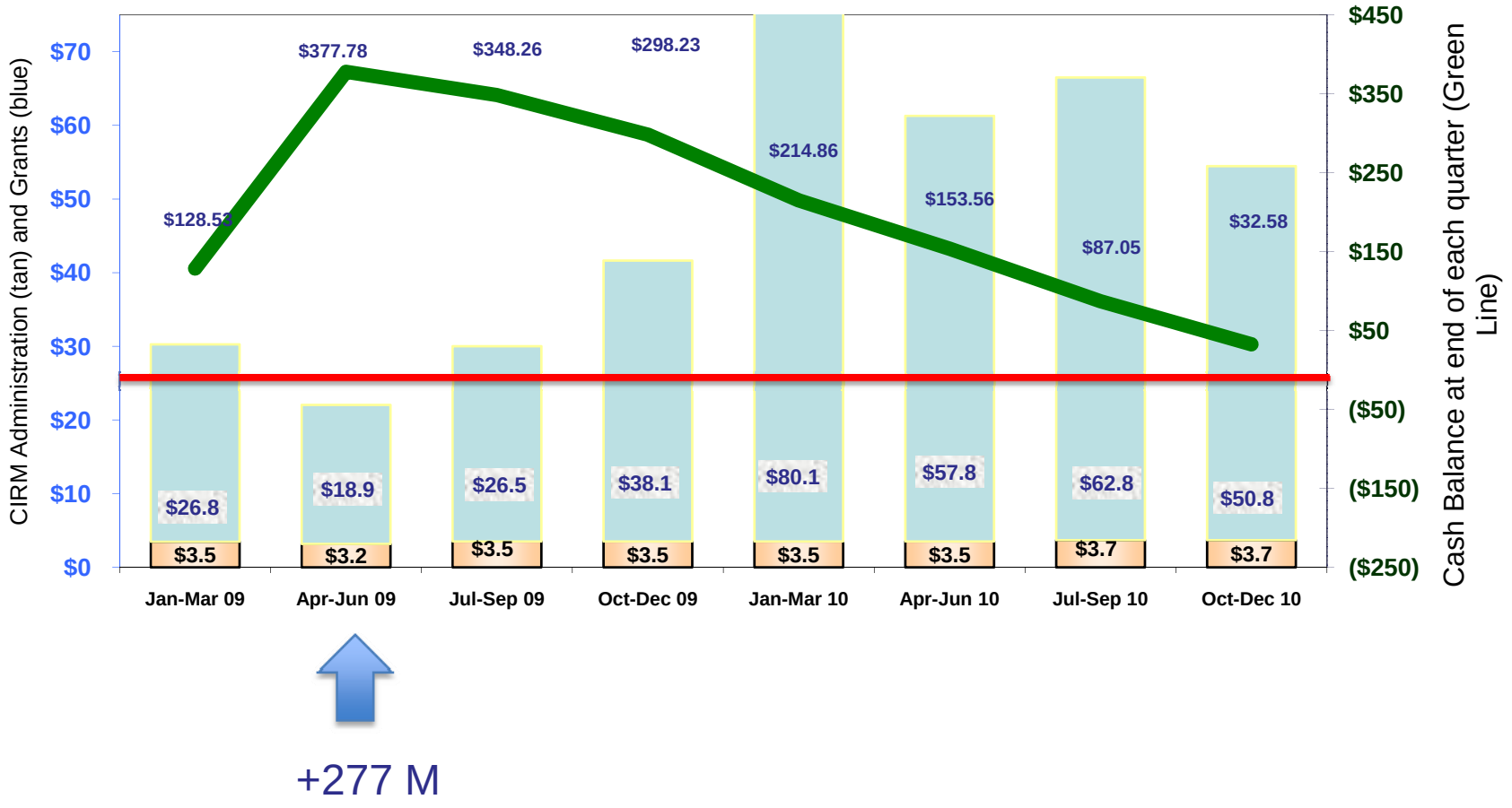
No New Funding



CIRM Funding

Financial Projections to 12/31/10

Concept-approved Programs



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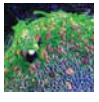
Scenario 15 Approved Concepts

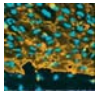


CIRM Future Funding Programs

Tentative programs presented to ICOC in January 2009

Program	Budget	Expenditure (thru 12/31/10)
Immunology	$30.0M	$2.5M
Early Translation	$60.0M	$5.0M
Disease Team	$210.0M	$6.6M
Total	**$300.0 M**	**$14.1M**

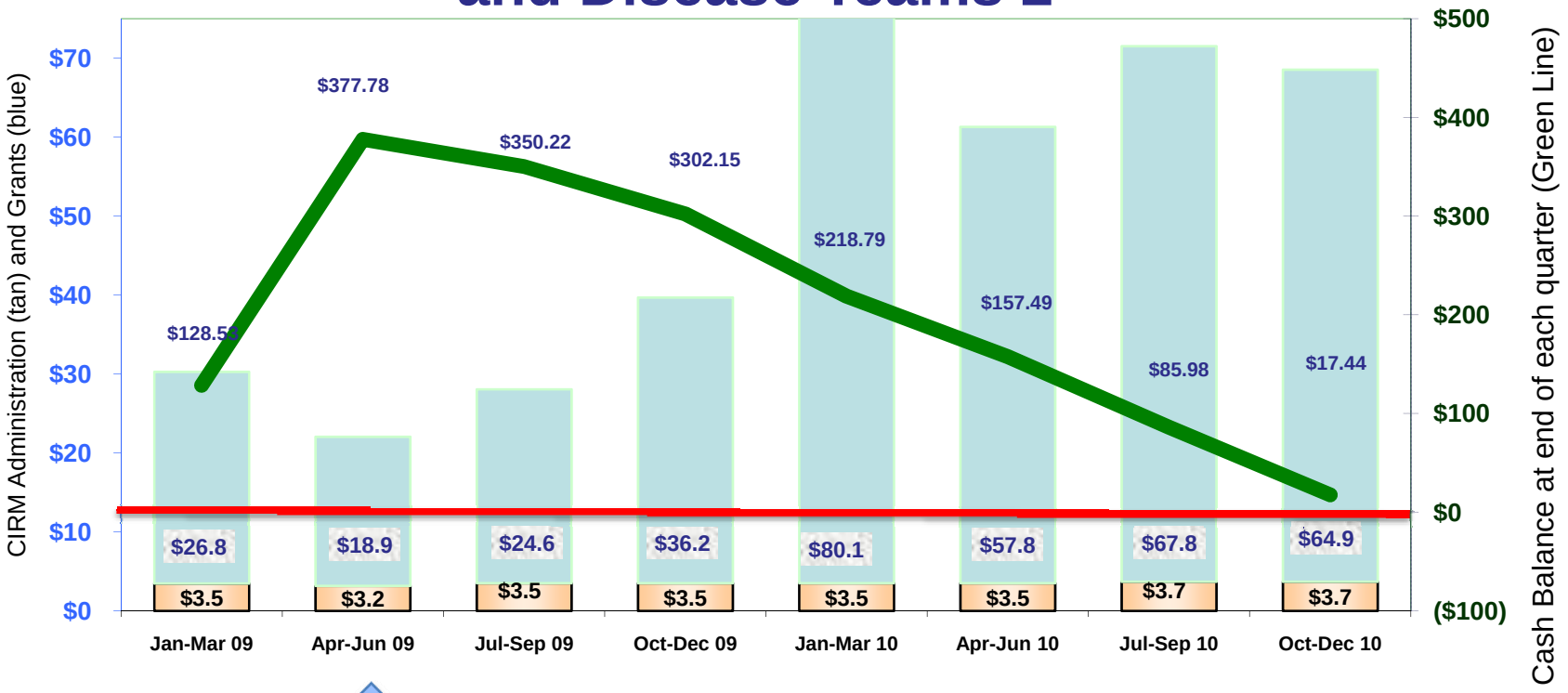




CIRM Funding

Financial Projections to 12/31/10

Concept-approved Programs Plus Immunology, Early Translation 2 and Disease Teams 2



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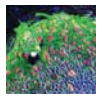

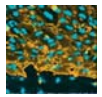

CIRM Funding
Financial Implications to 6/11