CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Presidents Report

Alan Trounson

March 12, 2009

Agenda Item 9

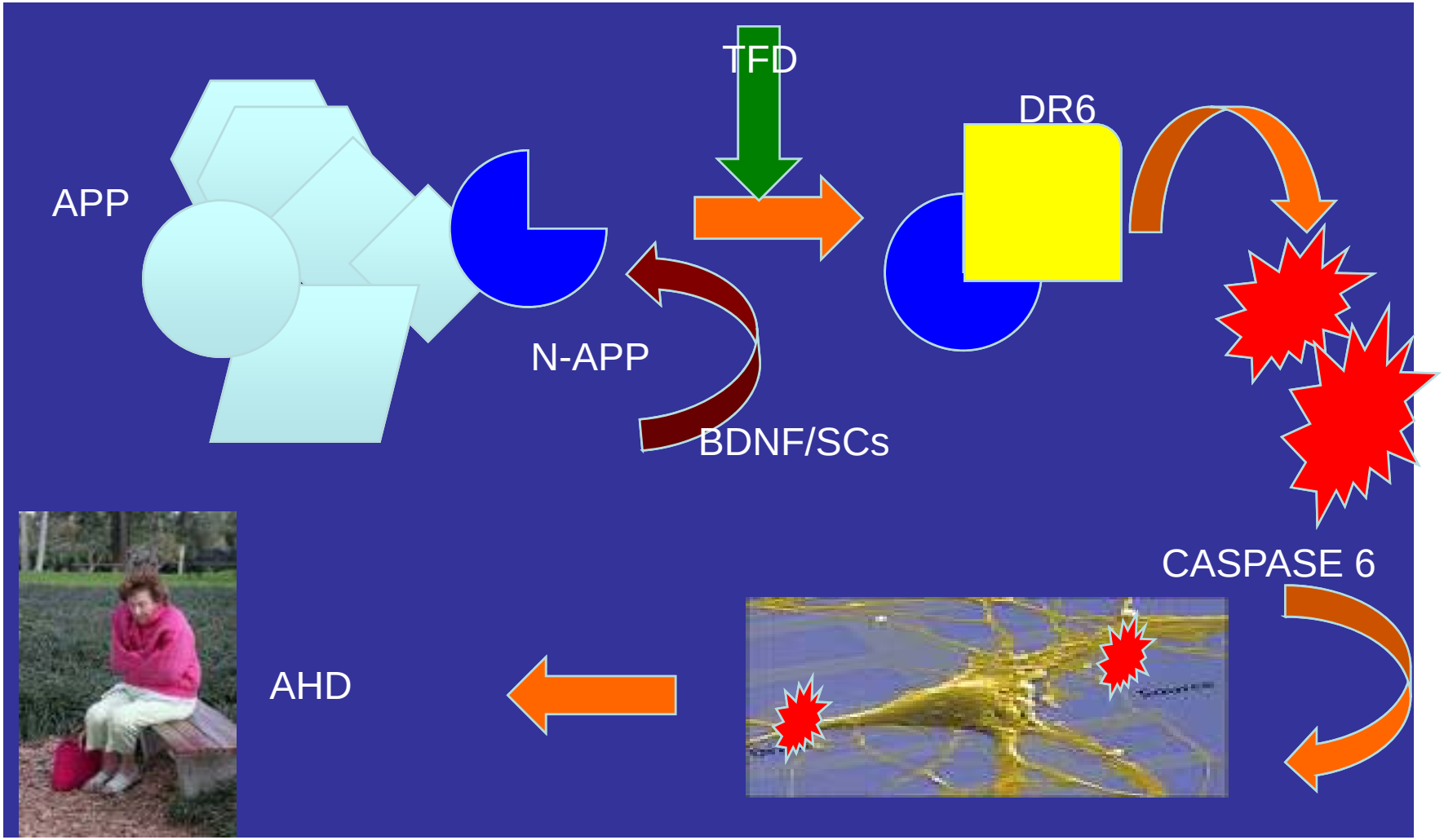
New Study Identifies Culprit in Alzheimer's Disease "APP binds DR6 to trigger axon pruning and neurone death via caspases" : Nikolaev etal in Marc Tessier-Lavigne's Lab, Genetech and Salk Institute; *Nature,457: Feb 2009*

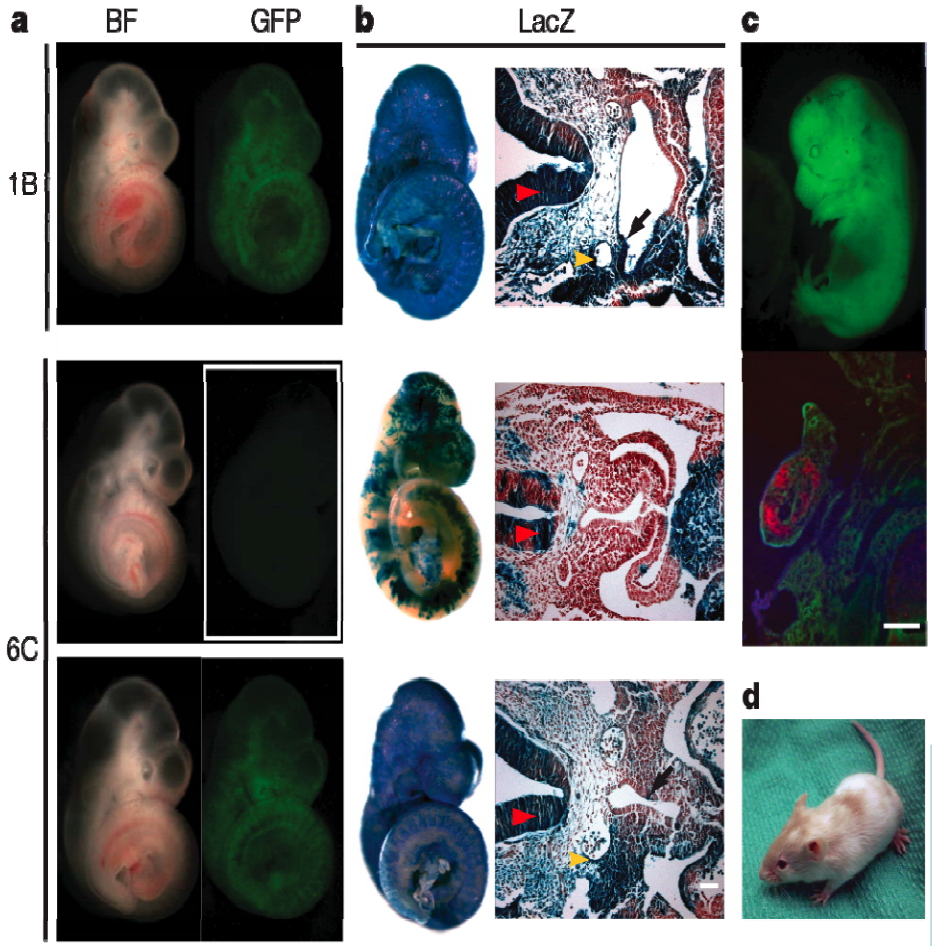
- Alheimers Disease – Abundant β-amyloid precursor protein (APP) – tangles and aggregates. APP and death receptor 6 (DR6) activate caspase self-destruction of neurones. DR6 is expressed in developing neurones and is required for normal cell body death and axonal pruning in vivo

- DR6 is activated locally by inactive surface ligand(s) released after ***trophic-factor deprivation (TFP) –*** APP is a DR6 ligand and ***TFP*** triggers ***shedding of APP and cleavage of an amino acid fragment*** **(N-APP)** that binds DR6 and triggers caspase 6 and axonal degeneration – Alzheimer's Disease

- ***TFP*** – lack of brain-derived neurotrophic factor **(BDNF**) and neurotrophin 3 (NTF3)
- ***Frank LaFerla,*** Irvine -- showed ESC derived transplants or **BDNF** (**reversing TFP?**) corrected behavioral phenotype in mouse model of Alzheimer's Disease (tangles and aggregates were unaffected)

New Study Identifies Culprit in Alzheimer's Disease "APP binds DR6 to trigger axon pruning and neurone death via caspases" : Nikolaev etal in Marc Tessier-Lavigne's Lab, Genetech and Salk Institute; *Nature,457: Feb 2009*





piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells

Knut Woltjen et al., Andras Nagy's Lab,
Samuel Lunenfeld Research Institute,
Toronto, Ontario
Nature March 09

piggyBac (PB) transposition has recently been demonstrated to be functional in various human and mouse cell lineS. The PB transposon/transposase system requires only the inverted terminal repeats flanking a transgene and transient expression of the transposase enzyme to catalyse insertion or excision events. piggyBac (PB) transposition is host-factor independent, and is explored for the repro- gramming process and future cell-based therapies.

Demonstrated successful and efficient reprogramming of murine and human embryonic fibroblasts using transcription factors delivered by PB transposition. By taking advantage of the natural propensity of the PB system for seamless excision, they show that the individual PB insertions can be removed from established iPS cell lines, providing an invaluable tool for discovery

Oct4-induced pluripotency in adult neural stem cells.

Kim et al., Hans Scholar's lab, Max Planck Institute for Molecular Biomedicine, Münster, Germany *Cell* 2009 Feb 6;136(3):411-9.

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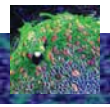
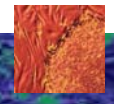
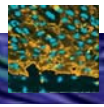
- The four transcription factors Oct4, Sox2, Klf4, and c-Myc can induce pluripotency in mouse and human fibroblasts.

- Showed that exogenous expression of the germline-specific transcription factor Oct4 is sufficient to generate pluripotent stem cells from adult mouse NSCs.

- These **one-factor induced pluripotent stem cells** (1F iPS) are similar to embryonic stem cells in vitro and in vivo. Not only can these cells can be efficiently differentiated into NSCs, cardiomyocytes, and germ cells in vitro, but they are also capable of teratoma formation and germline transmission in vivo.

- Demonstrate that Oct4 is required and sufficient to directly reprogram NSCs to pluripotency.

Tumors after Fetal Neural Transplants in Russia

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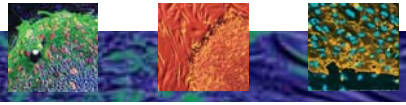
- A boy with ataxia telangiectasia (AT) was treated with intracerebellar and intrathecal injection of human fetal neural stem cells. Four years after the first treatment he was diagnosed with a multifocal brain tumor.

- The biopsied tumor was diagnosed as a glioneuronal neoplasm. The tumor cells and the patient's peripheral blood cells were compared by fluorescent in situ hybridization using X and Y chromosome probes, by PCR for the amelogenin gene X- and Y-specific alleles, by MassArray for the ATM patient specific mutation and for several SNPs, by PCR for polymorphic microsatellites, and by human leukocyte antigen (HLA) typing.

- Molecular and cytogenetic studies showed that the tumor was of non-host origin **suggesting it was derived from the transplanted neural stem cells**. Microsatellite and HLA analysis demonstrated that the tumor is derived from at least two donors.



Identification of small-molecule inducers of pancreatic beta-cell expansion

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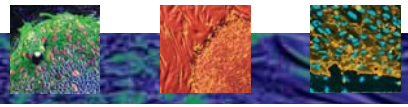
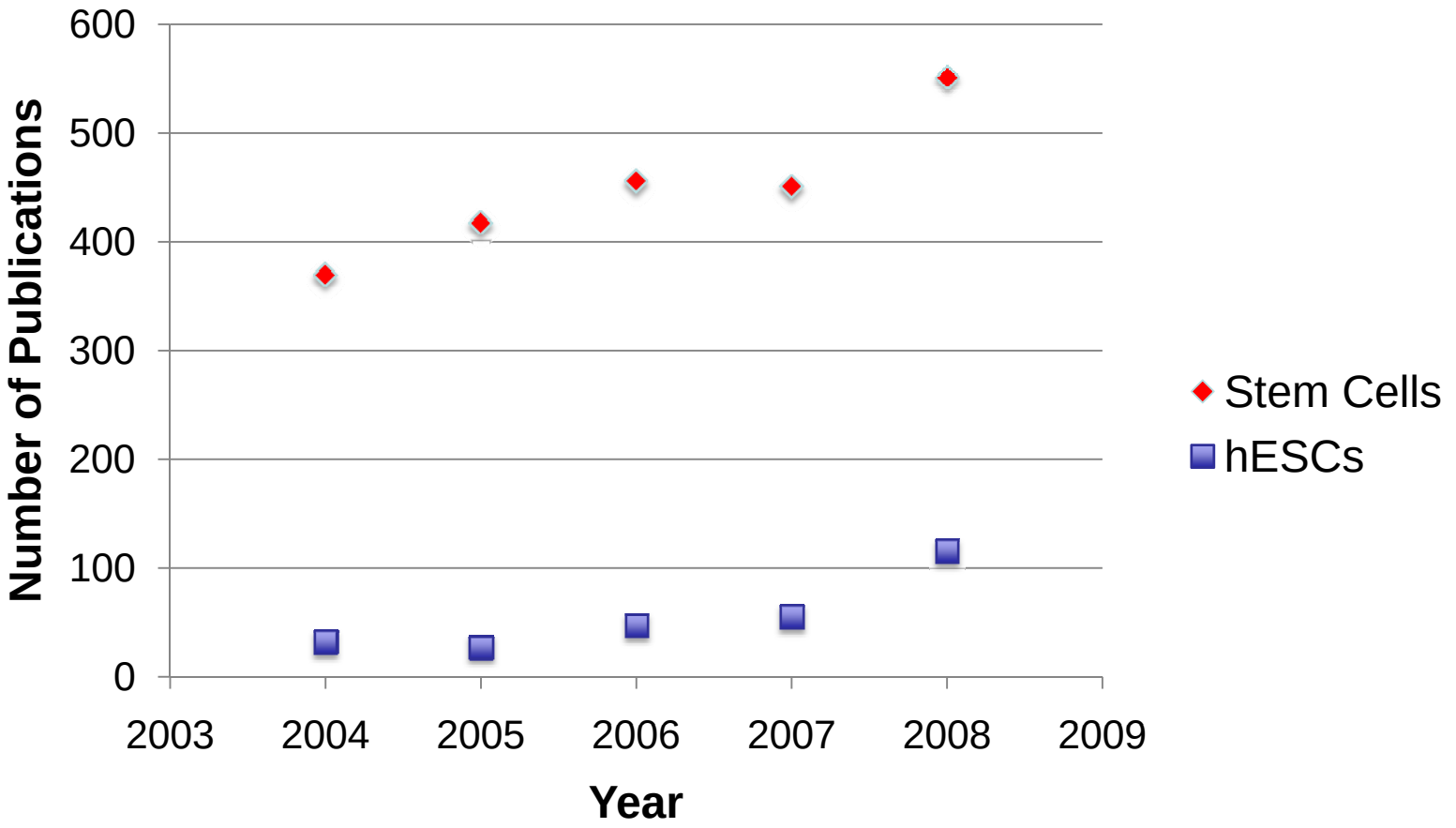
Wang W, Walker JR, Wang X, Tremblay MS, Lee JW, Wu X, Schultz PG, Scripps Research Institute, La Jolla, Proc Natl Acad Sci U S A. 2009 Feb 3;106(5):1427-32.

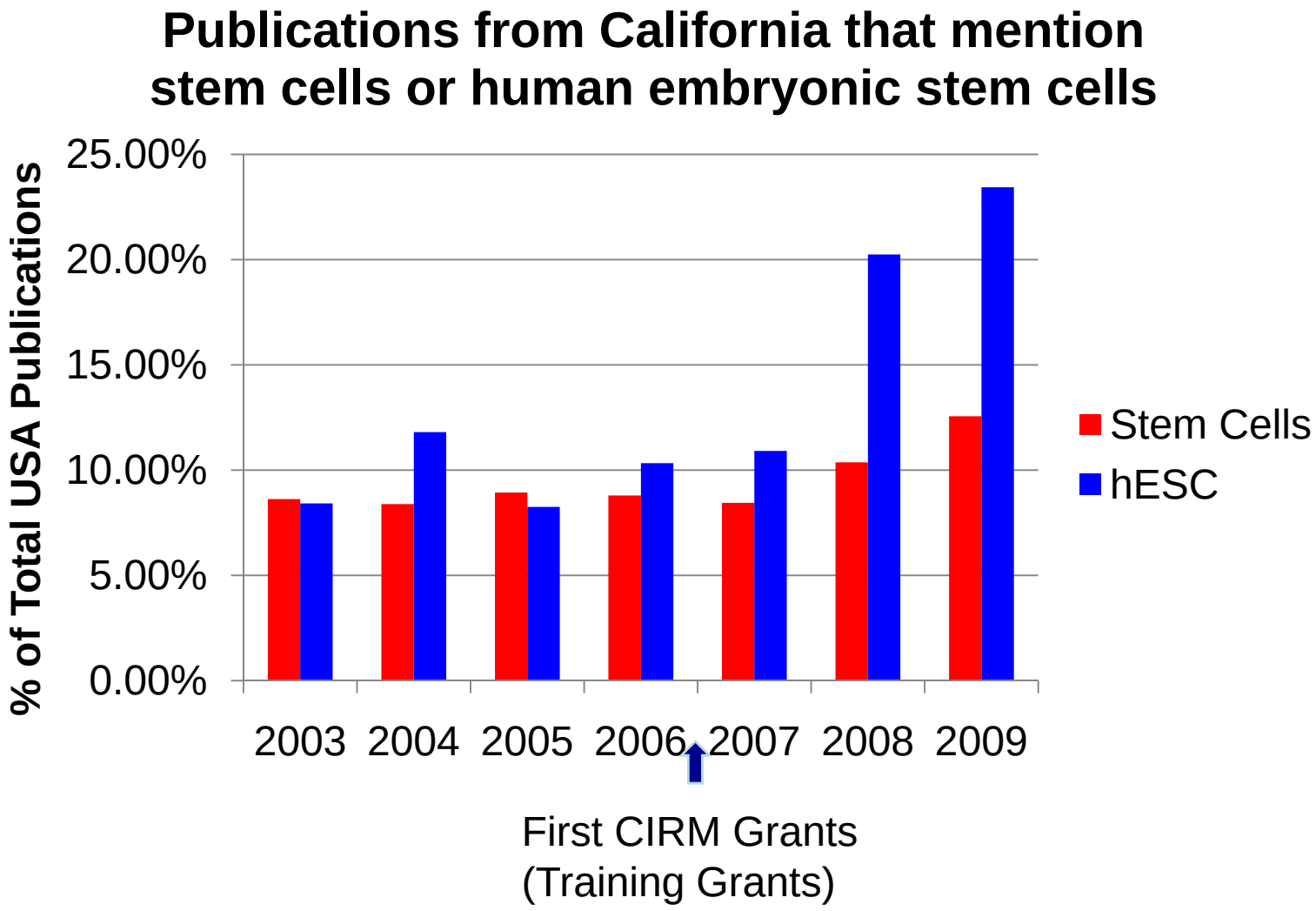
- A large chemical library was screened for proliferation of growth-arrested, reversibly immortalized mouse beta cells by using an automated high-throughput screening platform.
- A group of dihydropyridine (DHP) derivatives was shown to **reversibly induce beta-cell replication** in vitro by activating L-type calcium channels (LTCCs).
- The LTCC agonist 2a affects the expression of genes involved in cell cycle progression and cellular proliferation. Furthermore, treatment of beta cells with both LTCC agonist 2a and the Glp-1 receptor agonist Exendin-4 showed an **additive effect on beta-cell replication.**
- The identification of small molecules that induce beta-cell proliferation suggests that it may be possible to **reversibly expand other quiescent cells** to overcome deficits associated with degenerative and/or autoimmune diseases



Researchers in California are publishing more papers on stem cells and human embryonic stem cells

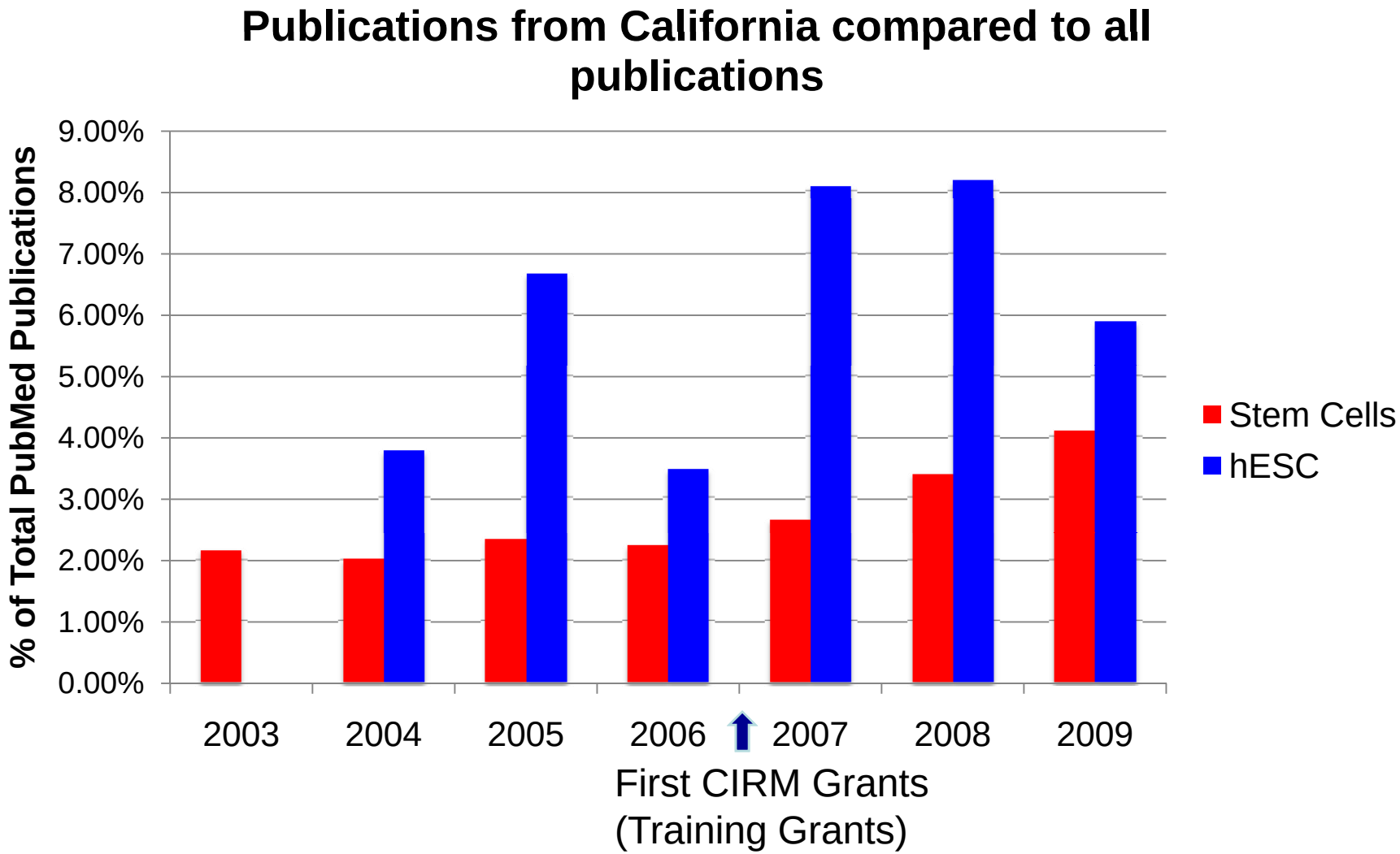


California institutions are increasing their representation in the hESC field



Publications with “stem cells” or “human embryonic stem cell” in their title or abstract

Note: these have very small n values



Personnel

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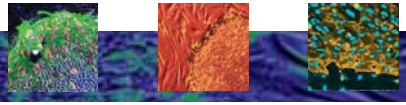
Kelly Shepard
Science Officer
(Parallel Synthesis Tech)

Rebecca Jorgenson
Science Officer (NIH)



President's Priorities

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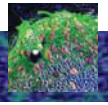
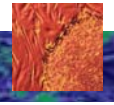
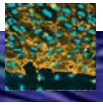
- Revision of the 2006 Strategic Plan
  - Meeting with Industry
  - Meetings with the Public
- Science and Research capability Meetings with Institutions and Commercial Groups
- Planning Financial and Strategic Adjustments to CIRM Activities
- Focus on Autism Opportunities for CIRM
- Examining Opportunities for Small Molecule Discoveries in Regenerative Medicine
- Developing Networks in US Science and Industry

Grant Reviews Completed

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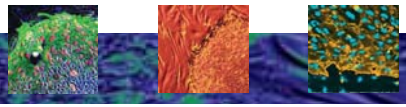
- **Early Translational Research**

  -GWG Review – February 09

  -ICOC Approval – April 09



Upcoming RFAs

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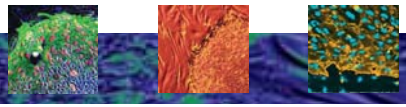
- **Basic Research Initiative I**
  - **RFA Released – December 08**
  - **GWG Review – June 09**
  - **ICOC Approval – August 09**
- **Disease Team Research Awards**
  - **RFA Released - February 09**
  - **Pre-Applications – March 09**
  - **GWG Review - Sept 09**
  - **ICOC Approval - Fall 09**



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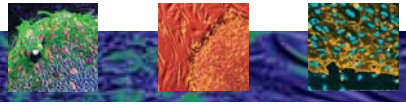
2008-09 Budget Allocation and Expenditure Report

As of January 31, 2008



Description	Budget Allocation	Expenditures Posted 7/1/08-1/31/08	Available Budget Allocation 2/1/09-6/30/09	Percentage of Budget Allocation Posted
Personnel Services				
Salaries and Benefits	**7,045,371**	**2,960,848**	**4,084,523**	**42%**
Operating Expenses and Equipment				
Interagency Agreements	491,000	140,164	350,836	29%
External Contracts	2,716,092	906,355	1,809,737	33%
ICOC, Science, WG Mtgs	1,574,175	343,340	1,230,835	22%
Other Travel	557,600	88,033	469,567	16%
Furniture and Equipment (Non-IT)	38,000	1,689	36,311	4%
Information Technology	52,770	20,551	32,219	39%
Other O.E.&E.	899,850	193,545	706,305	22%
Total Operating Exp and Equip	**6,329,487**	**1,693,678**	**4,635,809**	**27%**
Total CIRM Support Expenditures	**13,374,858**	**4,654,526**	**8,720,332**	**35%**

CIRM Audit Report FY 2007/2008

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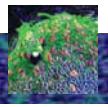
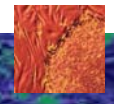
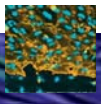
Macias Gini & O'Connell

Proposed CIRM Autism Workshop: May 28-29

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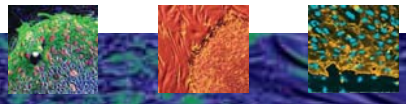
- Organizers: M. Csete & A. Nigh; Moderator: E. Penhoet
- Information gathering from multidisciplinary experts
  - -Not promoting any particular research agenda
- Interactive panels (Day 1)
  - -Update on pathophysiology
  - -Diverse animal models
  - -Disease in a dish (stem cell-based models)
  - -Current 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?

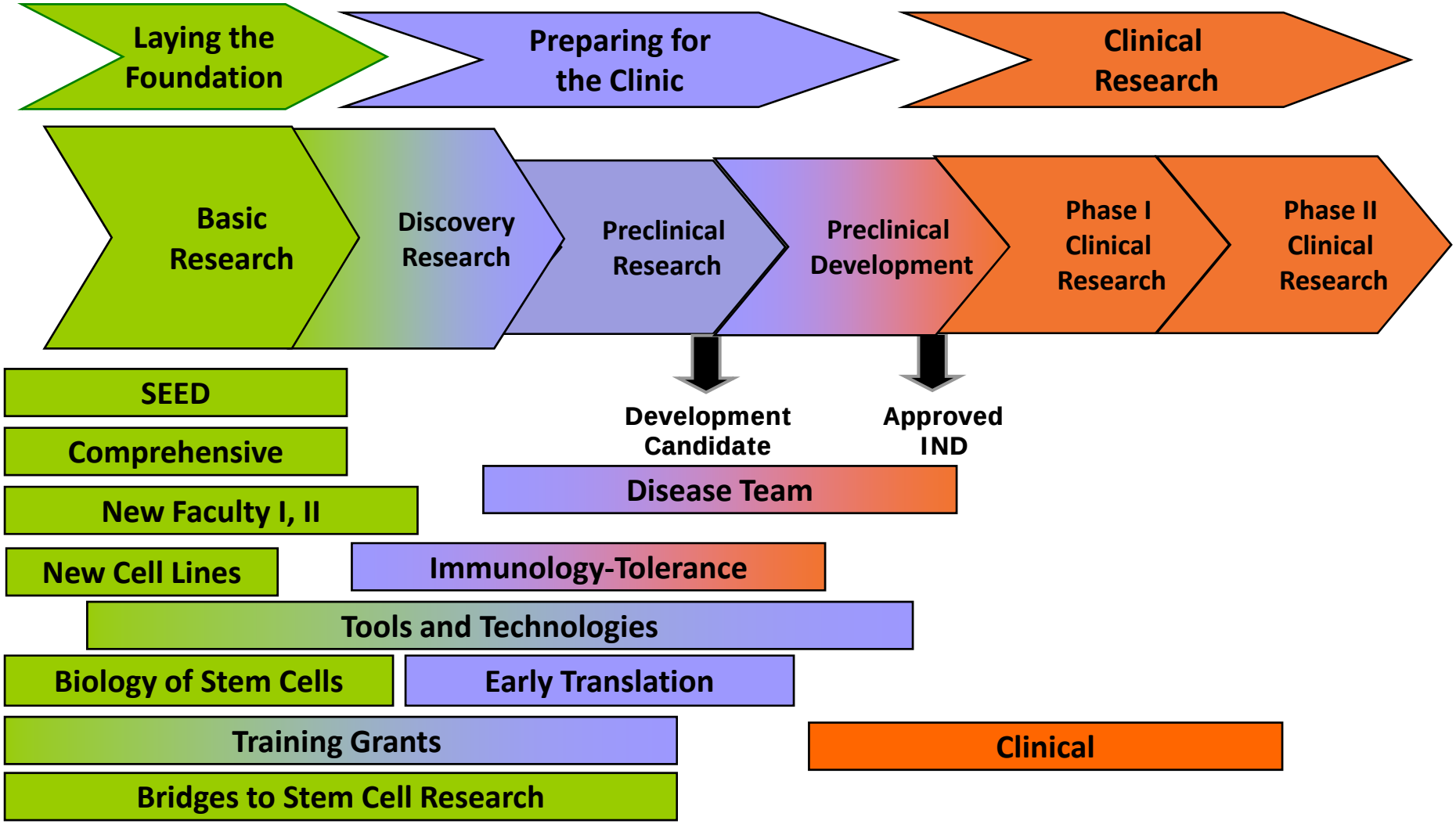


Staff Scientific Funding Priorities

Program	Budget	Expenditure (thru 12/31/10)
1. Early Translation (initial)	36.5	18.2
2. Bridges	17.5	8.8
3. Disease Team (initial)	105.0	26.2
4. Basic Biology 1 (initial)	10.0	3.3
5. Basic Biology 2 (initial)	10.0	1.7
6. Immunology	30.0	2.5
7. Training 2 (delay 12 months)	40.6	6.8
8. Disease Team (balance)	105.0	26.3
9. Basic Biology 1 (balance)	20.0	6.7
10. Basic Biology 2 (balance)	20.0	3.3
11. Tools and Technology 2	30.0	0
12. Early Translation (balance)	23.5	11.7

Moving the Pipeline Forward:

Awarded and Upcoming Funding Initiatives



What is Going to the Clinic?

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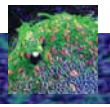
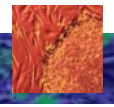
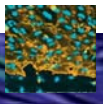
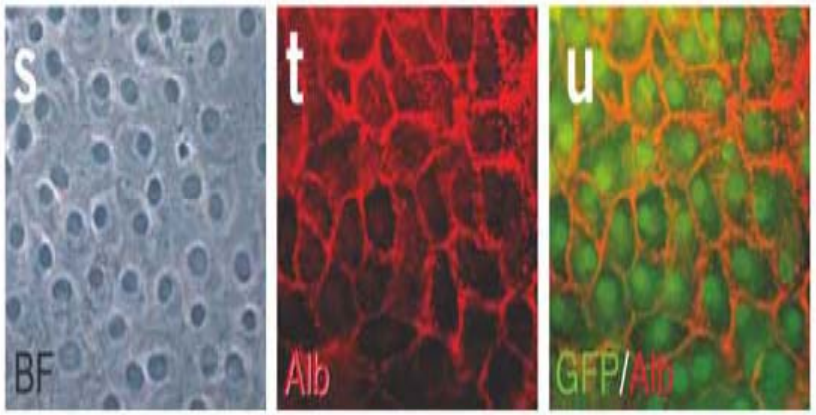
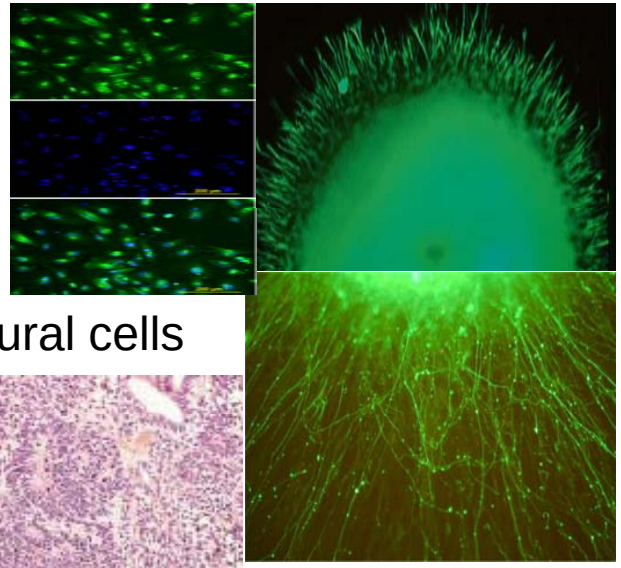
- Gerons hESC – oliogodendrocyte transplants for spinal injury
- Mesenchymal Stem Cells for Immune Suppression, Heart Muscle Repair, Bone and Cartilage Repair, Pulmonary Fibrosis
- Neural Stem Cells for Lysosomal Storage Diseases
- Small Molecules for a Wide Range of Tissue Regenerative Indications Based on Stem Cell Assays
- Cancer, Haematopoietic Stem cell Expansion, Mobilization of Adult Stem Cells

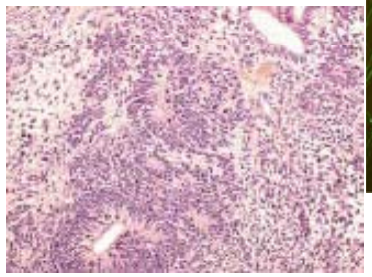


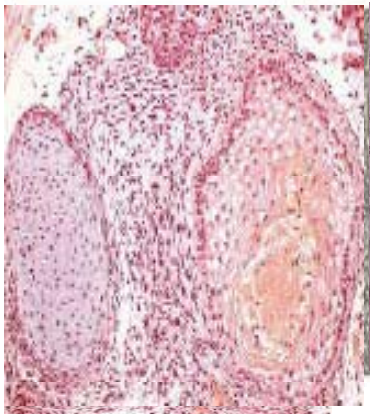
Pigmented Retinal Epithelium

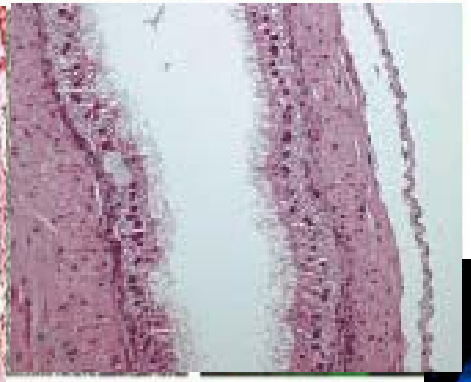


Cell Therapies

Neural cells

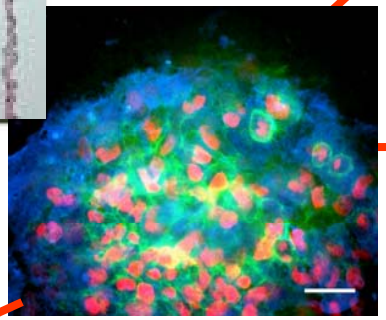




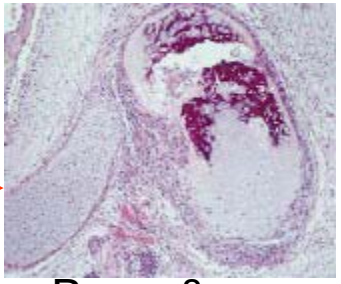


Cartilage & squamous epithelium

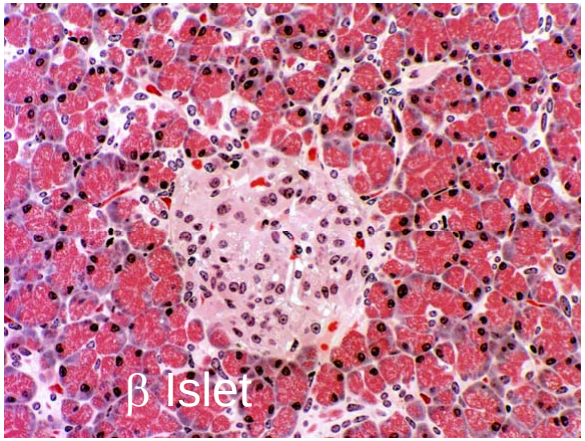
Ciliated columnar epithelium



Stem Cell Mobilization

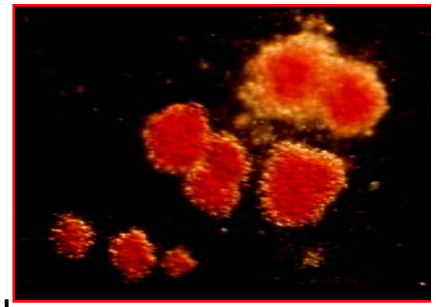


Bone & cartilage



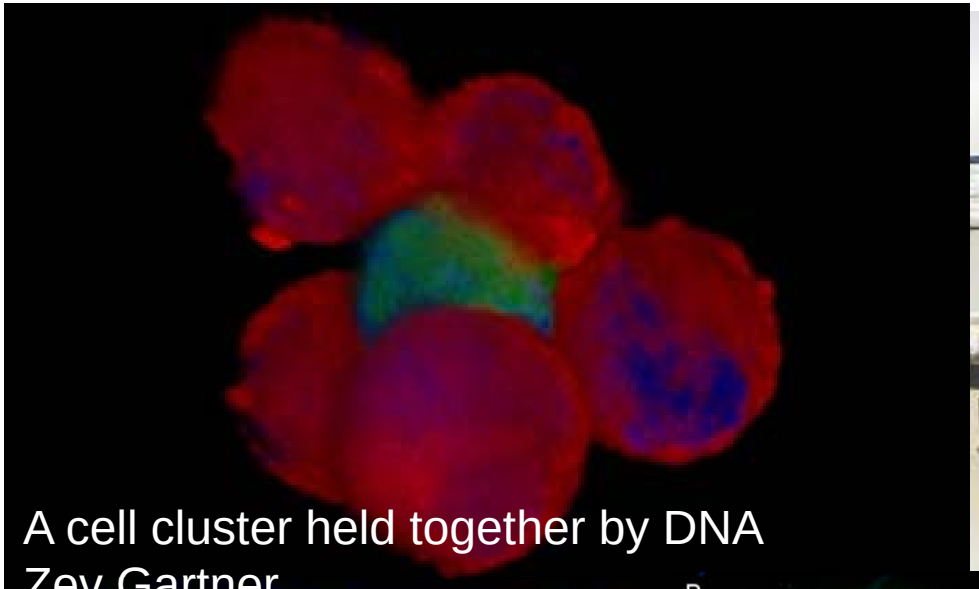
Small Molecules

Ganglion, gland & striated muscle

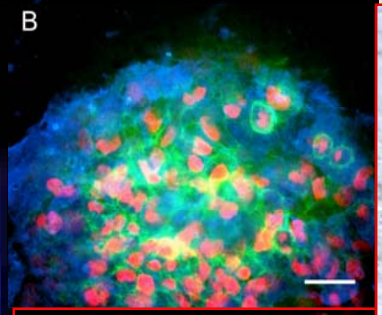


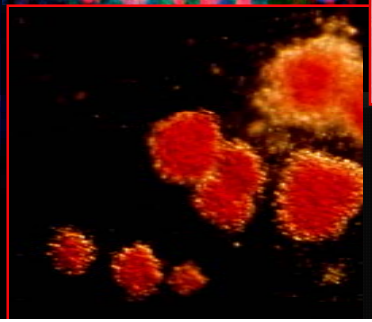
Blood

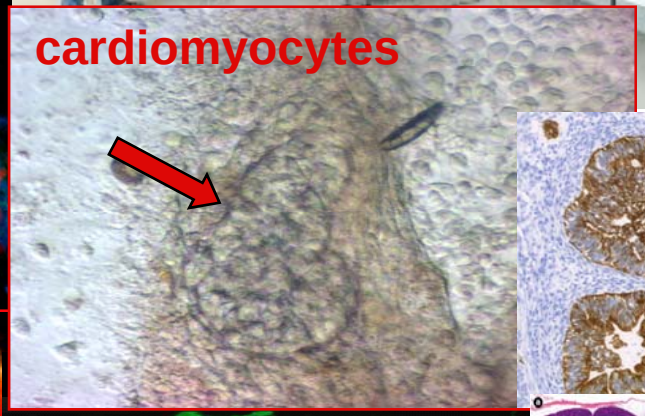
High Through-put Molecular Screening and Cell Production

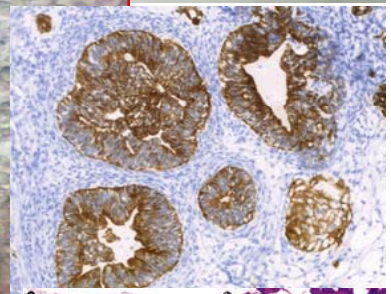


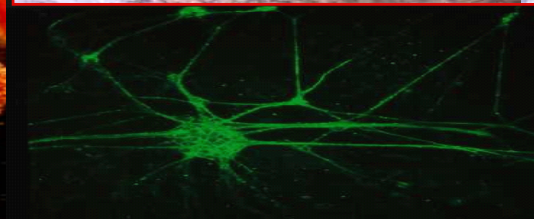
A cell cluster held together by DNA
Zev Gartner

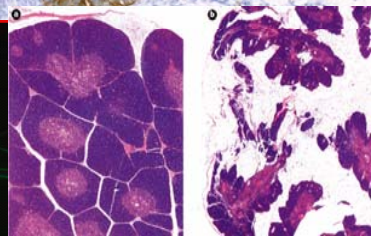












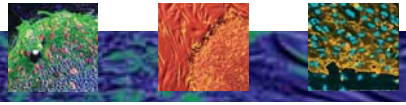
August 12 & 13, 2008

CRITICAL MASS: CO-LOCATE THE RESOURCES:
STATE OF THE ART EQUIPMENT: CREATE A COMPETITIVE AND SUPPORTIVE ENVIRONMENT: TRAIN TECHNICAL SUPPORT FOR RAPID GROWTH OF NEW FACILITIES AND INCOMING FACULTY/PIS

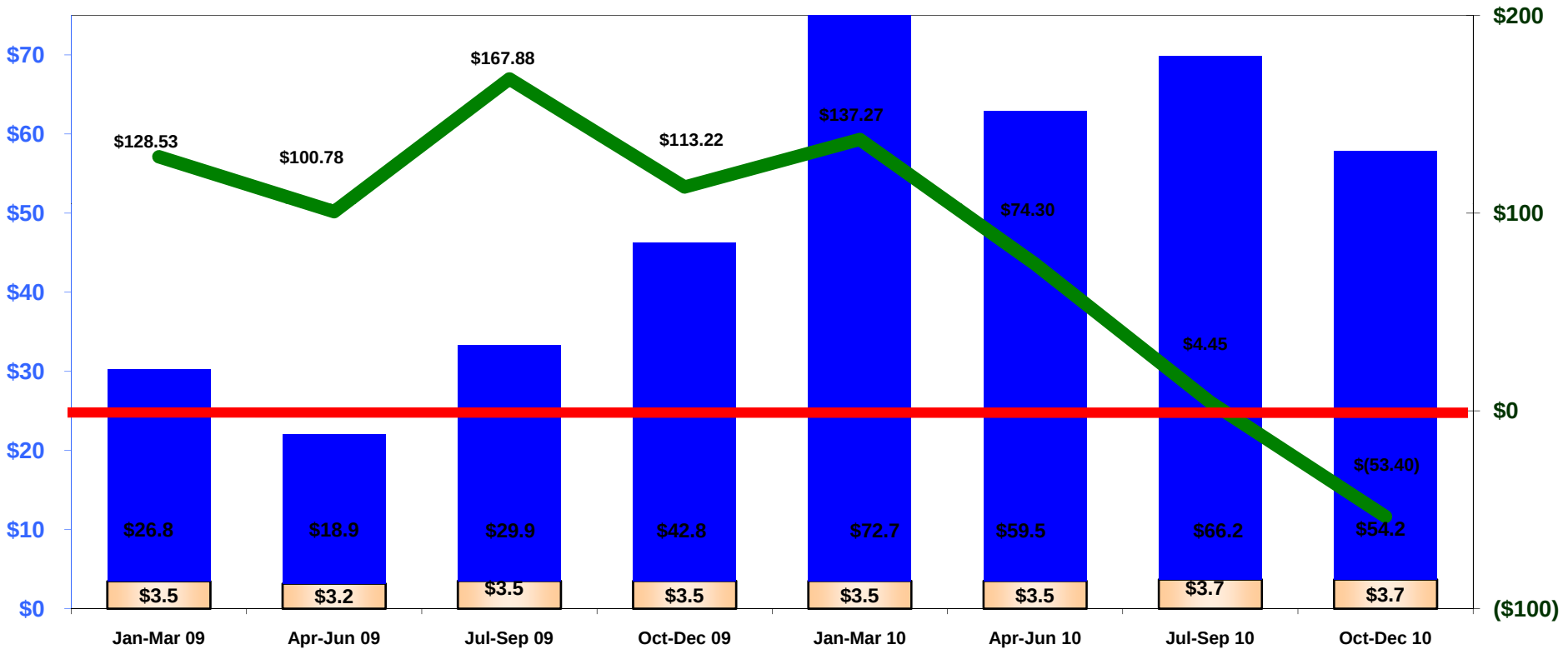
CIRM Programs
Concept-approved for Funding

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Program	Budget	Expenditure (thru 12/31/10)
Training 2	40.6	20.3
Bridges	17.5	8.8
Early Translation	60.0	30.0
Basic Biology 1	30.0	11.7
Disease Team	210.0	59.0
Basic Biology 2	30.0	5.0
TOTAL	388.1	134.8



CIRM Funding
Financial Implications to 12/31/10
(All concept approved programs)



Left Y Axis -
CIRM Administration (tan) and Grants (blue)

Right Y Axis –
Cash Balance at end of each quarter (green line)

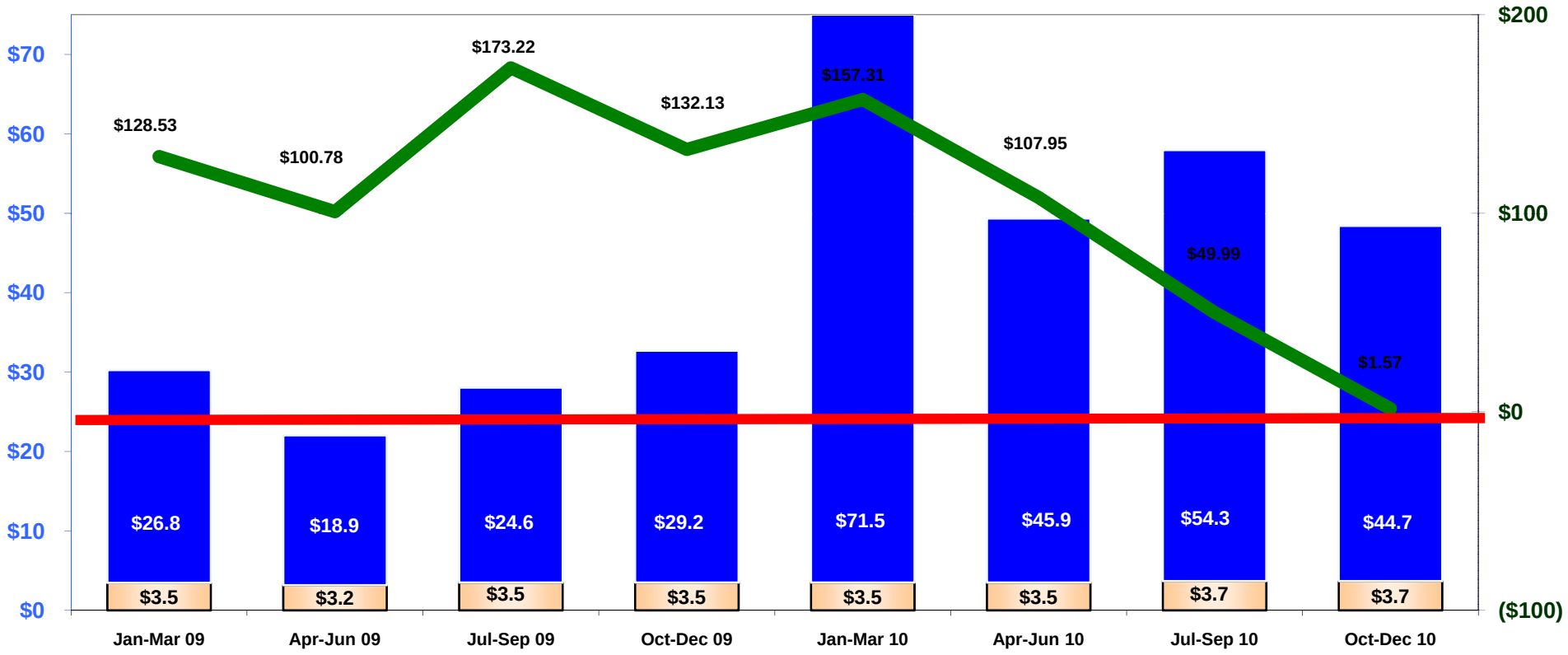
+ $100M

+ $100M

Staff Scientific Funding Priorities

Program	Budget	Expenditure (thru 12/31/10)
1. Early Translation (initial)	36.5	18.2
2. Bridges	17.5	8.8
3. Disease Team (initial)	105.0	26.2
4. Basic Biology 1 (initial)	10.0	3.3
5. Basic Biology 2 (initial)	10.0	1.7
6. Immunology	30.0	2.5
7. Training 2 (delay 12 months)	40.6	6.8
8. Disease Team (balance)	105.0	26.3
9. Basic Biology 1 (balance)	20.0	6.7
10. Basic Biology 2 (balance)	20.0	3.3
11. Tools and Technology 2	30.0	0
12. Early Translation (balance)	23.5	11.7

CIRM Priority Funding
Financial Implications to 12/31/10
(Early translation – Training 2)



Left Y Axis -
CIRM Administration (tan) and Grants (blue)

+ $100M

+ $100M

Right Y Axis –
Cash Balance at end of each quarter (green line)

CIRM Recommendations to the ICOC for programs reviewed by Grants Working Group

<u>Bridges</u> – Fund in full - $17.5M

<u>Training 2</u> – Delay funding for 12 months – grantee organizations could opt to self-fund programs and be reimbursed later.

<u>Early Translation</u> – Limit total funding to $36.5M

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