CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

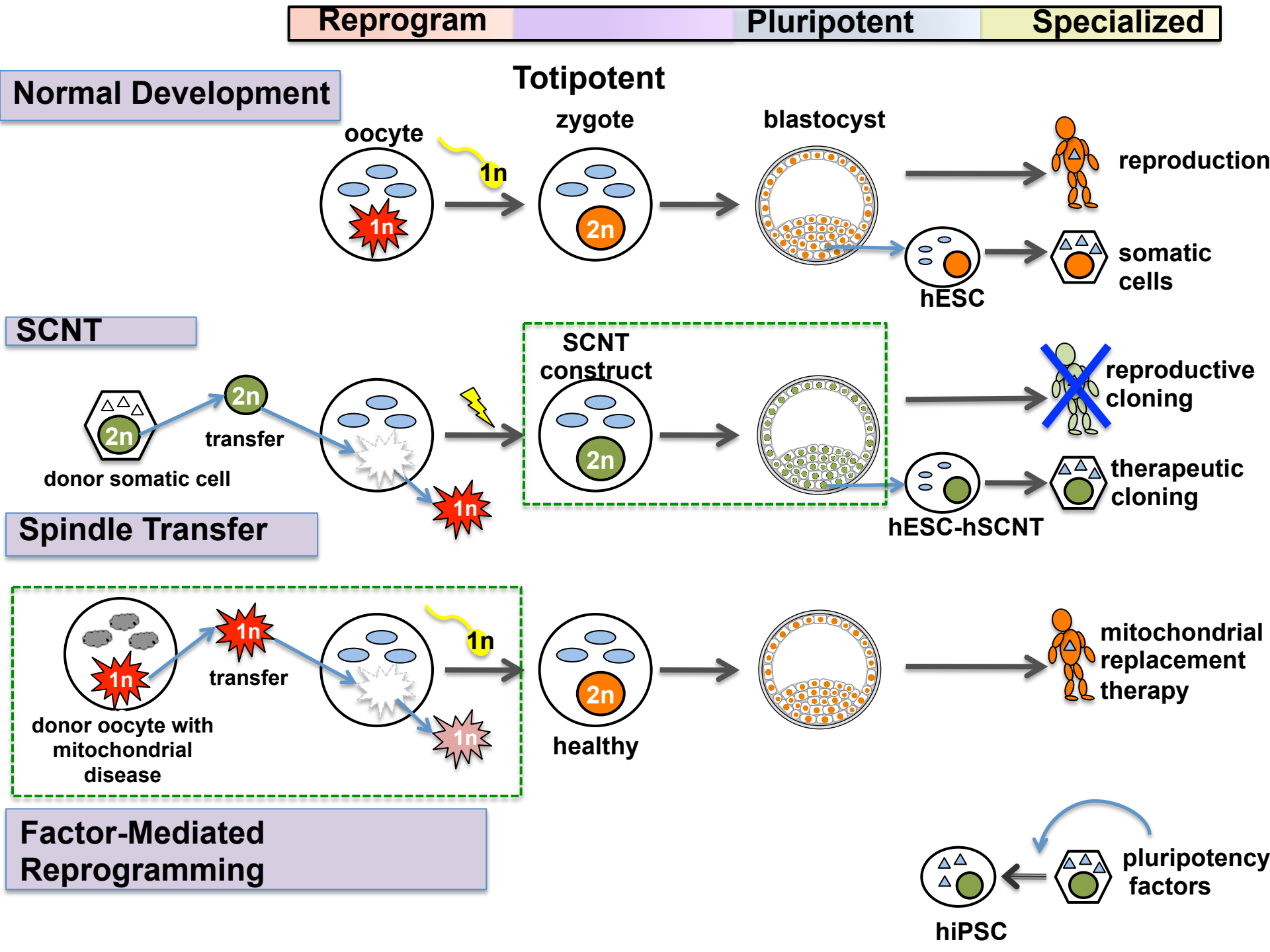
The state stem cell agency

President's Report

Alan O. Trounson

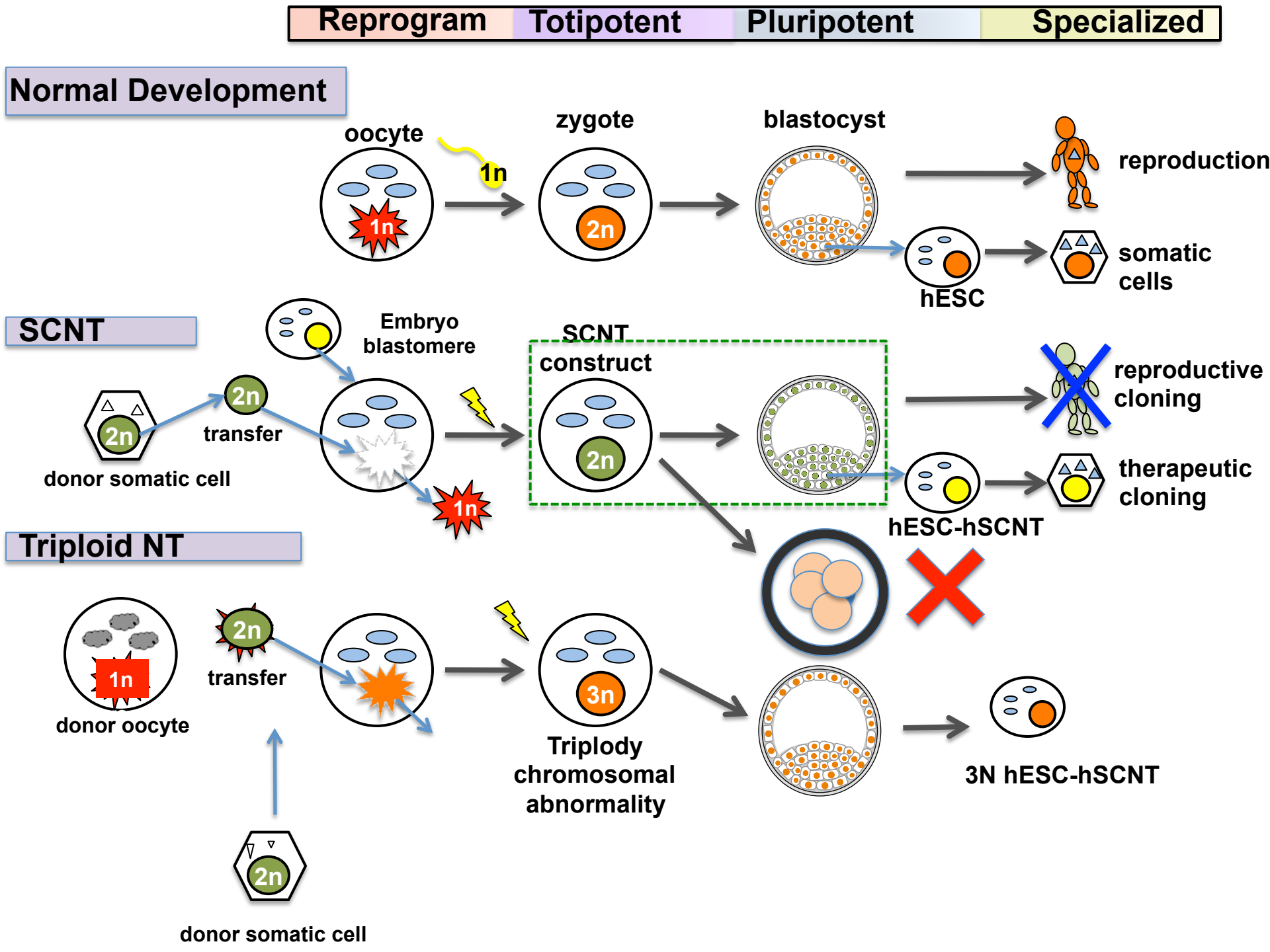
ICOC Meeting – October 2011

Irvine, CA


Reprogram
Pluripotent
Specialized
Normal Development
Totipotent
oocyte
zygote
blastocyst
1n
1n
2n
reproduction
hESC
somatic cells
SCNT
SCNT construct
2n
2n
transfer
donor somatic cell
1n
reproductive cloning
therapeutic cloning
hESC-hSCNT
Spindle Transfer
1n
1n
transfer
1n
donor oocyte with mitochondrial disease
2n
healthy
mitochondrial replacement therapy
Factor-Mediated Reprogramming
pluripotency factors
hiPSC

Human oocytes reprogram somatic cells to a pluripotent state. Noggle et. al., Elgi Lab NYSCF *Nature* Oct 2011 478:70-75

- SCNT embryos would not develop beyond a few cleavage stages [French et. al. grew blastocysts; monkey SCNT works for making reprogrammed ES cells]
- NT of diploid somatic cell into intact oocyte worked to produce blastocysts and rES cells BUT WERE TRIPLOID
- Triploid rES cells not very useful.
- Embryonic blastomere worked when injected into an enucleated oocyte + parthenogenetic activation of an intact oocyte produced blastocysts
- Therefore something wrong with somatic nucleus
- What is the next experiment?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2n
2n
transfer
donor somatic cell
1n
therapeutic cloning
hESC-hSCNT
Triploid NT
1n
donor oocyte
2n
transfer
3n
Triplody chromosomal abnormality
3N hESC-hSCNT
2n
donor somatic cell

"Donor Myocardial Infarction Impairs the Therapeutic Potential of Bone Marrow Cells by anInterleukin-1–Mediated Inflammatory Response" Wang etal M Springer Lab UCSF *Science Translational Med.* 14th Sept 2011

- Bone marrow (BM) infusions in mice result in improved cardiac function in mice but show little improvement in myocardial infarction in patients. Why?
- Showed autologous BM from mice with MI had impaired efficiency in repair because of the increased inflammatory state of BM
- This impairment was prevented by giving the MI mice anti-inflammatory drugs or interleukin-1 inhibitor after MI
- Raises the issue of when to collect BM cells for MI and whether it is appropriate to suppress inflammatory response in MI patients.

“Corridors of migrating neurons in the human brain and their decline during infancy” Sanai etal. Arturo Alvarez-Buylla’s Lab UCSF Nature Oct 2011

- The subventriucular zone is where there are many neural stem cells destined to migrate to the olfactory bulb in non-human mammals
- They form a migratory stream
- Adult human is different – has a hypocellular gap separating the ependymal lining from a periventricular ribbon of astrocytes
- Show that the infant human has a subventricular zone and a rostral migratory stream with robust corridor of migrating immature neurons before 18 months of age
- This subsides in older children and almost extinct in adulthood
- These neurones are not all destined for the olfactory bulb but is a stream that targets the prefrontal cortex which is a site for major neural maturation – learning and memory and cognitive tasks in adulthood. This is a very important and sensitive region susceptible to damage and resultant handicap

Evaluating the Genomic and Sequence Integrity of human ES cell lines; Comparison to Normal Genomes
Funk et al, *Stem Cell Research* October 2011 doi:10.1016

- 5 hES cells were derived under GMP compliant conditions– do they have chromosomal rearrangements or high rate of mutations? Can transplantation and presence of disease gene variants be detected?
  - In early passage, the cells did not differ from genomes of normal individuals in terms of copy number variation and sequence variation
  - Important gene classes like tumor suppressors and disease genes did not show overt changes in gene expression
  - The identity of important transplantation antigens (HLA, blood type) and ApoE gene (associated with Alzheimer's and cardiovascular disease) was also characterized. No deleterious ApoE variants were detected
  - Classical karyotypic abnormalities emerged only in late stage cultures and could be detected even when present in only a small percentage of cells.

Genome sequencing of mouse induced pluripotent stem cells reveals retroelement stability and infrequent DNA rearrangement during Reprogramming
Quinlan et al *Cell Stem Cell* 9, 366-373 October 2011

Earlier studies have shown there is high levels of genome structural variation in human iPSCs compared with fibroblasts. Is reprogramming inherently mutagenic?

- These authors performed whole genome sequencing and analysis of 3 iPSC lines and their parent fibroblasts using a method with 30 fold greater resolution than earlier studies
- They detected only one de novo copy number variation event in one of the lines
- 79% of structural variation (SVs) breakpoints were also found in parental cells
- Of the 45 de novo SVs detected:
  - 41 were insertions of exogenous retroelement (probably batch specific from feeder cells)
  - 4 were canonical deletions, duplications or inversions
- No evidence of endogenous retroelement transposition

Conclusions: In contrast with earlier studies on human IPSCs, very few de novo SVs exist in the studied mouse iPSC lines, at least in early passages. More studies are needed to determine if this is related to reprogramming method, or onherent differences in the mouse and human lines.

Upcoming RFAs

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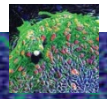
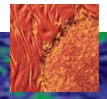
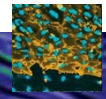
- **Disease Team Therapy Development**
  - Part 1 Planning Funding period begun September 1
  - Part 2 Research Award Posted – September 2011
- **Early Translational III**
  - GWG Review of Applications – March 2012
- **Basic Biology IV**
  - Concept proposal - October 2011
- **Creativity Awards**
  - Concept Proposal – October 2011
- **iPSC Initiative**
  - Concept Proposal – December 2011

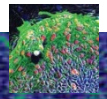
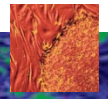
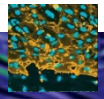




CFP Update

- NIH MOU and the Scotland MOU's were signed in September
- In the ET III RFA, potential CFPs are Australia, China, Germany and Japan. This is our first joint funding effort with China and with Australia (NHMRC).

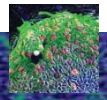
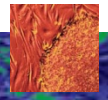
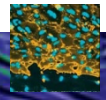
CIRM Collaboration with NIH

- Goal is to bring NIH and CIRM researcher expertise together to accelerate clinical and translational stem cell and regenerative medicine research
- Among the potential areas of collaboration:
  - Rare and neglected diseases
  - Early translation and/or basic biology
  - CIRM funded Disease team therapy development researchers and NIH intramural scientists in early preclinical/early clinical development and clinical trials
  - Access to NIH clinical center training to CIRM investigators or visiting fellowship programs, or a visiting guest researcher program
  - Access to apply to National Chemical Genomics Center to utilize samples and assays in high throughput screening assays

CIRM Collaboration with NIH (cont)

- MOU executed on September 2, 2011, and kick-off meeting held October 24, 2011 at NIH
- Signatories
  - Alan Trounson, PhD, President CIRM
  - Story Landis, PhD, Director NINDS, and NIH stem cell task force
  - Michael Gottesman, MD Deputy Director for Intramural Research, NIH
- Points of Contact for each agency
  - Ellen Feigal, MD, SVP R & D CIRM
  - Mahendra Rao PhD, Director NIH Center for Regenerative Medicine

CIRM-CP Workshop Report

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

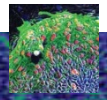
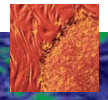
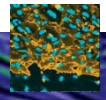
Goal

- Review our current understanding of neurobiological defects underlying cerebral palsy (CP) & to identify emerging areas of therapeutic development

- Explore the role that stem cell research might have on the development of therapies for Neurological disorders of childhood (NDCs)

Outcomes

- raise awareness of CP & other NDCs among stem cell scientists
- encourage stem cell community to expand its studies on:
  - human neural and glial development
  - effect of injury and timing of injury
- explore funding opportunities for basic and clinical research on CP and related developing disorders in humans

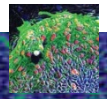
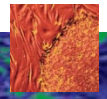
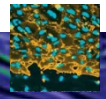
CIRM-CP Workshop Report (cont)

NDCs as priority areas for stem cell research

- understudied
- amenable to in vitro studies using human stem cells and iPSCs
- good candidate for cell therapy in the brain

Moving Forward: Stem Cells and CP

- mechanisms in endogenous stem cells and animal models
- *in vitro* human models of CP

Organizational Structure of the CIRM Basic & Clinical CP research collaboratives

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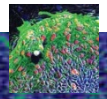
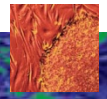
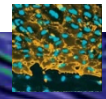
CIRM CP Collaborative Network

Goals	Basic / Preclinical	Clinical Development
	*Define appropriate preclinical models (*in vitro & in vivo*) *Animal models of CP *Perform cell-based & drug preclinical screens	* Select agents for IND & Phase I *Perform Phase I/II trials *Identify short-term biomarkers of brain injury, treatment efficacy (imaging, genetic, protein, metabolic) * Engage biotech industry *Long-term follow up

CIRM Immunology Roundtable with the FDA on October 24, 2011

- CIRM Roundtable is part of an ongoing series of interactive and educational collaborations with the FDA to address challenges or bottlenecks on the regulatory pathway for stem cell-based therapies
  - October 24th Roundtable brought together researchers, including CIRM funded investigators, with the FDA in an interactive one-day meeting that focused on the immune response challenges in bring stem cell-based therapies towards and into the clinic

Roundtable focused on approaches to address immune response challenges

- Built upon CIRM's immune response workshop from 2009, and areas covered included:
  - Strategies for inducing immune tolerance
  - Predictive assays for rejection or tolerance
    - Non-invasive assays, e.g., bioimaging
    - Lab based assays
  - Disease models
    - Issues of alloreactivity must be studied in the context of specific diseases, considering particular transplant paradigm and the tissue
    - Differences between alloreactivity and xenoreactivity complicate analysis of studies in which human cells transplanted in nonhuman animal models

Statement regarding CIRM's Consideration of Therapy Development Projects

- CIRM has historically balanced its obligation to provide information to the public with its responsibility to protect the proprietary information of applicants.

- Engaging industry requires that CIRM assure the companies with which it works of CIRM's capacity to protect the companies' proprietary information and their ability to obtain follow-on financing. This is particularly true for companies involved in clinical research

Alpha Clinics: stakeholder input

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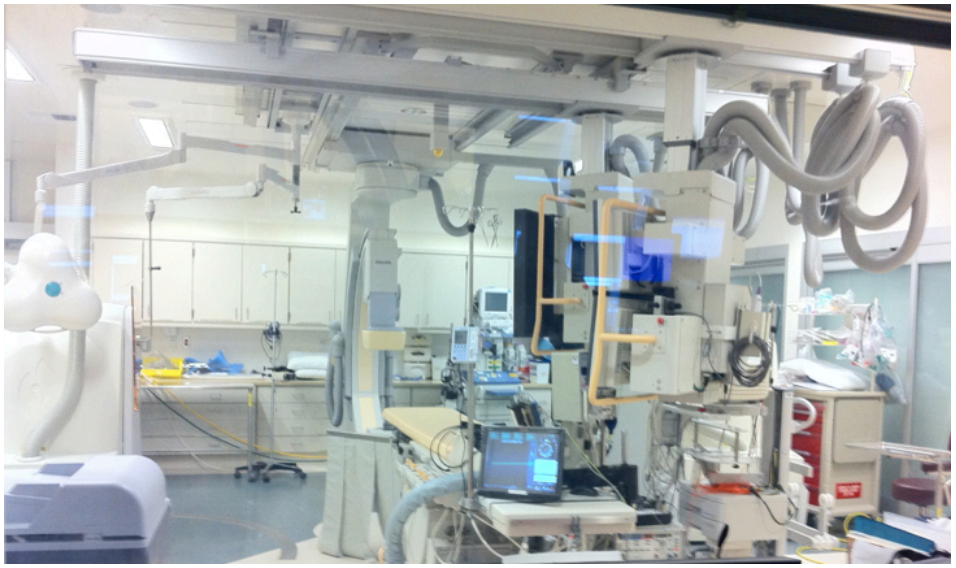
Alpha Stem Cell Clinics

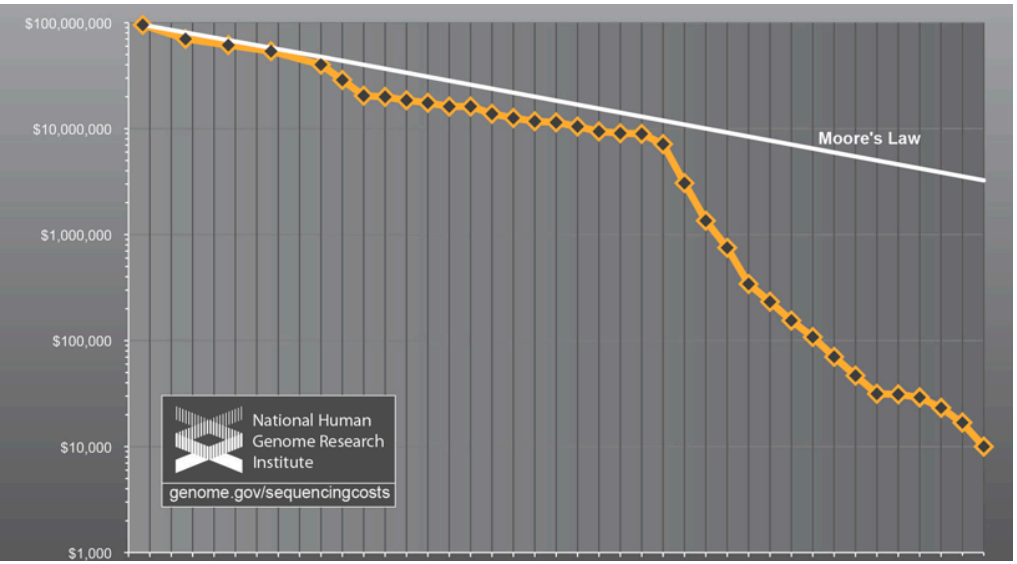
Develop knowledge infrastructure for cell therapies in clinical trials and beyond

- Build expertise of medical and clinical trial staff
- Facilitate regulatory compliance
- Build informational networks
- Establish standards for cell handling, patient care and assessing outcomes
- Test business models for bringing cell therapies to marketplace



The UCD cardiac catheterization clinic

Genomics: stakeholder input



Stem cell genomics

Provide California scientists and clinicians access to technologies for analyzing stem cell genomes.

- Understanding the variability of stem cells
  - Improving handling
  - Characterization
- Develop new methods for single cell genome sequencing and quantitative analytics
- Stratifying cancer patients to target therapies to the right patients

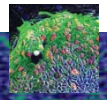
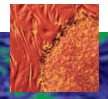
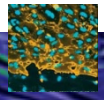
ARM Committee Updates October 2011

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- **Voted on a slate of nominees for the Executive Committee**
- ARM membership continues to grow with more than 85 member organizations. In addition, its activities expand.

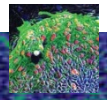
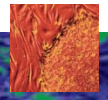
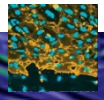
Recent developments include:

- an upcoming meeting with FDA/CBER Office of Cell, Tissue and Gene Therapy Director Celia Witten to discuss cell potency assay development and validation.
- recent meetings with congressional health leadership to advocate for the Regenerative Medicine Promotion Act.
- a briefing for the US House of Representatives Tri-Caucus
- the upcoming Stem Cell on the Mesa meeting held in conjunction with CIRM and the Sanford Consortium.

World Stem Cell Summit

- **Estimated 1,400 attended some portion of event**
  - 125 on CIRM Scholarships
    - 98 young investigators
    - 27 patient advocates
- **CIRM at the podium for 48 presentations**
  - 34 by CIRM grantees
  - 10 by members of CIRM management team
  - 4 by CIRM board members (incl. Chair Emeritus)
- **CIRM hosted a reception for advocates**
  - Jon Thomas told the CIRM story
  - Afterward Sherry Lansing received a leadership award for ICOC role
- **The program theme was translational science**
  - We had requested this as a condition of participation
  - Don Gibbons served on the program committee to ensure it

Stem Cell Awareness Day 2011

- **Events: lab tours, public symposia, even an animal fair**
  - 30 in California
  - (Davis event included two ponies and a dog treated with stem cells)
  - 15 in other states and six countries
- **Reaching high school students**
  - 60 classrooms had CIRM grantee guest lectures
  - More than 15 classes bused to CIRM funded labs (Gladstone and Irvine)
- **CIRM Patient Advocacy Days**
  - October 22 in Bakersfield, Jon Thomas to keynote
  - October 29 in Santa Rosa, Art Torres to keynote

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

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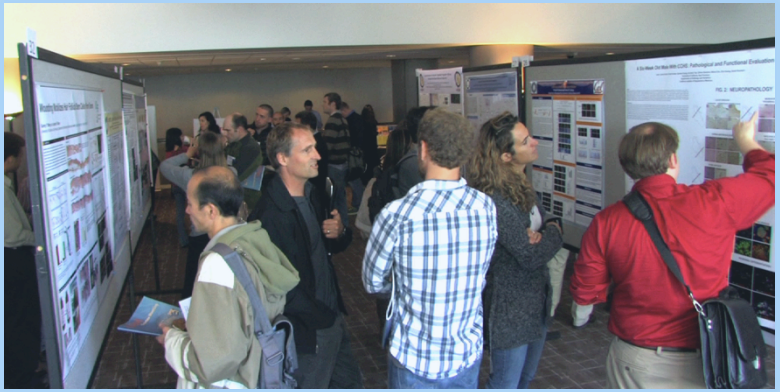
- **Attendance:**
  - ~ 400 CIRM-funded investigators, program directors, trainees
  - Partner-PIs, CFP representatives
- **Purpose:**
  - Scientific exchange / CIRM grantee networking
  - Outreach to grantees:
  - Communications workshop
  - Target Product Profile workshop
  - Panel Discussion on Commercialization
  - California vendor booths



- **Highlights:**
  - Showcasing CIRM- and CFP-funded cutting edge research – basic and translational
  - Poster session – ~ 150 posters
  - Focus areas with prominent speakers
  - Genomics - Craig Venter
  - Systems Biology – Leroy Hood
  - Fulfilling the promise – John Wagner – video on CIRM's web site is must see!

CIRM Tissue Engineering Workshop: *Engineering Strategies, Opportunities, and Challenges for Tissue Repair and Regeneration*

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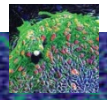
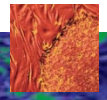
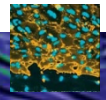
- Goal: To educate ICOC members and CIRM staff on the opportunities for stem cell use in tissue engineering through a series of scientific talks and moderated group discussions
- When / Where: Thursday-Friday, January 12-13, 2012 in Downtown San Francisco
- Internationally renowned leaders in the field have confirmed their attendance
- Closed meeting; Cold Spring Harbor rules to enable free discussion of unpublished results

New Appointments

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- Candace Bagley, Senior Executive Assistant to the President, 10/3/11
- Melanie Miller, Administrative Assistant to the General Counsel, 9/26/11
- Anka Urbahn, Program Manager, 9/19/11
- Kim Williams, Administrative Assistant to Executive Director of Scientific Activities, 9/6/11

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The state stem cell agency

2010-11 Budget Allocation and Expenditure Report

Final Report

Fiscal Year 2010-11
Expenditures Posted Through June 2011