CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

President's Report

ICOC Meeting

June 2009

Agenda Item # 7

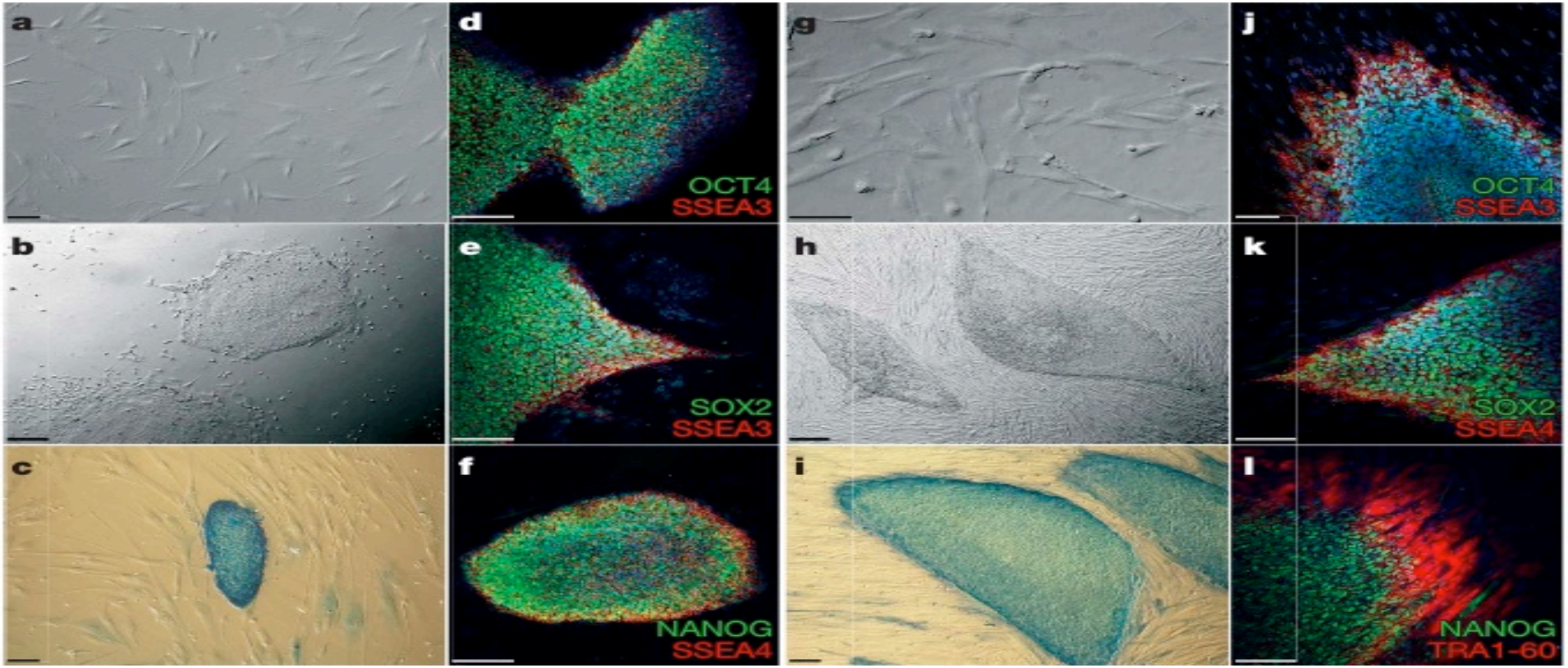
Fanconi anaemia corrected in cells

Angel Raya, Ignasi Rodrıguez-Piza, Guillermo Guenechea, Rita Vassena, Susana Navarro, Marıa Jose Barrero, Antonella Consiglio, Maria Castella, Paula Rıo, Eduard Sleep, Federico Gonzalez, Gustavo Tiscornia, Elena Garreta, Trond Aasen, Anna Veiga, Inder M. Verma, Jordi Surralles, Juan Bueren & Juan Carlos Izpisua Belmonte
Center for Regenerative Medicine in Barcelona, Salk Institute La Jolla,
Nature June 2009

- Prepared skin biopsies from patients with a variety of genetic mutations that express as Franconi Anaemia (FA) – corrected the gene defect by using gene therapy
- The genetically corrected cells were reprogrammed to make lines of iPS cells
- The iPS cells were differentiated into haematopoietic progenitors of the erythroid and myeloid lineages
- FA-iPS-derived haematopoietic progenitors maintained the disease-free phenotype

Fanconi anaemia corrected in cells

FA is a relatively common genetic disease that cannot be corrected by viral-vector gene therapy. Corrected iPS cells offer a very attractive avenue to correct the disease – demonstrated as proof of concept in vitro in this important study



Remyelination is induced by hESC transplant in a mouse model of multiple sclerosis (MS)

Maya N. Hatch, Chris S. Schaumburg, Thomas E. Lane, Hans S. Keirstead
UC Irvine, *J Neuroimmunology* June 2009

- Examined capacity of hESC-derived oligodendrocyte precursor cells (OPCs) to integrate and remyelinate CNS neurones in mice with neuropathogenesis resembling MS.
- Transplanted hESC-derived OPCs were not able to survive within recipient mice for longer than 2 weeks post- transplant even with immunosuppressive regimes
- Despite the absence of human OPCs at 3 weeks, remyelination and reduced demyelation was seen at the site of transplantation.
- Oligodendrocytes secrete a variety of neurotrophic factors that aid in recovery suggesting a trophic effect of OPCs.
- “long-term survival of human allograft transplants faces significant hurdles in neurologic diseases associated with robust and widespread neuroinflammation”

Long-term Safety and Function of Retinal Pigment Epithelium from hESCs in Models of Macular Degeneration

Lu B, Malcuit C, Wang S, Girman S, Francis P, Lemieux L, Lanza R, Lund R,
Casey Eye Institute, Oregon Health & Science University, *Stem Cells* 2009 Jun 11

- Two important early potential hESC applications are the use of retinal pigment epithelium (RPE) for the treatment of age-related macular degeneration and Stargardt disease, an untreatable form of macular dystrophy
- Showed long-term functional rescue using hESC-derived RPE in both the RCS rat and Elov14 mouse, animal models of retinal degeneration and Stargardt, respectively
- GMP-compliant hESC-RPE survived subretinal transplantation in RCS rats for prolonged periods (>220 days). The cells sustained visual function and photoreceptor integrity in a dose dependent fashion without teratoma formation or untoward pathological reactions.
- Near-normal functional measurements were recorded at >60 days survival in RCS rats
- A GLP-compliant study was carried out in the NIH III immune deficient mouse model. Long-term data (spanning the life of the animals) revealed no gross or microscopic evidence of teratoma/tumor formation after subretinal hESC-RPE transplantation.
- These results suggest that hESCs could serve as a potentially safe and inexhaustible source of RPE for the efficacious treatment of a range of retinal degenerative diseases

Directed differentiation of hESCs towards kidney precursors showed pathways similar to that in the rhesus monkey

Batchelder CA, Lee CC, Matsell DG, Yoder MC, Tarantal AF, UC Davis, *Differentiation* 2009 Jun 3.

- A model of gene expression based on human and nonhuman primate kidney development was created and incorporated into studies of hESC differentiation
- Directed hESC differentiation was also evaluated various culture substrate conditions
- Spontaneous hESC differentiation revealed markers of metanephric mesenchyme that increased over time, followed by upregulation of kidney precursor markers
- Studies show monkey and human kidney differentiation markers are similar and will be useful in modeling hESC differentiation and transplantation

N-Myc regulates expression of pluripotency genes in neuroblastoma

Cotterman R, Knoepfler PS, UC Davis, *PLoS ONE*. 2009 Jun 4;4(6):e5799

- Myc genes are best known for causing tumors when overexpressed, but recent studies suggest endogenous Myc regulates pluripotency and self-renewal of stem cells.
- Amongst putative N-Myc target genes in expression microarray studies in neuroblastoma were lif and three additional important embryonic stem cell (ESC)-related factors that are linked to production of iPSC: klf2, klf4, and lin28b
- N-Myc regulates overlapping stem-related gene expression programs in neuroblastoma and ESC, supporting a novel model by which amplification of the N-Myc gene may drive formation of neuroblastoma
- These data also suggest mechanisms by which Myc proteins more generally contribute to maintenance of pluripotency and self-renewal of ESC as well as to iPSC formation.

Generation of T cells from human embryonic stem cell-derived hematopoietic zones

Timmermans F, Velghe I, Vanwalleghem L, De Smedt M, Van Coppernolle S, Taghon T, Moore HD, Leclercq G, Langerak AW, Kerre T, Plum J, Vandekerckhove B, Ghent University, Ghent, Belgium, *J Immunol.* 2009 Jun 1;182(11):6879-88

- Showed that T cells can be generated in vitro from hESC-derived hematopoietic precursor cells present in hematopoietic zones (HZs). These zones are morphologically similar to blood islands during embryonic development and are formed when hESC are cultured on OP9 stromal cells

- The mature T cells are polyclonal, proliferate, and secrete cytokines in response to mitogens. This protocol for the de novo generation of T cells from hESC could be clinically and scientifically relevant

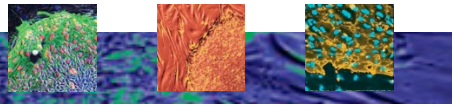
Personnel

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Elena White-Negrete

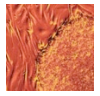
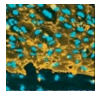
(Women's Foundation)

Grants Management Specialist II



National Linkages

- FDA – Proposals for regular consortium/ liaison update meetings on stem cell science, quality control and risk management
- NIH meeting – Working on harmonization of interests – collaborations
- State Stem Cell Agencies – Discussions underway for potential collaborations with several states

President's Priorities

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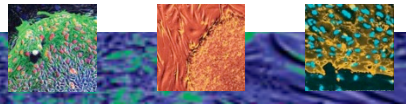
- Issues raised about CIRM IP Regs and Loans for companies
- Major Facilities Programs – completing processes
- Developing networks in US science and industry
- Working with Californian scientists on issues relating to CIRM
- CIRM Budget planning
- Continued development of a program of CIRM Awards for Exceptional Scientists
- Chair Swedish Research Council major facilities grants
- Dialogue established with major pharmaceutical interests
- CIRM-Victorian Gov. joint funding of Early Translation grants



Upcoming Grant Reviews

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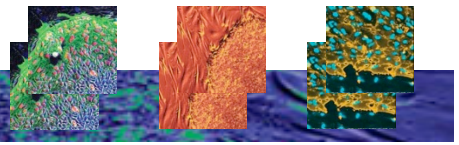
- **Basic Biology I – June 09**
- **Disease Teams I - Sept. 09**



Disease Team Research Award - Invited

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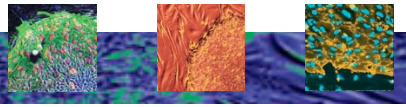
- 32 Preliminary Applications (Pre-Apps) Invited
  - 8 total apps with PI and/or CO-PI at For Profit institution
  - 28 Non-Profit (13 institutions)
- 9 designate an International Collaborative Funding Partner
- Evidence of new partnerships/collaborations within California
- hESC, iPSC and adult SC well represented
- Diversity of therapeutic approaches
  - Approximately 4/5 are cell therapy (or cell and gene therapy)
  - 1/5 are small molecule or biologic therapies (SC for discovery/ development)



Disease Team Research Awards - Invited

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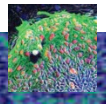
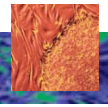
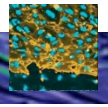
- Autoimmune diseases
- Cancer
- Cardiovascular disease
- Diabetes
- Eye diseases
- Hematopoietic disorders
- HIV / AIDS
- Liver disease
- Musculoskeletal diseases
- Neurological disorders and injury
- Peripheral vascular disease
- Tissue repair

Upcoming RFAs

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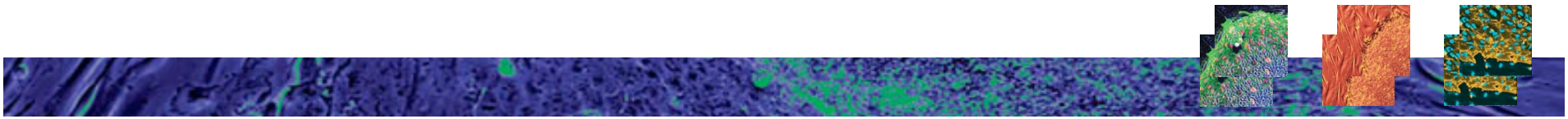
- **Basic Biology II**
  - **Post RFA – Aug 2009**
- **Stem Cell Immunology**
  - **ICOC Concept Clearance – Aug 09**
  - **Post RFA – 4 Qtr 2009**
- **Early Translational II**
  - **Concept Clearance – Dec 09**
  - **Post RFA – Feb 10**



Conference Grant Program

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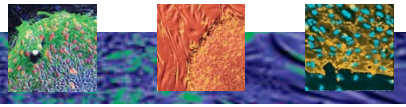
- Up to $300,000 per year to Non-Profit Organizations
- Maximum award the lesser of $50,000 or 50% of budget
- To Date: 5 Grants Awarded – Total approx. $100,000
- Attendees: approx. 800
  - patient advocates, engineers, geneticists, stem cell and gene transfer scientists, transplant scientists, immunologists, cell biologists, endocrinologists, diabetologists, health care professionals, FDA



President's Conference Grants

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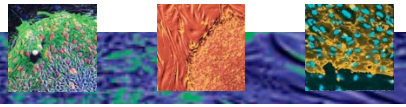
- Stem Cell Therapies for Pediatric Diseases and Injuries: A Critical Evaluation 2009 ($11K)
- Rachmiel Levine Diabetes and Obesity Symposium: Advances in Diabetes Biology, Immunology and Cell Biology ($15K)
- Translation of Stem Cell Therapies: Best Practices and Regulatory Considerations ($30K)
- Weinstein Cardiovascular Development Conference ($35K)
- San Diego Stem Cell Science Education Symposium at UCSD ($8K)



JST/CIRM workshop

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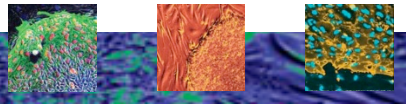
- 15 Japanese scientists joined CIRM funded scientists
- Panels: Neurobiology, disease models, new technologies, reprogramming, aging
- Teams were formed on the spot!
- Participation in Basic Biology, interest in Immunology



CIRM Autism Workshop Report.

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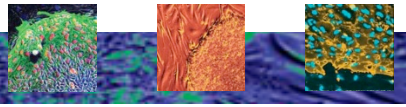
- Multidisciplinary experts in panels & breakouts
  - Pediatric neurologists, neurobiologists, mouse behavioral model experts, iPS cell experts, patient advocates and CIRM science officers
- Consensus from discussion
  - <u>iPS disease model cells from many different individuals could:</u>
    - Reveal the pathophysiology of the various forms
    - Assess the role of potential environmental insults
    - Screen for potential therapies and diagnostics
  - <u>Other critical research needs</u>
    - Multidisciplinary research into etiology and time course
    - Standardize and refine diagnostics
    - Remove roadblocks to access to tissue samples



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

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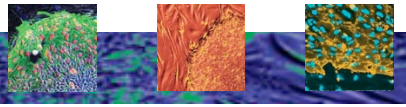
- **June 30 –July 1, 2009**

- This day and a half workshop will 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.



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CIRM Progress Reports

Marie Csete

SEED Grants

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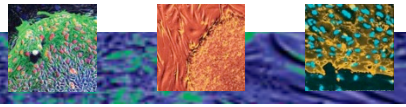
- Human embryonic stem cells only
- Idea-based, rather than preliminary data
- Attract non-stem cell biologists to the field, and developmental/SC biologists to hESC
- High risk, high gain
- Despite slow start, SEEDs are overwhelmingly successful



Progress Reports

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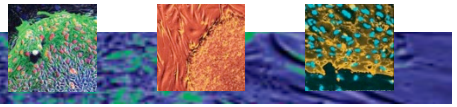
- Allow update on the advances and problems
- Interaction between the SO and PI
- Heads-up on papers, patents
- Allow SO's to match-make with other investigators in similar areas, or who overcame problems
- Positive feedback from PIs



- SO: Project not advancing
- Requests supplement
- CSO/entire science office
- Conference call: PI/AOO
- More time/data required
- Inadequate progress
- (Potential) termination letter
- Final termination letter

Ongoing process

- SO working with PIs to get grants back on track
- SO worked to continue critical research programs where PI could not continue
- Helped us fine-tune our processes for larger scale grants
- Final success of SEED will be seen over the next year
  - Continued hESC research
  - Success in further CIRM programs