President's Report

-Alan Trounson

-May 2008

New Developments in Stem Cells

Human cardiovascular progenitor cells develop from a KDR+ embryonic-stem-cell-derived population

Lei Yang et al. (Gordon Keller's group - McEwen Center Regenerative Medicine, Toronto, VistaGen Therapeutics, CA) - Nature April 2008

Functional cardiovascular cells derived from human embryonic stem cells

Using a serial growth factor recipe (BMP4, FGF2, Activin, VEGF, DKK1) serum free culture over 14 days

Produced a progenitor population that developed into cardiac, vascular and endothelial smooth muscle with appropriate signals - cultures contained >50% contracting cardiomyocytes

Improved by 31% the heart ejection fraction in mice with induced infarcts (a measure of heat function)

New Developments in Stem Cells

Selective Inhibition of JAK2-Driven Erythroid Differentiation of Polycythemia Vera Progenitors

Ifat Geron et al.* (Catriona Jamieson's lab UCSD - CIRM funded, Stanford, TargeGen, Transgenomic, Mayo Clinic) - Cancer Cell April 2008

Inhibition of the JAK2 pathway prevents myeloproliferative Polycythemia Vera (PV) - may cause thrombosis, myelofibrosis and acute leukemia

Showed that the PV mutation activates JAK2 tyrosine kinase and excessive erythroid production and is mimicked in lentiviral- enforced JAK2 expression of human cord blood progenitor assays. Showed the JAK2 inhibitor TG101348 prevented myloid expansion.

Mice transplanted human stem cells with lentiviral enforced expression colonized the bone marrow and showed excessive myeloprolioferation that was blocked by TG101348.

Clinical trials have been initiated with patients with PV.

*CIRM Trainee 4th Author: Edward Kavalerchik

New Developments in Stem Cells

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Ifat Geron et al. (Catriona Jamieson's lab UCSD - CIRM funded, Stanford, TargeGen, Transgenomic, Mayo Clinic) - Cancer Cell April 2008

Conclusion: The specific JAK2 inhibitor will likely prevent myloproliferation (excessive blood cell production) and sequel (possible leukemia) for the 10,000+ patients with this condition.

New Developments in Stem Cells

Long-term haematopoietic reconstitution by Trp532/2p16Ink4a2/2p19Arf2/2 deficient multipotent

Omobolaji Akala et al. (Michael Clarke's lab, Stanford and Univ Michigan) - Nature April 2008

Bone marrow of mice deficient in 3 genes - $p16^{Ink4a}$, $p19^{Arf}$, Trp^{53} have ~10x number of blood reconstituting cells (multipotential projenitor cells) long term. These pathways are repressed in cancer. Differences in the regulation of self renewal in normal and cancer states may be useful therapeutic targets.

These studies may provide the direction for development of hematopoietic cell expansion (in vivo and invitro)

These proteins may also be useful targets to control excessive expansion and blood cell cancer.

New Developments in Stem Cells

Therapeutic cloning in individual parkinsonian (PD) mice

Vivian Tabar et al. (Lorenz Studer's lab, Sloan-Kettering and Wakayama RIKEN, Kobe) - Nature Medicine March 2008

Used SCNT of individual mice to produce individual embryonic stem cells and showed that the use of neural progenitors derived from these NTSC lines were extremely effective in reversing Parkinson's phenotype when compared to using non-matched cells.

Demonstrates the importance of genomic identity for stem cell therapy and demonstrates proof of concept of NTSC in this mouse model - implications for NTSC and PD in patients.

Personnel

Marie Csete
Chief Scientific Officer

- John E. Steinhaus Professor of Anesthesiology at Emory University
- Adjunct Appointment in Cell Biology
- Program faculty appointments in Biochemistry, Cell and Developmental Biology, Neurosciences, and the Emory/Georgia Tech Biomedical Engineering Program
- Director of Liver Transplant Anesthesiology at the Emory University Hospital in Atlanta
- Director of the Emory/Georgia Tech Human Embryonic Stem Cell Core
- Co-Director of the Emory MD/PhD Program

Grant Reviews

Completed

Major Facilities Part II
Disease Team Planning Awards (June)
New Cell Lines Awards (June)

Upcoming

CIRM New Faculty Awards II

Upcoming RFAs

- Tools and Technologies
- Training Grants II (CIRM Scholars)
- Bridges to Stem Cell Research (Internship Program)
- Early Translational Research (concept clearance at June ICOC)

Proposed Workshops

- Predictive Toxicology
- Immunology Tools
- Cell Production Facilities

(for therapeutic and research purposes)

Science Meetings

- CIRM 2008 Grantee Conference
  17- 19th September 2008
  San Francisco

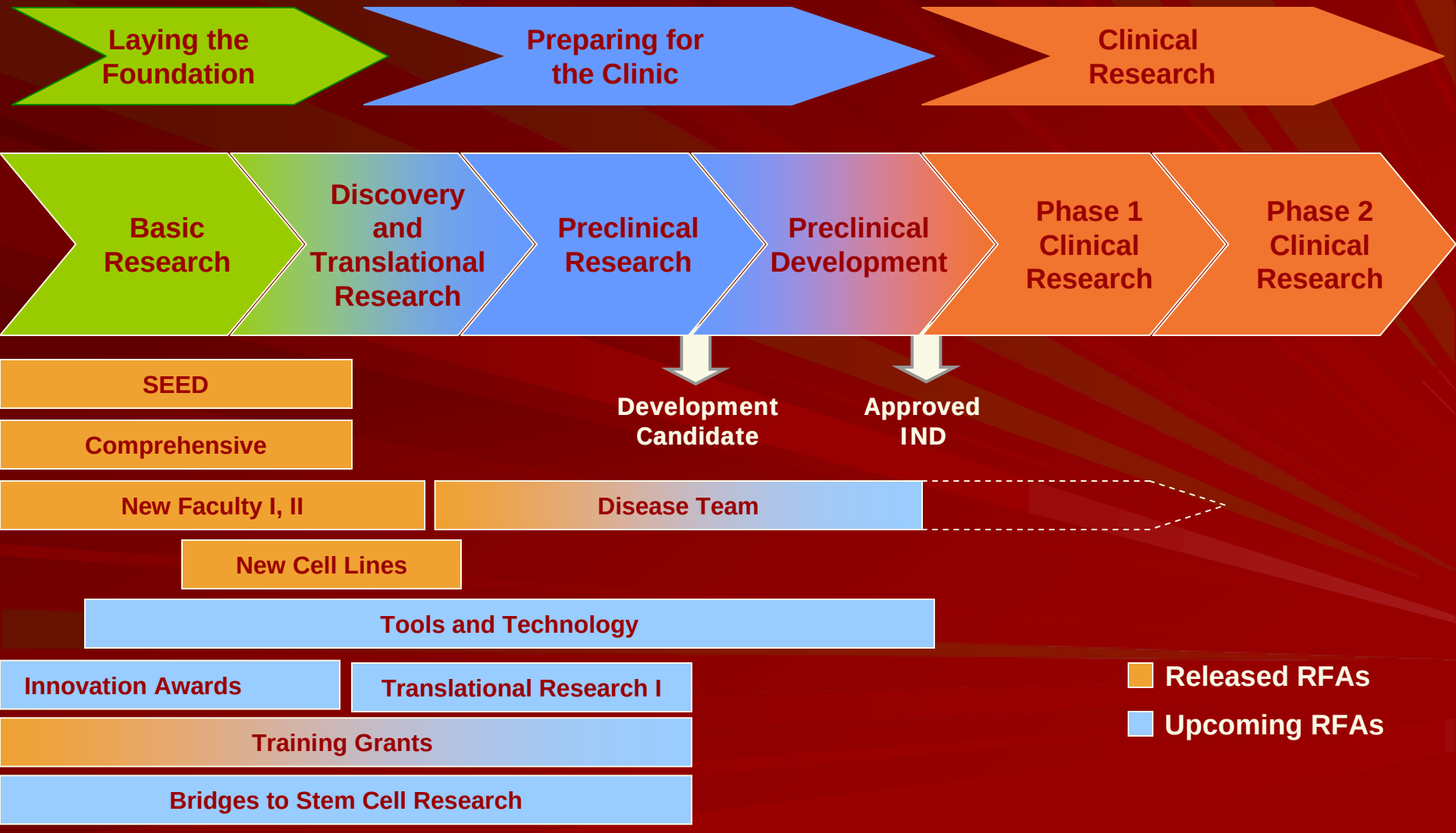
President's Report Updates

- CIRM Strategic Plan Update
- Review of caps on number of Grant Applications per PI
- Report on diversity of grants working group members
- Canada/California Cancer Stem Cell Meeting

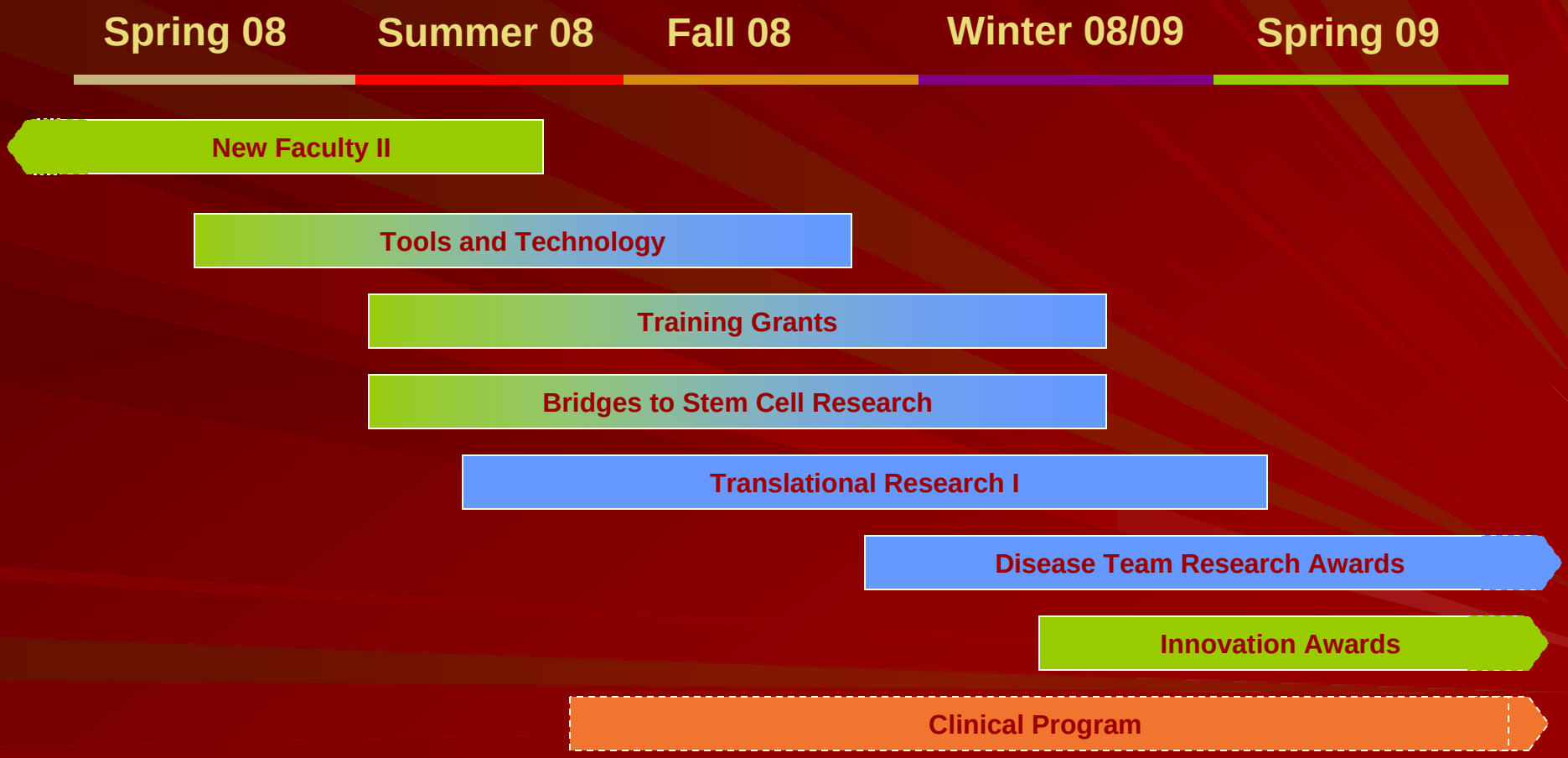
President's Report Updates

- Meeting with NIH
- SCO Audit - TP
- Forecast of CIRM Portfolio - PO
- FDA - Clinical Trials for hESCs - PO

Moving the Pipeline Forward: Awarded and Upcoming Initiatives



Initiatives: Provisional Timing



FDA Advisory Committee Meeting

- April 10 meeting of the Cellular, Tissue and Gene Therapies Advisory Committee
- Addressed “Safety of Cell Therapies Derived from Human Embryonic Stem Cells”
  - Inappropriate differentiation/tumorgenicity
  - Characterization of hESC-derived cellular populations
  - Patient monitoring, trial design

Commercial Presentations

- Novocell (hESC-derived insulin producing cells)
  - Emphasis: Characterization of cells, starting population, throughout differentiation, final product
- ACT (hESC-derived retinal cells)
  - Emphasis: Eye is uniquely suited to clinical application of cell transplant because site can be readily monitored
- Geron (hESC-derived oligodendrocyte precursors)
  - Emphasis: Teratoma formation is proportional to numbers of undifferentiated hES cells in final products

NOTE: ALL COMPANIES ARE RELYING ON DIFFERENTIATION PROCESSES TO WEED OUT UNDIFFERENTIATED CELLS; NO SEPARATION STEPS

Major points in panel discussions

- Risk of tumorigenesis is unknown
- Any teratoma formation in CNS is unacceptable risk
- Animals should be followed for long time horizons for tumor formation (life-long?); long term patient follow-up
- Cell characterization of starting hESC and product must be established under manufacturing conditions used for clinical production
  - If cell product heterogeneity, must be defined and consistent

Major points…

- Every effort must be made to avoid transplanting undifferentiated hESC
- Phase I study design incorporate efficacy as well as safety because of novelty of these trials
- Currently no good non-invasive methods to track infused/transplanted cells, optimize delivery as much as possible
- Sponsors need to demonstrate adequate immunosuppression regimen