CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

President's Report

Alan O. Trounson

ICOC Meeting – August 2010

Agenda Item #6

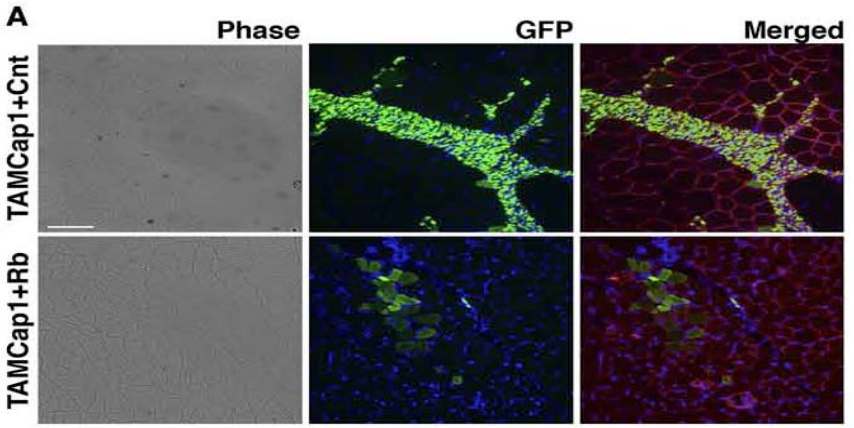
"Transient Inactivation of Rb and ARF Yields Regenerative Cells from Postmitotic Mammalian Muscle*"

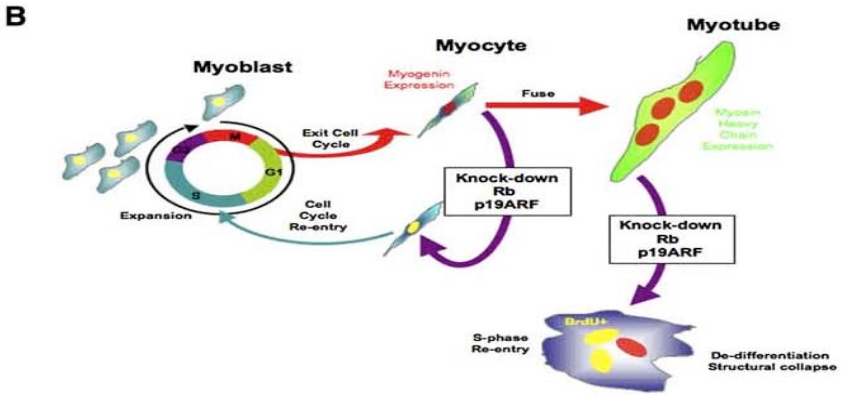
Pajcini et al., Helen Blau's Lab, Stanford

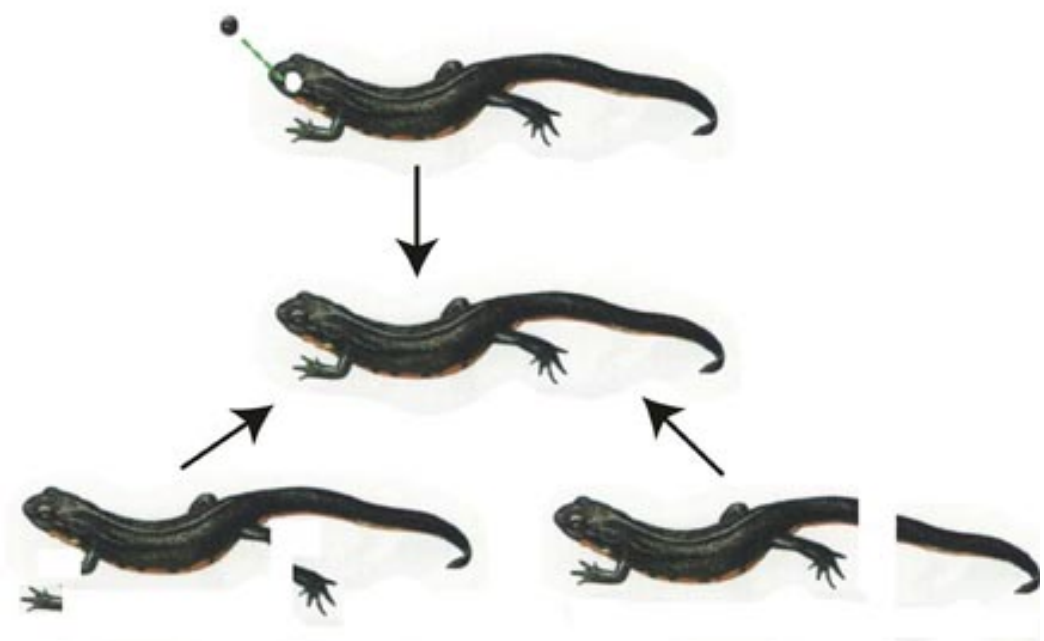
***Cell Stem Cell* 7:198-213 Aug 6 2010**

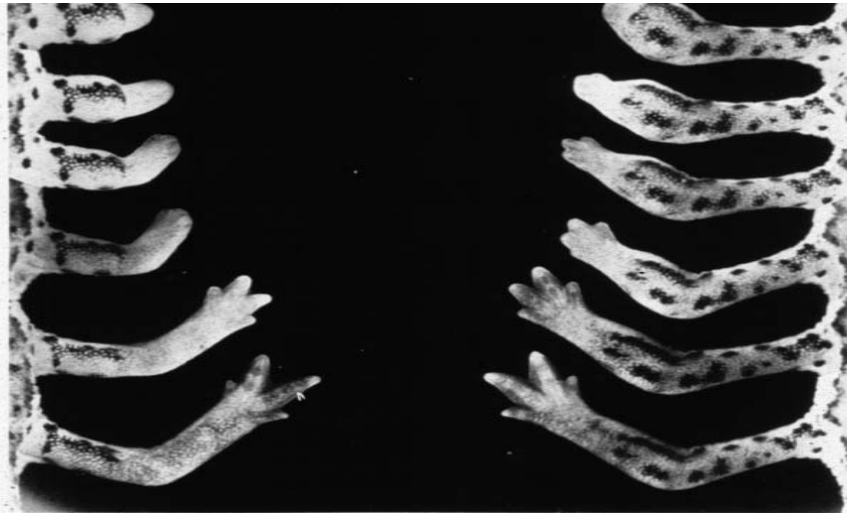
- Amphibia and fish regenerate limbs, heart by cell cycle reentry eg inactivation of the gene Rb induces cell cycle reentry and proliferation of skeletal muscle in limb formation
- Rb in mammals has been adopted as a tumor suppressor – enforces mitotic arrest and stable tissue-specific gene expression, prevents cell cycle reentry and inhibits apoptosis – as a trade off for limb regeneration (as in newts)
- In Mammals ARF is a regeneration repressor
- If you inactivate both Rb and ARF leads to mammalian muscle regeneration by cell cycle reentry, dedifferentiation and upregulation of cytokinetic cell machinery.
- Single post-mitotic muscle cells can be transiently suppressed for both Rb and ARF – they form myoblast colonies – differentiate and fuse into myofibers when transplanted into muscle in vivo
- Can this process be used for autologous regenerative therapies in the human?

*CIRM Funded


A
Phase
GFP
Merged
TAMCap1+Cnt
TAMCap1+Rb


B
Myoblast
Myocyte
Myotube
Myogenin Expression
Fuse
Exit Cell Cycle
Cell Cycle Re-entry
Expansion
Knock-down Rb p19ARF
Knock-down Rb p19ARF
BrdU+
S-phase Re-entry
De-differentiation Structural collapse





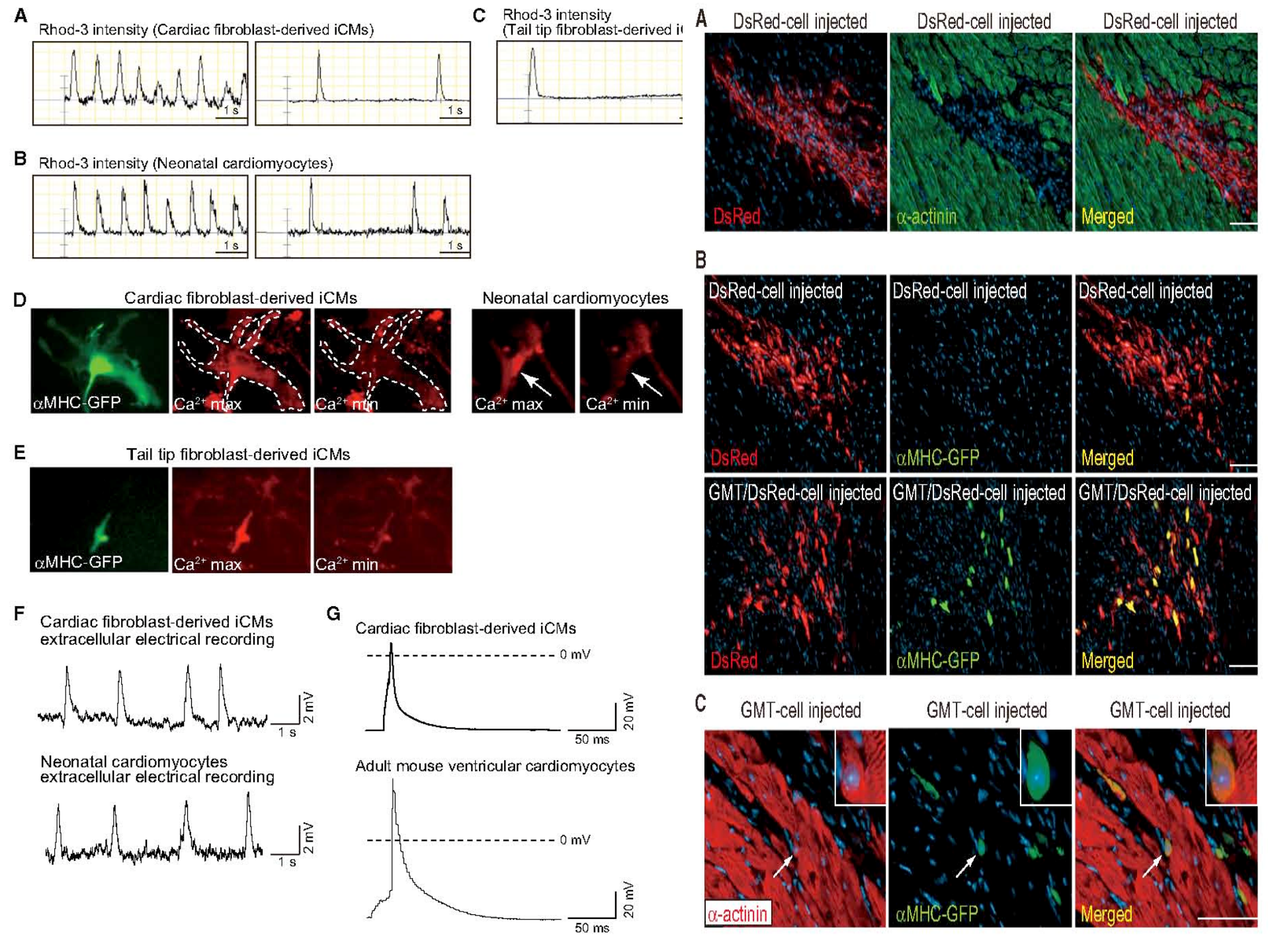
"Direct Reprogramming of Fibroblasts into Functional Cardiomyocytes by Defined Factors"*

Ieda et al., Deepak Srivastava's lab, Gladstone Institute

***Cell* 142:375-86 Aug 6 2010**

- Three transcription factors – ***Gata4, Mef2c, Tbx5*** – are needed to rapidly and efficiently reprogram cardiac stromal or dermal fibroblasts into cardiomyocytes
- They express the cardiac specific markers, have expression profiles equivalent to cardiac cells and contract spontaneously in culture
- When transplanted into mouse hearts 1 day after transduction – differentiated into cardiomyocyte-like cells
- This may be a useful clinical application for human cardiomyopathies

*CIRM Funded

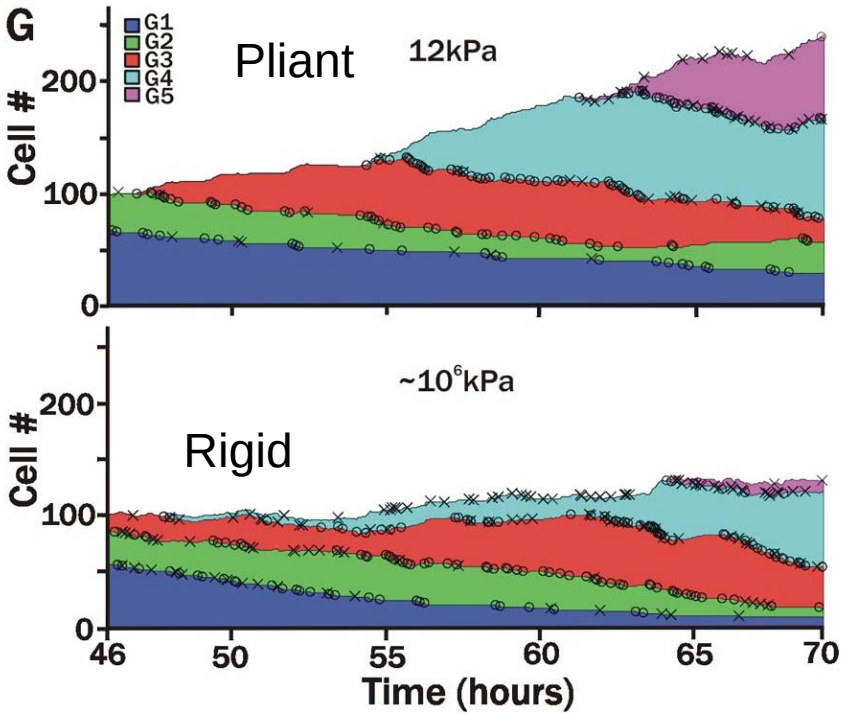

A
Rhod-3 intensity (Cardiac fibroblast-derived iCMs)
1 s
1 s
B
Rhod-3 intensity (Neonatal cardiomyocytes)
1 s
1 s
C
Rhod-3 intensity
(Tail tip fibroblast-derived i
D
Cardiac fibroblast-derived iCMs
Neonatal cardiomyocytes
αMHC-GFP
Ca2+ max
Ca2+ min
Ca2+ max
Ca2+ min
E
Tail tip fibroblast-derived iCMs
αMHC-GFP
Ca2+ max
Ca2+ min
F
Cardiac fibroblast-derived iCMs
extracellular electrical recording
2 mV
1 s
Neonatal cardiomyocytes
extracellular electrical recording
2 mV
1 s
G
Cardiac fibroblast-derived iCMs
0 mV
20 mV
50 ms
Adult mouse ventricular cardiomyocytes
0 mV
20 mV
50 ms
A
DsRed-cell injected
DsRed-cell injected
DsRed-cell injected
DsRed
α-actinin
Merged
B
DsRed-cell injected
DsRed-cell injected
DsRed-cell injected
DsRed
αMHC-GFP
Merged
GMT/DsRed-cell injected
GMT/DsRed-cell injected
GMT/DsRed-cell injected
DsRed
αMHC-GFP
Merged
C
GMT-cell injected
GMT-cell injected
GMT-cell injected
α-actinin
αMHC-GFP
Merged

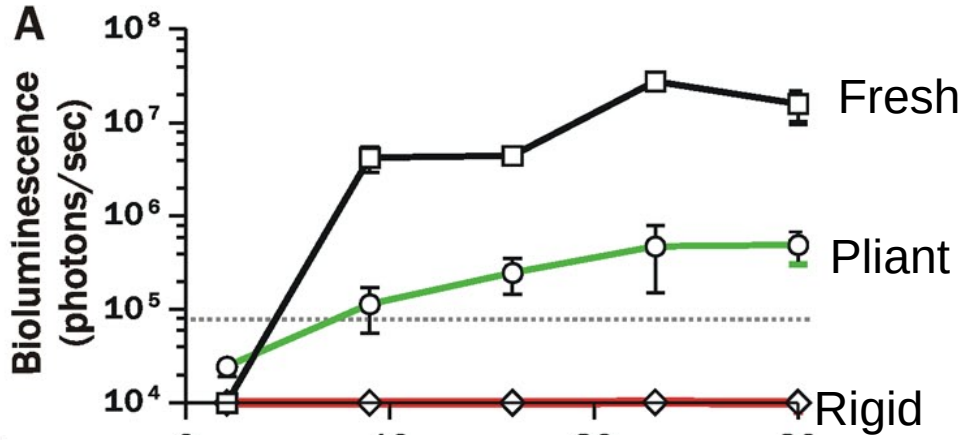
"Substrate Elasticity Regulates Skeletal Muscle Stem Cell Self-renewal in Culture*"

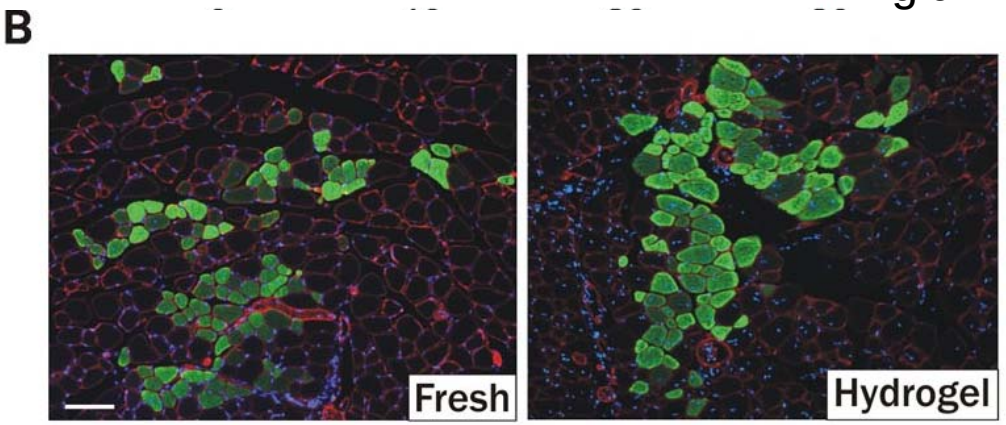
Gilbert et al., Helen Blau's lab, Stanford

Science Express July 15 2010

- Used a bioengineered substrate and a novel automated cell tracking algorithm to show that substrate elasticity is a potent regulator of muscle stem cell fate.







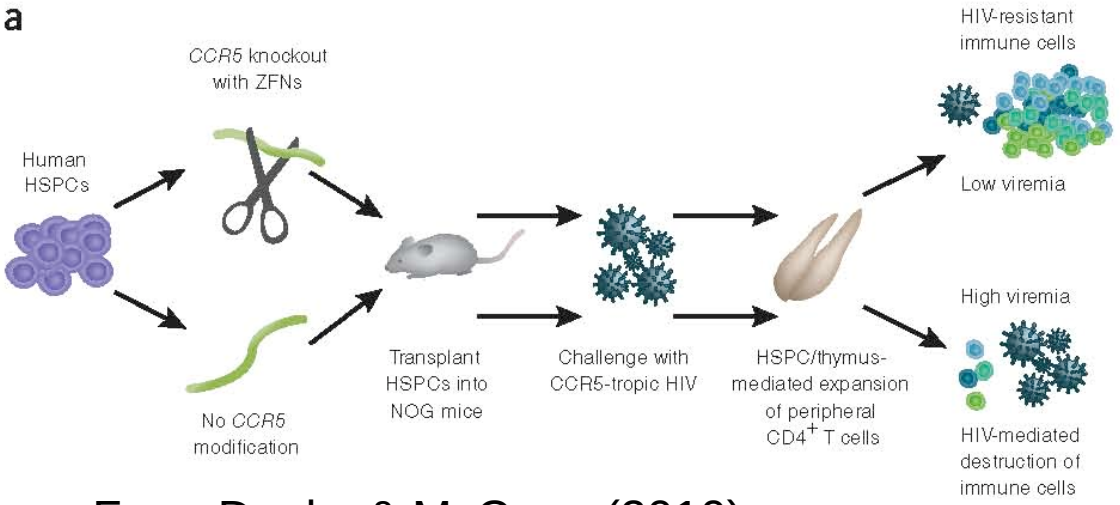
*CIRM Funded

"Human Hematopoietic Stem/Progenitor Modified by Zinc-finger Nucleases targeted to CCR5 Control HIV-1 in vivo*"

Holt et al., Paula Cannon's Lab, USC

Nature Biotech July 2nd 2010

- CCR5 gene was disrupted in human CD34+ hematopoietic stem cells using engineered zinc-finger nuclease at an efficiency of 17% with both mono- and bi-allelic disruption
- Human HSCs engrafted in mice with permanently disrupted CCR5
- When challenged with CCR5-tropic HIV-1 there was a rapid selection for CCR5– cells and these cells were preserved and signif lower HIV-1 than controls – that showed profound CD34+ T-cell loss



From Deeks & McCune (2010)

*Paper not CIRM funded – authors, P. Cannon, D. Kohn and G. Crooks are CIRM Grantees

"Bone Marrow Transplantation for Recessive Dystrophic Epidermolysis Bullosa"

John Wagner* et al., University of Minnesota

***New Engl J Med* Aug 12 2010**

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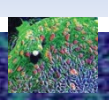
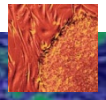
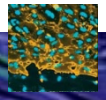
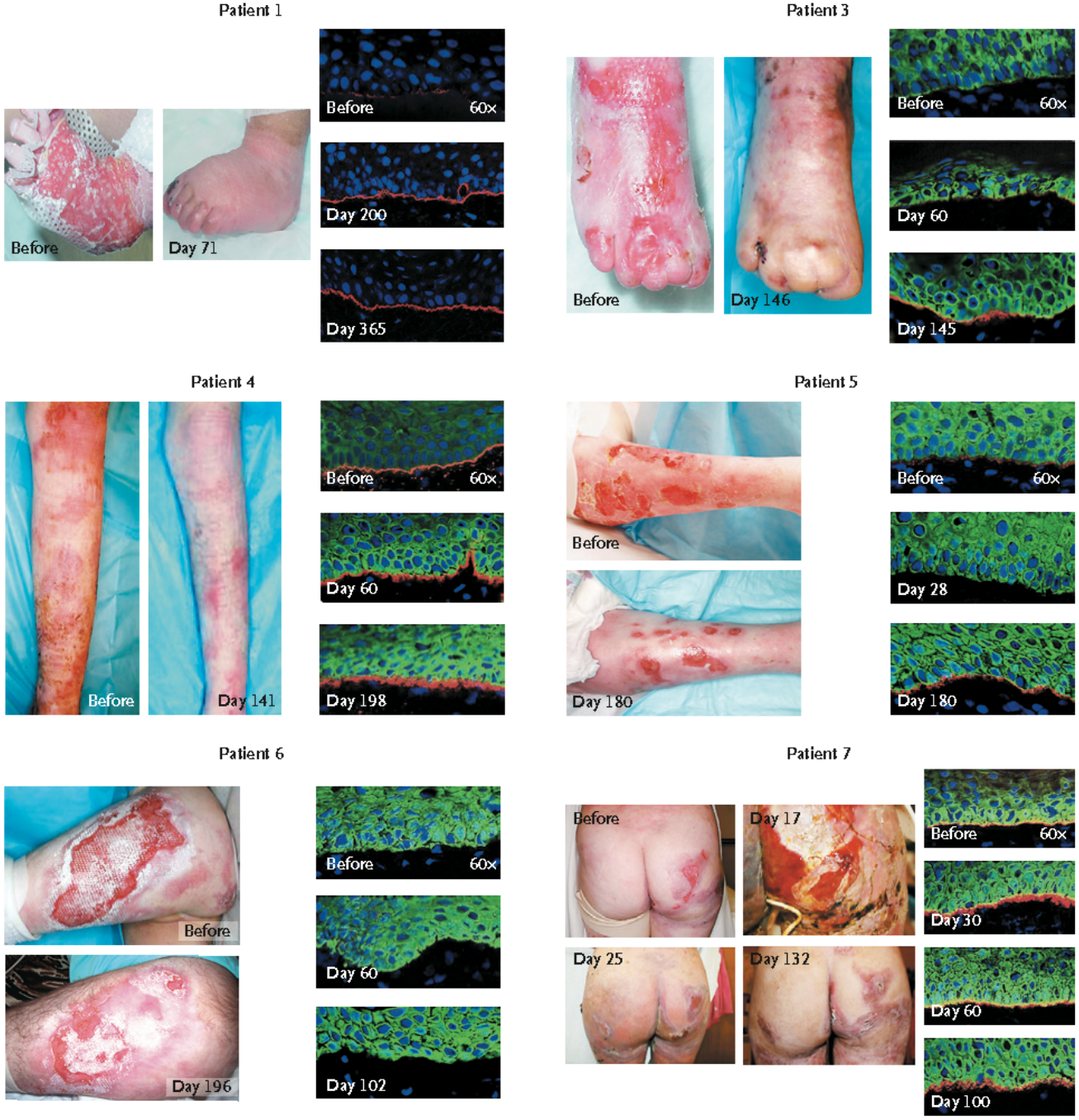
- DEB is incurable genetic disease caused by mutations in the Collagen 7 gene (COL7A1) which interferes with the anchoring of skin (epidermis) to dermis.
- Treated 7 children with recessive DEB with immunomyeloablative chemotherapy and allogeneic HLA matched sibling bone marrow stem cell transplantation or umbilical cord blood.
- One patient died. One had severe regimen-related cutaneous toxicity on day 17 (due probably to chemotherapy). All 6 surviving patients had improved wound healing , reduced blister formation 30-130 after transplantation. One died as a result of graft rejection and infection at 183 days (unrelated cord blood donor x2).
- The 6 patients had substantial proportions of donor cells in the skin – bone marrow to skin transdifferentiation? or rare pluripotent cells present in bone marrow?

*Member of CIRM Grants and Standards Working Group


Patient 1
Before
Day 71
Before
60×
Day 200
Day 365
Patient 3
Before
Day 146
Before
60×
Day 60
Day 145
Patient 4
Before
Day 141
Before
60×
Day 60
Day 198
Patient 5
Before
Day 180
Before
60×
Day 28
Day 180
Patient 6
Before
Day 196
Before
60×
Day 60
Day 102
Patient 7
Before
Day 17
Day 25
Day 132
Before
60×
Day 30
Day 60
Day 100

Personnel

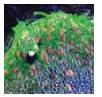
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Mani Vessal, PhD, Science Officer (Stanford University)

Arie Abo, PhD, Science Officer (Nuvelo Inc.)

President's Priorities

- External 2010 Review Committee
- Visits with CIRM Grantees at California Institutes
- VP R&D Search
- Clinical RFA
- Disease Teams
- President's Evaluation
- California Stem Cell Research Leadership Awards
- Alliance for Regenerative Medicine
- Online Journal
- Communications and Collaborative Funding Agreements/Contracts
- CIRM Scientific Creativity Internships
- Workshop Reports



Upcoming RFAs

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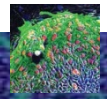
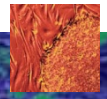
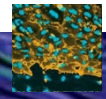
- **Early Translational II**
  - Review – September 2010
  - ICOC – October 2010
- **Tools, Technologies & Bottlenecks**
  - Full Grant applications – August 26, 2010
  - Review – November 2010
  - ICOC – January 2011
- **Clinical**
  - Posting RFA – August 31, 2010
  - Review – February 2011
  - ICOC – May 2011
- **Basic Biology III**
  - Receipt of pre-apps – October 7, 2010
  - Full Grant applications – January 2011
  - Review – March 2011
  - ICOC – May 2011

Upcoming RFAs

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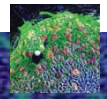
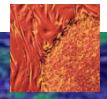
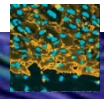
- **Disease Team II**
  - **Concept Clearance (Today)**

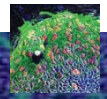
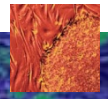
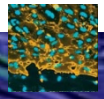




Workshop Reports:
MRC UK/CIRM - SCNT/Parthenogenesis – June, S.F.

- **Main question:** how does human SCNT fit into current stem cell field?
  - Attended by leading stem cell scientists with expertise related to human SCNT
  - Comprehensive discussion spanned topics ranging from
    - techniques employed
    - status of the technology
    - comparisons to other methodologies (including interspecies SCNT, parthenogenesis)
    - barriers to progress
    - potential applications for therapy and research
- **Overall conclusions:**
  - Human SCNT warrants further exploration
  - Call for collaboration amongst labs attempting human SCNT

Workshop Report: 2nd Annual Meeting of Collaborative Funders Network – SF (ISSCR)

- 10 agencies sent representatives (including Germany, UK, Japan, Korea, India)
- Evaluated contribution of bi-national research teams to date
- Discussed challenges of joint funding and best practices for addressing same
- Opportunity for numerous side meetings: interest in working with California scientists remains strong

Workshop Report: The Netherlands/CIRM Science Collaboration - June, S.F.

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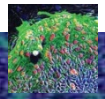
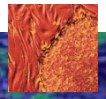
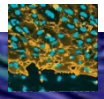
- Meeting attended by CIRM leaders, Dutch officials, and stem cell scientists from California and The Netherlands
- Discussed opportunities for cooperative programs and potential MOU
- Proposed networking workshop to facilitate collaborations between California and scientists from The Netherlands

Bridges Program 2010 Trainee Meeting

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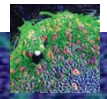
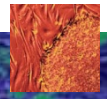
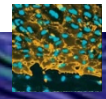
- **July 8-9, 2010 in San Francisco**
- **Meeting attended by 155 including Bridges Trainees (81), Program Directors, Trainee Mentors, and CIRM Staff**
- **Highlights of program included:**
  - **Poster presentations of internship research by trainees**
  - **Lectures by leading scientists including Drs. Gail Martin, Larry Goldstein, Victor Corces, Ted Love, and Ann Tsukamoto**
  - **Networking and career opportunities sessions**

Upcoming Workshop: CIRM-iPSC Banking Workshop - Nov 17-18, 2010

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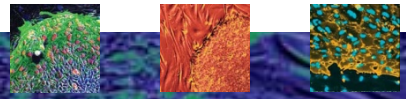
- Attendees: clinicians, researchers and cell banking professionals from the academic institutions as well as industry

- Patient-specific induced pluripotent stem cell (iPSC) provides unprecedented opportunities in regenerative medicine, drug discovery and toxicology.

- This advance in stem cell research has intensified the need for the development of iPSC bank from patients with broad haplotype from variety of diseases using a single method and a centralized cell processing, banking and distribution facility

- Forum for the thought leaders in the field to discuss issues and considerations related to the development of the iPS bank that could be used for applications, such as disease in a dish



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The state stem cell agency

Legal Office Update

Elona Baum, Esq.
General Counsel

Workshop Report: ISSCR/CIRM/ISCT Regulatory Harmonization- June, S.F.

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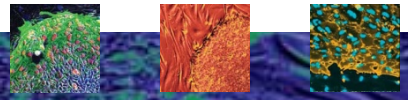
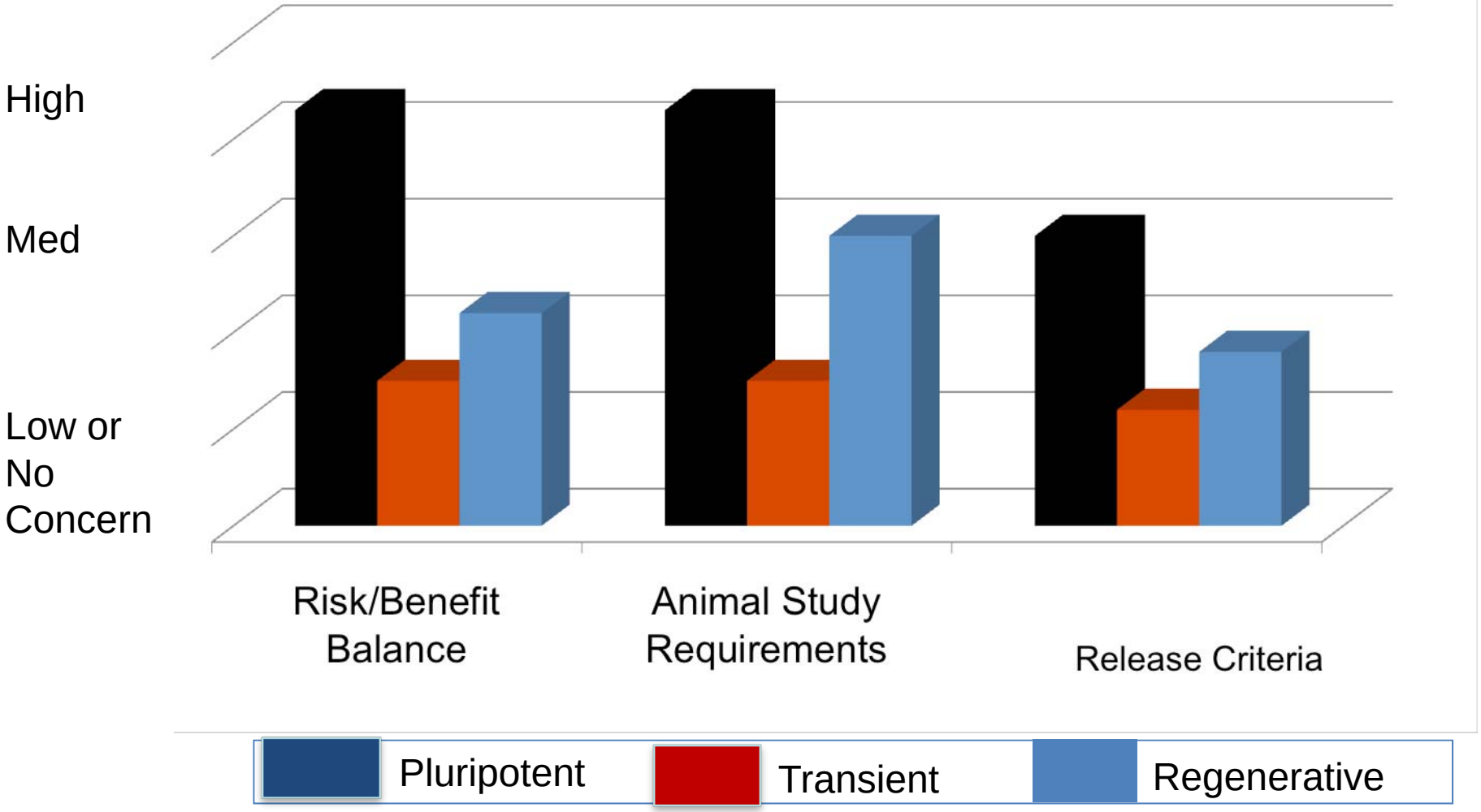
- Regulatory Frameworks
  - Agencies: FDA, EMA, Japan, Argentina – Experts: China and India
- Risk Tolerance and Regulatory Oversight Vary by Country
  - China: Dr. Wise Young - 400 patient PH III trial, cord blood mononuclear cells transplanted into patients with chronic spinal cord injuries; oral lithium or placebo (Note: prior pre-clinical animal studies not conducted)
  - Argentina: Media-driven hype drives patient interest, regulatory framework being developed
- Stem Cell Tourism – arises from lack of legislation and/or enforcement and differing approval paradigms
- CIRM-sponsored survey: Status of stem cell clinical trials in U.S.
  - The FDA readily permits transient therapeutics into the clinic but it is very difficult to get pluripotent or non-transient therapeutics into trials.
  - Greater certainty desired, hampered in part by lack of technologies,
  - A number of respondents stated that they had concerns relating to risk/benefit



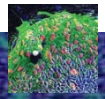
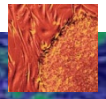
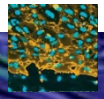
Some Challenges Identified



CIRM/Regenerative Medicine Consortium FDA Activities

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- September 28th: Webinar – Preclinical Animal Model Considerations: hESC, adult stem cells;
  - 2 hours
  - Mercedes Serabian, FDA; Robert Deans, Athersys and Melissa Carpenter, Carpenter Group
- October 8th: Roundtable – Preclinical Animal Model Considerations
  - Washington DC
  - Approximately 25 key thought leaders
  - Format: Consideration of hypotheticals
  - Objective: Understand key scientific issues and hear best practices, approaches for addressing these

UCLA Meeting July 21, 2010- IP Regulations

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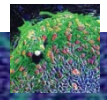
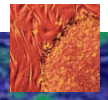
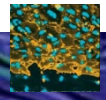
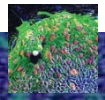
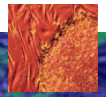
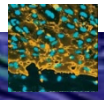
- **Staff Scientists:**
  - Overview of IP regulations
- **Tech Transfer Staff:**
  - Discussed finer points of our IP regulations
  - Provided clarification of a number of issues.
  - Agreed to prepare FAQs that addressed collaborator and exclusive licensee obligations
- Reiterated commitment to enhance understanding of our regulations through FAQ's, Workshops etc.

Upcoming Workshops
Stanford – CIRM IP Sept 24, 2010

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- Purpose: Discuss emerging "best practices" among Grantees for managing CIRM grants (including administrative and IP regulation compliance)
- Attendees: Personnel from technology transfer and sponsored research offices
- CIRM funding for travel expenses being provided ($7,500)
- California academic institutions being invited

CIRM Operations Report

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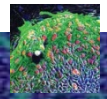
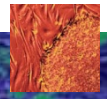
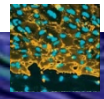
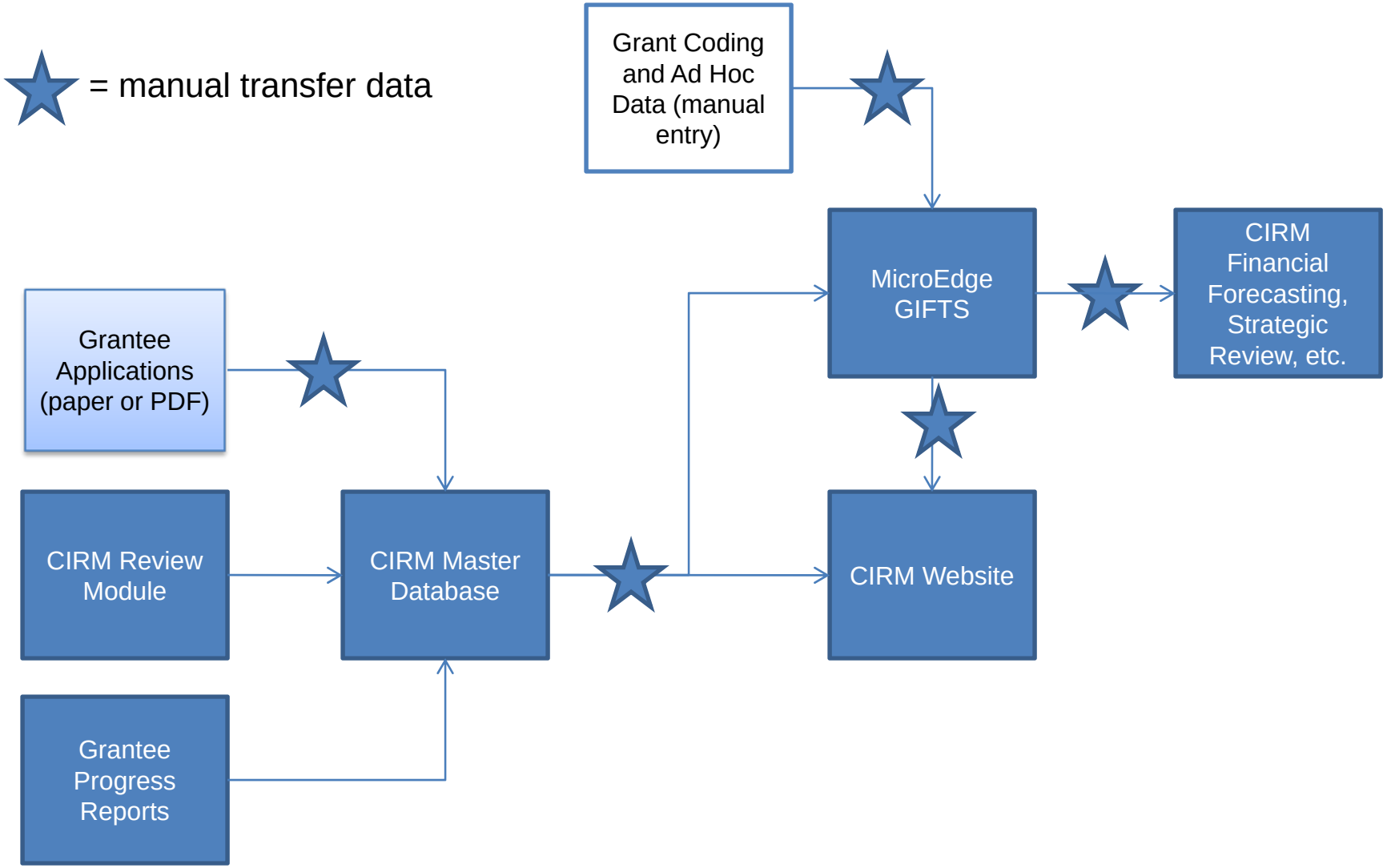
Grants Management Reporting

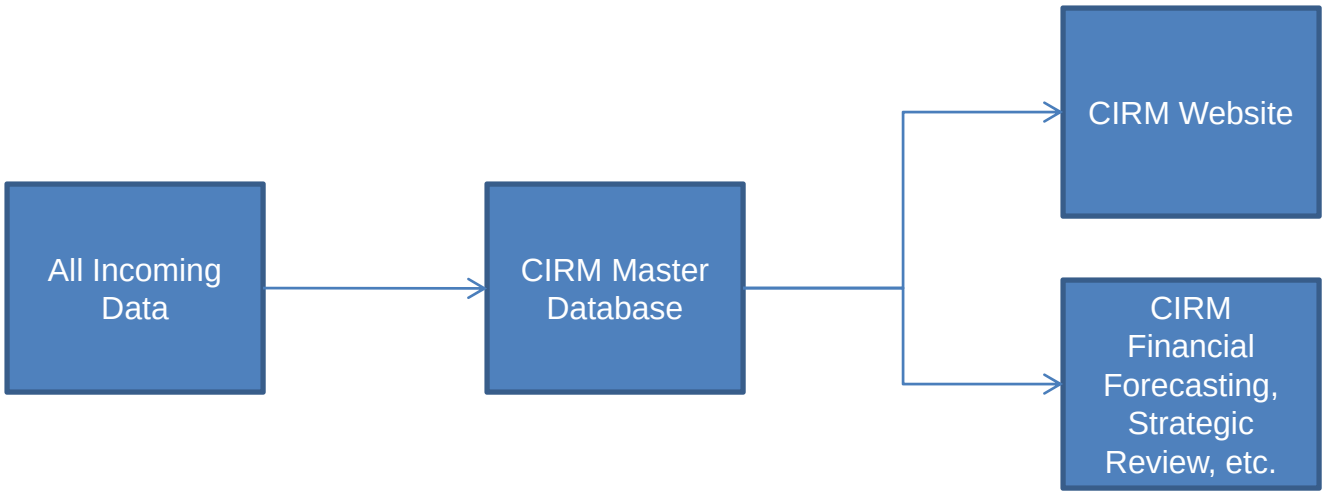
Amy Lewis

Grants Management Officer



CIRM Grants Management System - Current



CIRM Grants Management System - Future

CIRM Operations Report

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Public Data Reporting

Amy Adams

Communications Manager