CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

CIRM/Regenerative Medicine Consortium Roundtable on the Immune Response

Ellen G. Feigal, M.D.
Senior Vice President, Research and Development

Rockville, MD
October 24, 2011

Welcome to our participants from the FDA, industry, academia, NIH

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FDA	
Celia Witten	Pakwai Au
Stephanie Simek	Wei Liang
Mercedes Serabian	Theresa Chen
Raj Puri	Mark Borigini
Rachael Anatol	Alex Bailey
Wilson Bryan	Steve Bauer
Changting Haudenschild	Brian Niland
Bruce Schneider	Yolanda Warren Henderson (Lonnie) – coordinator

Welcome to our participants from the FDA, industry, academia, NIH, CIRM

Academia, NIH	Industry
Bruce Blazar	Amitabh Gaur
Christene Huang	Anthony J. Gringeri
David Hinton	Evert Kroon
Heike Daldrup-Link	Jane Lebkowski
John Zaia	Michael Holmes
Judy Shizuru	
Lucy Ghoda	
Michael Brehm	
Peter Stock	
Mahendra Rao, NIH	

Welcome to our participants from the FDA, industry, academia, NIH, CIRM

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CIRM
Alan Trounson
Ellen Feigal
Pat Olson
Bettina Steffen
Sohel Talib
Cynthia Schaffer - coordinator

Agenda for Immune Response Roundtable

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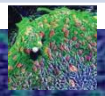
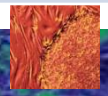
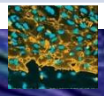
8:30-9:00	Welcome, intros, setting the context – E. Feigal
9:00-9:30	FDA (CBER) perspective on immune tolerance/immune response to cellular therapies – T. Chen, W. Bryan
break	
9:50-11:30	Strategies to induce tolerance or overcome immune response – Moderator B. Blazar; panel J. Shizuru, P.Stock/E.Kroon, D.Hinton
11:30-12:45	Animal models to study immune tolerance, immune response – Moderator C. Huang; panel J.Zaia, M. Brehm
12:45-2:30 Working lunch	Predictive immunology – assessment of immune response to stem cells and tissues – Moderator H. Daldrup-Link; panel A. Gaur, J. Lebkowski
2:30-3:15	Wrap-up panel with moderators
3:15-3:30	Closing remarks and action items

Context for today's roundtable…

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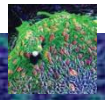
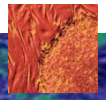
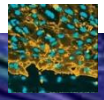
- Roundtable is part of a continuing series of roundtables focused on regulatory challenges in moving stem cell-based therapies towards and into the clinic
- CIRM held a workshop in 2009 on immune response, and challenges identified:
  - Different strategies for inducing immune tolerance
  - Predictive assays for rejection or tolerance, and non-invasive ways, such as biomedical imaging, to measure such response
  - Appropriate disease models
    - Issues of alloreactivity must be studied in context of specific diseases, considering transplant paradigm and tissue that is involved in the therapy
    - Differences between allo- and xeno-reactivity complicate analysis of studies in which human cells transplanted into nonhuman animal models of disease

Objectives include…

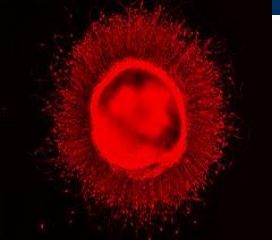
- Interactive discussion with expertise from academia, industry, NIH, FDA to exchange experiences and perspectives on various approaches to tackling bottlenecks/addressing challenges in this area from preclinical and clinical
- Advance understanding so that we can more appropriately advance stem cell-based therapies towards and into the clinic, and ways in which we can more effectively assess and monitor immune response with the tools we have in hand now
- Consider ways to share/communicate lessons learned from these various approaches

California Institute for Regenerative Medicine

- California taxpayer supported research institute – proposition 71 approved by voters (2004)

- Authorized $3 billion of State Obligation Bonds to fund stem cell research in California (max $300mill/yr) <6% for admin.

- Created an environment that supports both public and private sector research into life-saving and life-improving therapies for patients, based on stem cell science



CIRM activities towards our scientific mission

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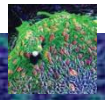
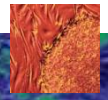
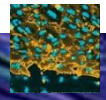
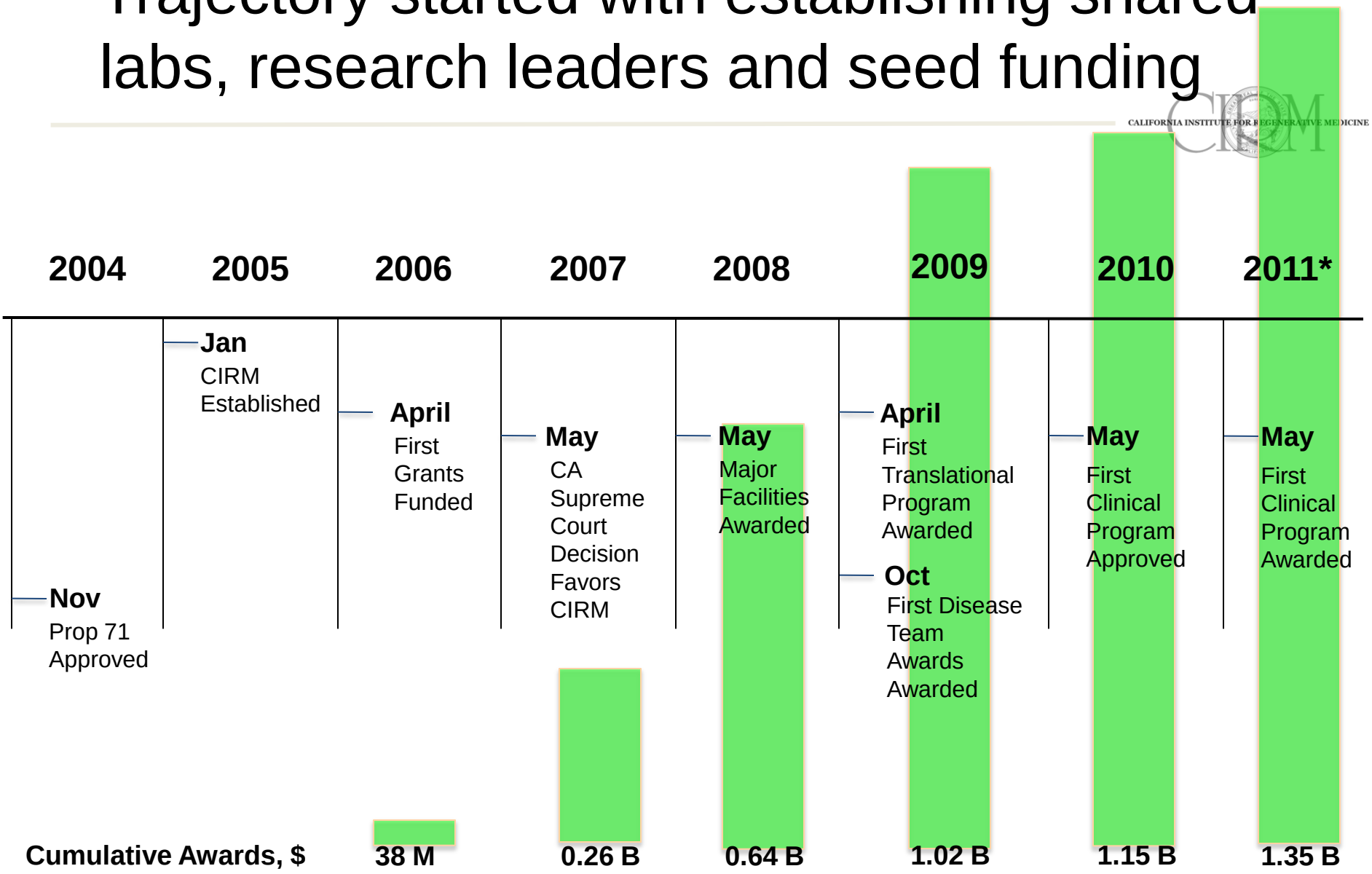
- 453 research and facilities awards
- 59 Institutes/Companies with CIRM awards
- 12 new institutes and centers of regenerative medicine ~$1 B ($271M from CIRM)
- $1.35 B allocated
- Over 900 major scientific papers published (24% high impact journals)
- Over 100 new major stem cell researchers in California
- 14 Disease Teams (preclinical) awarded – up to $20 M/award aimed for IND (FDA) within 4yrs
- First Clinical RFA awarded for hESC derived therapy, patients enrolling

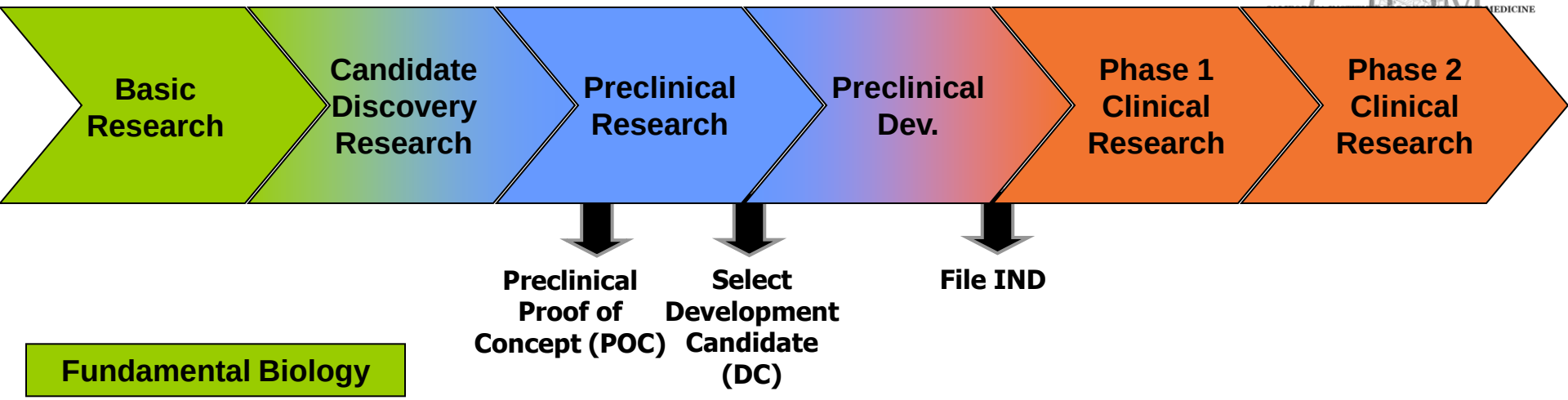




Trajectory started with establishing shared labs, research leaders and seed funding



* through 0911

Programs cover product development spectrum



Fundamental Biology

Early Translational Research I,II,III

Disease Team Research I

Targeted Clinical Development

Tools & Technologies

Disease Team Research II

Transplantation Immunology

RFA 09-03: CIRM Stem Cell Transplantation Immunology

- Potential for stem cells to replace or restore tissues lost to injury or disease represents one of the most promising outcomes of regenerative medicine.
- As with whole organ transplantation, stem cell grafts are often not host derived, and possess major and minor histocompatability antigen differences that, when recognized by the host immune system as foreign, can ultimately lead to their rejection.
- Purpose of the CIRM Stem Cell Transplantation Immunology initiative was to support transformative research leading to the development of immune tolerance of pluripotent stem cell derivatives and the potential correction of autoimmunity

Inducing immune tolerance, developing animal models and assays

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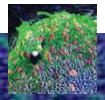
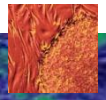
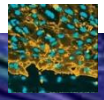
- Specifically directed towards the goal of inducing tolerance to stem cell grafts.
  - Potential strategies include means to manipulate the host immune system or engineer allogeneic grafts to promote their acceptance.
  - Development and verification of animal models to predict the human immune response to allogeneic transplantation as well as the development of sensitive immunological assays to monitor graft acceptance or rejection.

CIRM funded 19 awards in transplantation immunology June 2010

RM1-01725	Robert Negrin	Stanford University
RM1-01730	David Raulet	UC Berkeley
RM1-01703	Jeffrey Bluestone	UC San Francisco
RM1-01702	Mark Anderson	UC San Francisco
RM1-01720	Martin Marsala	UC San Diego
RM1-01729	Anjana Rao	La Jolla Institute for Allergy and Immunology
RM1-01739	Kenneth Weinberg **Australian Partner** Claude C. Bernard	Stanford University Monash University
RM1-01735	Terrence Town	Cedars-Sinai Medical Center
RM1-01706	Christopher Contag	Stanford University
RM1-01711	Basil Hantash	Escape Therapeutics, Inc

CIRM funded 19 awards in transplantation immunology June 2010

RM1-01707	Gay Crooks	UC Los Angeles
RM1-01709	Nicholas Gascoigne	Scripps Research Institute
RM1-01732	Ellen Robey	UC Berkeley
RM1-01718	Tippi MacKenzie	UC San Francisco
RM1-01724	William Murphy	UC Davis
RM1-01743	Yang Xu	UC San Diego
RM1-01717	Jeanne Loring **Australian Partner** Ban-Hock Toh	Scripps Research Institute Monash University
RM1-01710	Husein Hadeiba	Palo Alto Institute for Research and Education, Inc
RM1-01733	Judith Shizuru	Stanford University

Programs moving towards the clinic

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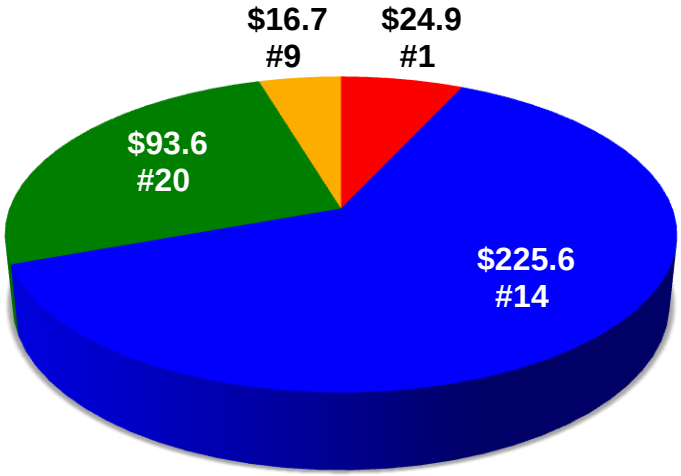
CIRM Investment translational
$361 M 44 awards



Preclinical Proof of Concept

Development Candidate

IND enabling

Phase I Clinical Study

Focus is on stem-cell based platforms

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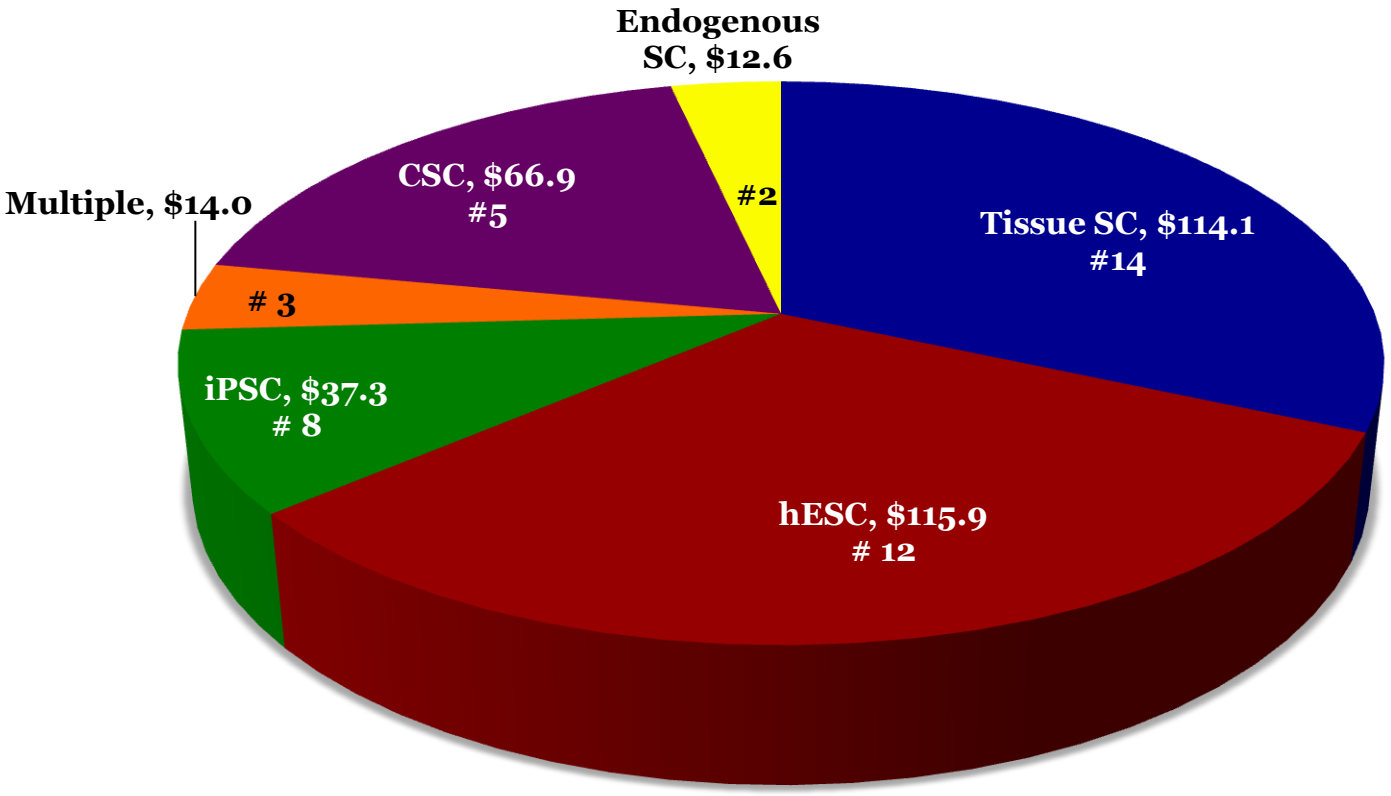
CIRM Investment translational ($361 M) 44 projects



Largest investments in neurological and eye diseases, cancer, and HIV/AIDS

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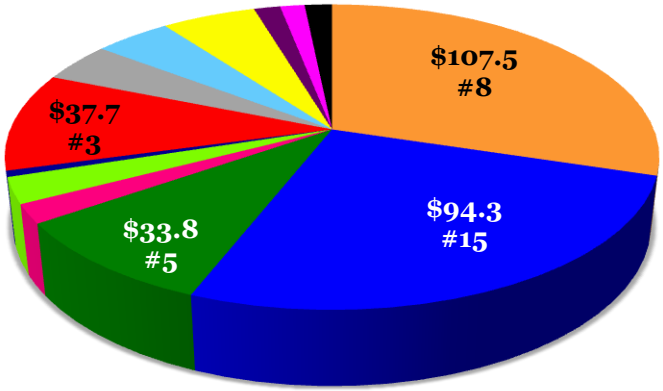
Disease Area, CIRM Investment translational ($361 M) 44 awards



- Cancer
- Neurological Disorders
- Eye Disorders
- Bone Disorders
- Cartilage Disorders
- Skeletal Muscle Disorders
- HIV/AIDS
- Blood Disorders
- Skin Disorders
- Endocrine Disorders
- Heart Disease
- GI/Liver Disorder
- Multiple: Bone Fractures, Wound Healing, Heart Disease, Stroke

Driven by science and evidence needed on regulatory pathway

- Prior to award
  - mutually agreed upon Go, no go and progress milestones, success criteria
  - During the conduct of research
    - Interactive ongoing discussions between CIRM scientists and funded research team
    - Updates on interval progress on bi-annual to quarterly basis and overall annual progress updates
    - clinical development advisor meetings yearly/ key milestones (DT1 at 12-18 month milestones)
  - CIRM/FDA webinars, educational roundtables, conferences, seminars

For more information…

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- www.cirm.ca.gov
  - Disease information
  - Complete list of funded awards
  - Interactive map