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The state stem cell agency

CIRM/Regenerative Medicine Consortium Roundtable: Best Practices in Clinical Design for FIH Cell-based Therapy

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

Rockville, MD
October 16, 2012

Goals for this session

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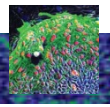
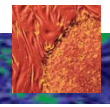
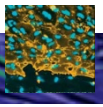
- ***Goal: gaining a better understanding of the challenges in clinical trial design for first-in-human studies***
- Issues across therapeutic areas and cell types:
  - setting objectives for the trial; choosing the patient population; selecting doses and delivery; selecting outcomes that can be measured; identifying proof of concept, and designing clinical trials based on preclinical data. Discuss issues unique to particular disease areas:
    - Cardiovascular
    - HIV/AIDS
    - Neuro

Setting the context and objectives…

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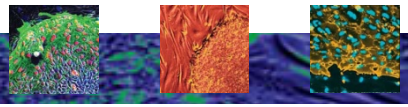
Roundtable is part of a continuing series of discussions focused on regulatory challenges in moving stem cell-based therapies towards and into the clinic. Objectives include:

- Catalyze interactive discussion with experts from academia, industry, NIH, FDA to exchange experiences and perspectives on various approaches to tackling bottlenecks/addressing challenges in advancing towards and into the clinic
- Advance understanding so that we can more appropriately advance stem cell-based therapies towards and into the clinic,
- Consider ways to share/communicate lessons learned from these various approaches



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

FDA	
Celia Witten	Lei Xu
Stephanie Simek	Wei Liang
Mercedes Serabian	Yao-Yao Zhu
Raj Puri	Ke Liu
Rachael Anatol	Steve Winitsky
Wilson Bryan	Ilan Irony
Changting Haudenschild	
Bruce Schneider	Yolanda Warren Henderson (Lonnie) – coordinator

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

Academia, NIH	
Sonia Skarlatos	Pablo Tebas
Eduardo Marban	James Guest
Marc Penn	S. Thomas Carmichael
Phillip Yang	**Industry**
Wolfram Zimmermann	Dale Ando
John Zaia	Stephen Huhn
Ronald Mitsuyasu	Ann Tsukamoto

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

CIRM	
Alan Trounson	Sohel Talib
Ellen Feigal	Ingrid Caras
Pat Olson	Karen Berry
Bettina Steffen	
	Anka Urbahn - coordinator

Agenda

8:30-9:00	Welcome, intros, setting the context – E. Feigal
9:00-9:30	FDA (CBER) perspectives on first-in-human trials of cellular therapies – W. Bryan
9:30-11:00	Cardiovascular session – Moderator S. Skarlatos panel E. Marban, M. Penn, P.Yang, and W. Zimmermann
Break	
11:20-12:45	HIV/AIDS session – Moderator J. Zaia panel D. Ando, R. Mitsuyasu, P. Tebas
12:45-2:30	Working Lunch and Neurodegenerative/Stroke/Spinal Cord Injury session – Moderator J. Guest panel S.T. Carmichael, S. Huhn, A. Tsukamoto
2:30-3:15	Wrap-up panel with moderators
3:15-3:30	Closing remarks and action items

Cardiovascular

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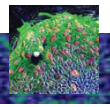
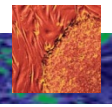
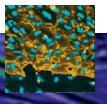
- What are the most important questions to answer to get the ball rolling forward? Will it depend on cell type, whether tissue engineered, and proposed MOA?
- Patient population: acute MI, CHF – subacute, chronic? What threshhold of function?
- Cell types and dose: which cells are best? What dose is optimal? When to deliver? How to deliver – intracoronary, direct injection, tissue engineered
- Cell Preparation: do we have a standard process?
- Selection of endpoints: imaging, laboratory, clinical
  - Discussion of ejection fraction; ventricular volumes; measures of scar, viability, and perfusion; regional contractility; functional tests such as 6 min walk or anaerobic threshold; how will this lead to the eventual registrational endpoints for approval?

HIV/AIDS

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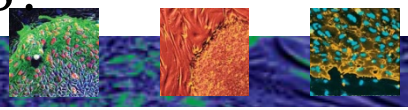
- What are the most important questions to answer to advance to a functional cure? A real cure? What patient populations do we envision for this therapy? Which patient populations do we start with?
- Viral Endpoints/Biologic Markers/HIV Latency - What are the endpoint measures of antiviral efficacy? Blood vs other body compartments? What are the best, most reliable assays? Do we need new assays to assess outcomes for cell-based therapy?
- What are the uses and limits of anti-retroviral treatment interruption?
- Is there a strong rationale, justified by benefit/risk, for cytoreductive therapy as a conditioning regimen in HIV/AIDS? Is there a role for allogeneic therapy in HIV/AIDS?



Neuro

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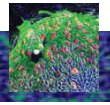
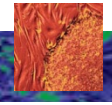
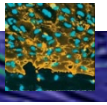
- What are the important questions to answer?
- Which patient population? acute vs subacute vs chronic spinal cord injury – complete or incomplete injury – which anatomic site? acute vs subacute vs chronic stroke? what stage of disease for neurodegenerative disorders e.g., early vs. advanced ALS, Parkinson's, Alzheimer's, Huntington's?
- Dosing, delivery, timing are all significant challenges – do you inject directly in injured area, peri-injury, systemic?
- What happens to the cells – do they survive, engraft, migrate? How to assess? What is the proposed MOA?
- What are relevant and measurable outcomes to measure – e.g., is it walking or bladder/control of bodily functions for SCI
- If it doesn't work, how do you figure out why?

California Institute for Regenerative Medicine www.cirm.ca.gov

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- 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

Funding, partnerships, facilitating pathway into the clinic

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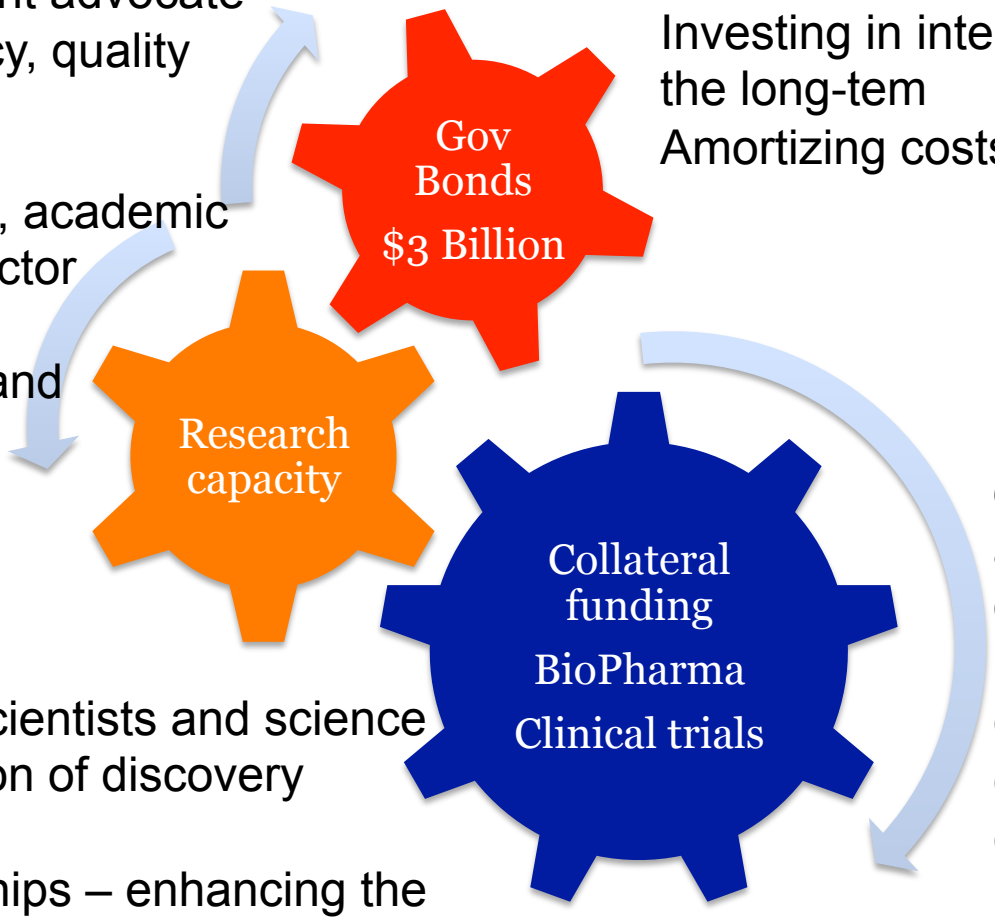
Community support, industry and academia support, patient advocate partnership, transparency, quality

Investing in intellectual capital for the long-tem
Amortizing costs across benefits

Stimulus to California, academic and biotechnology sector
Building institutional research excellence and collaborations



Economic benefits of patient cures and
quality of life, reduced health care costs, commercialization concurrent benefit but not sole driver

Supporting the best scientists and science
Encouraging translation of discovery to clinical opportunity
International partnerships – enhancing the best - critical to success

The Vision

Mission

"To support and advance stem cell research and regenerative medicine under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics, and research technologies to relieve human suffering from chronic disease and injury"

Explore (2004-2010)

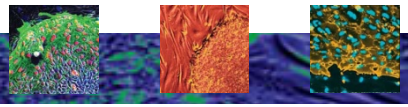
- Fund broad number of diseases and projects
- Establish foundation for leadership in stem cell research

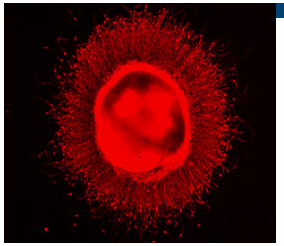
Focus (2011-2016)

- Prioritize projects and investments
- Drive clinical trials for patients to generate preliminary evidence of therapeutic benefit
- Develop partnerships

Deliver (2016+)

- Facilitate commercialization of therapies
- Advance therapies to patients
- Enable business model for stem cell-based therapies





CIRM activities towards our scientific mission

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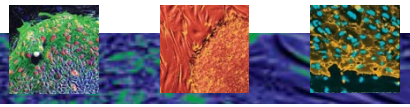
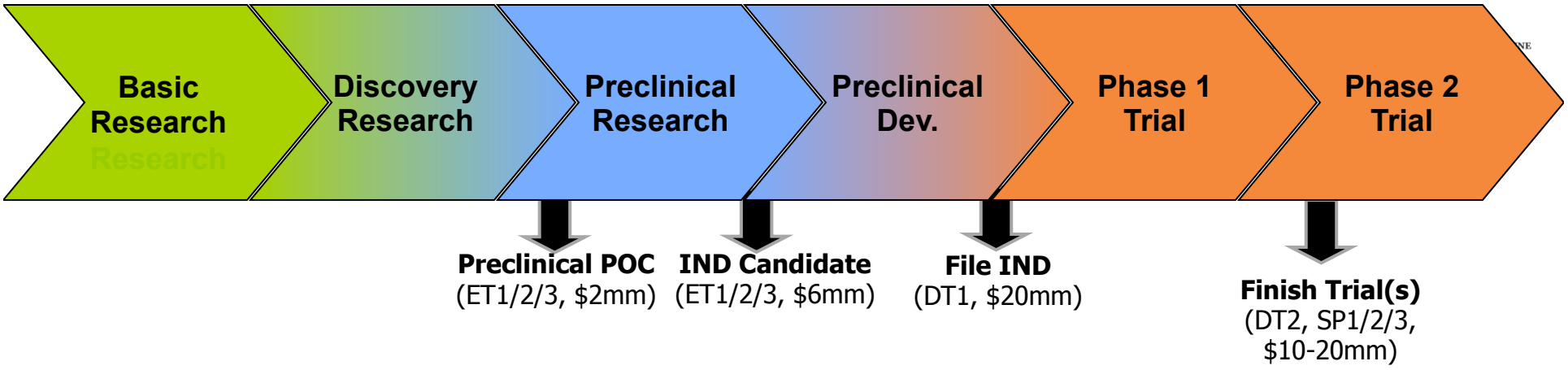
- Over 480 research and facilities awards
- Over 60 Institutes/Companies with CIRM awards
- 12 new institutes and centers of regenerative medicine
- Over 1000 major scientific papers published
- Over 130 new major stem cell researchers in California
- 75 translational/development programs to date
  - 14 Disease Teams I awarded 2010 – aimed for IND (FDA) to enter patient clinical trials within 4yrs, with 1 DT terminated March (did not reach Go/ No Go milestone), and 1 DT reached their goal (FDA approved IND June), and 12 being reviewed by clinical development advisor panels between July – Nov 2012
  - 11 Disease Teams II awards approved July/Sept, 2012



CIRM's Translational Portfolio



Early Translational I,II, III (ET1/2/3)

Disease Team I (DT1)

Disease Team II (DT2)

75 current translational programs

Early Translational IV (ET4)

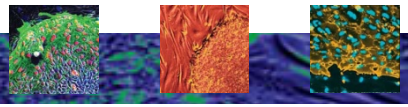
Strategic Partner I (SP1/2/3)

~30 awards in 2012 & 2013

Fundamental research, Training and Faculty Awards, Tools and Technologies

CIRM's Translational Portfolio

- 75 grants (Early Translation; Disease Teams)
  - 13 (Disease Team I) target an Investigational New Drug (IND) filing
  - 11 (DTTD awarded July/Sept 2012) target an IND and/or early phase clinical trials
  - 51 (Early Translational I, II, III) target identification and selection of a Development Candidate (DC) or preclinical proof of concept
- Neurodegenerative, cardiovascular and cancer
  - 14 neurodegenerative, 6 neurological injury and 5 neurological disorders in children; 9 cancer; 9 cardiovascular/vascular; 5 eye diseases; 4 blood disorders; 4 cartilage disorders; 3 HIV/AIDS; 2 diabetes; 3 bone disorders; 3 liver; 2 skeletal muscle; and others



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

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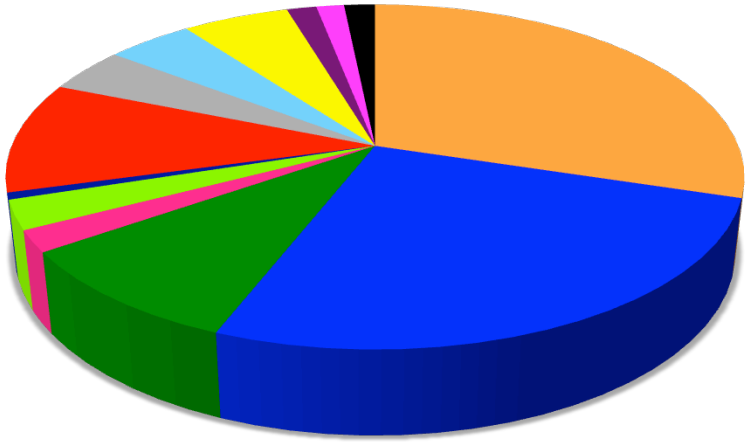
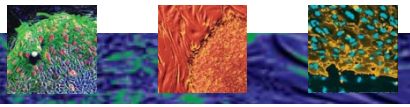
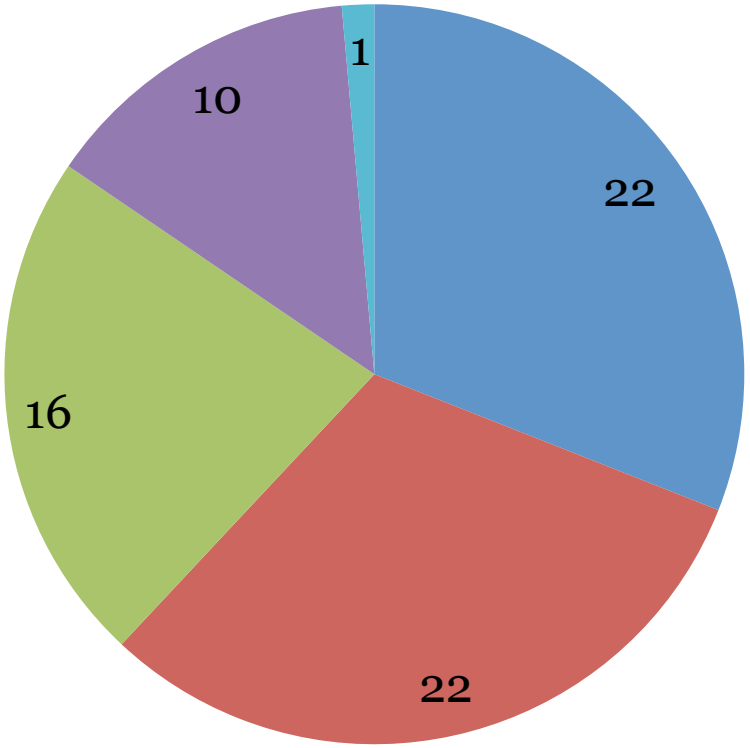


Cancer
Neurological Disorders
Eye Disorders
Bone Disorders
Cartilage Disorders
Skeletal Muscle Disorders
HIV/AIDS
Blood Disorders
Skin Disorders
Endocrine Disorders
Heart Disease
GI/Liver Disorder
Multiple: Bone Fractures, Wound Healing, Heart Disease, Stroke



Therapeutic modalities are varied



- Cell Therapy
- Gene-Modified Cell Therapy
- Small Molecule/mAb/ Protein
- Cell Therapy Combination Product
- Gene-Modified Cell Therapy Combination Product

Therapeutic modality of CIRM translational portfolio current as of July 26, 2012

Driven by science and evidence needed on regulatory pathway

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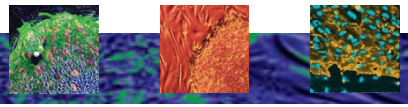
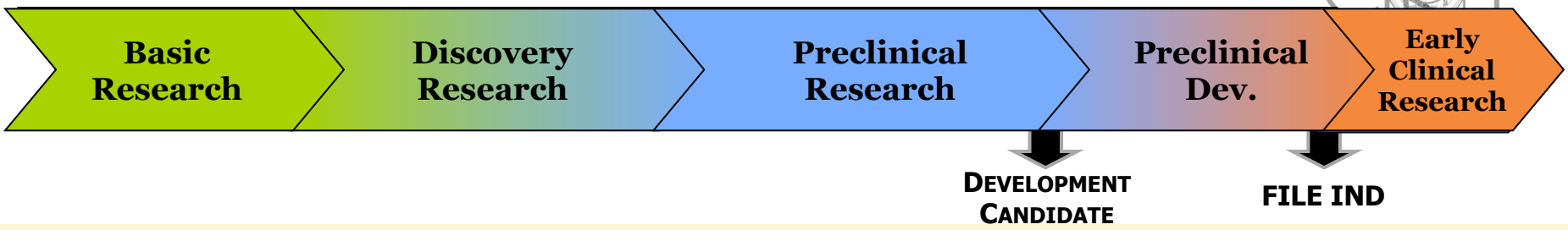
- Prior to award
  - mutually agreed upon Go, no go and progress milestones, success criteria
  - During the conduct of research
    - Interactive ongoing discussions between CIRM scientists and funded research team
    - Updates on interval progress on bi-annual to quarterly basis and overall annual progress updates
    - clinical development advisor meetings yearly/ key milestones (DT1s have been assessed in 2011 at 12-18 month milestone, now at 24-36 month milestone)
  - CIRM/FDA webinars, roundtables, conferences, seminars



CIRM's Disease Teams, addressing major unmet clinical needs, are moving towards the clinic



Diabetes (1)

Neurological Dis (2)

Eye Disease (1)

Cardiac Disease (1)

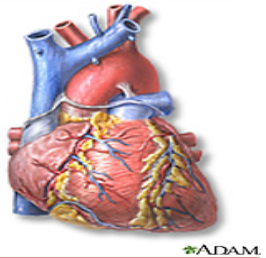
HIV/AIDS (2)

Cancer (4)

Blood Disorders (1)

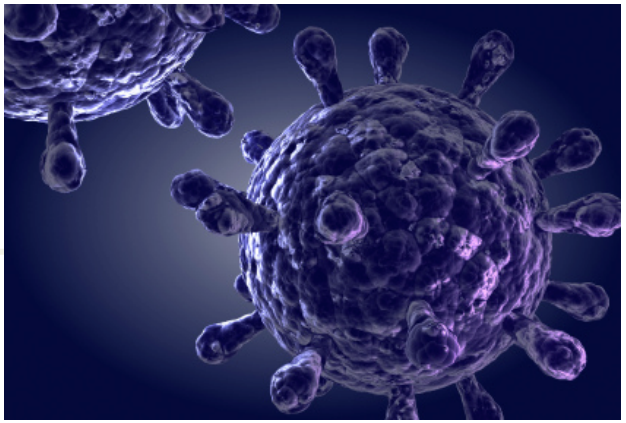
Skin Disease (1)

Cardiovascular



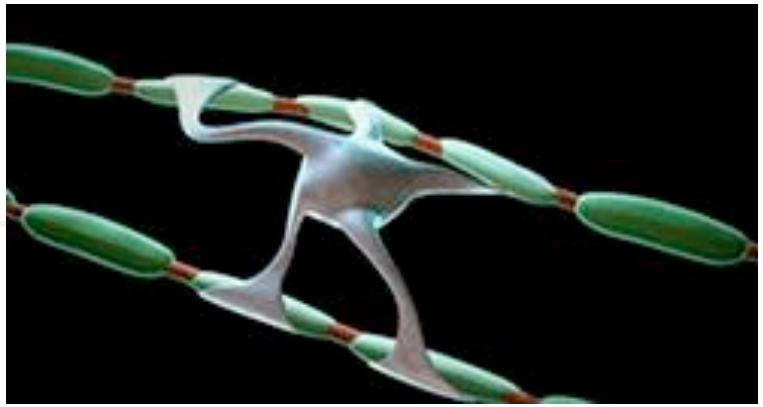
Award	Goal	Disease	Approach
Robert Robbins Stanford	Phase 1 Trial	End-stage heart failure	hESCs differentiated into cardiomyocytes
John Laird UC Davis	Phase 1 Trial	Critical Limb Ischemia	Allogeneic MSCs engineered to express VEGF. Delivered to ischemic tissue / blood vessels by IM injection
Eduardo Marban Cedars-Sinai Linda Marban (Capricor)	IND advancing to Phase 1/2	Advanced Ischemic Cardiomyopathy (heart failure)	Allogeneic cardiac-derived stem cells following large myocardial infarctions (MI)
Deepak Srivastava Gladstone	IND Candidate	Acute myocardial infarction	Direct reprogramming of endogenous cardiac fibroblasts into functional cardiomyocytes by gene transfer
Walter Boyd UC Davis	IND Candidate	Chronic myocardial infarction	Allogeneic human bone marrow-derived MSCs embedded in a biological scaffold
Joseph Wu Stanford	IND Candidate	End-stage heart failure	Engineered tissue patches seeded with hESC-derived cardiomyocytes

HIV / AIDS



Award	Goal	Disease	Approach
John Zaia City of Hope; USC; Sangamo	IND	AIDS Lymphoma	Autologous HSC transduced *ex vivo* with non-integrating vector engineered to express zinc finger nuclease against CCR5. IV administration after myeloablation
Irvin Chen UCLA; Calimmune	IND	AIDS Lymphoma	Autologous HSC transduced *ex vivo* with a lentiviral vector engineered to express a shRNA against CCR5 & fusion inhibitor. IV administration after myeloablation.
David DiGiusto City of Hope	IND Candidate	AIDS Lymphoma	Autologous HSC genetically modified *ex vivo* with multiple anti-HIV resistance genes and a drug resistance gene

Neurological Injury



Awardee	Goal	Injury	Approach
Gary Steinberg Stanford; UCLA	IND	Stroke	Allogeneic hESC-derived NSC line transplanted alone or in combination with matrix
Nobuko Uchida / StemCells Inc.	IND	Cervical Spinal Cord Injury	Allogeneic neural stem cells
Mark Tuszynski UCSD	IND Candidate	Spinal Cord Injury	Allogeneic hESC-derived NSCs in a scaffold for injection

Neurodegenerative Disease

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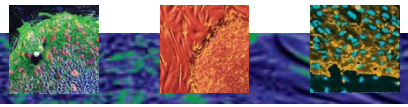
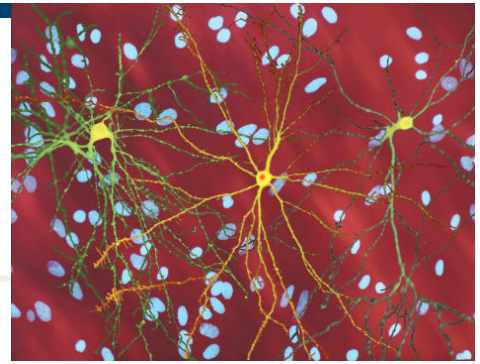
Award	Goal	Disease	Approach
Vicki Wheelock UC Davis	Phase 1 Trial	Huntington's Disease	Genetically-modified allogeneic MSCs expressing BDNF transplanted into patients
Clive Svendsen Cedars Sinai	Phase 1 Trial	ALS	Allogeneic neural progenitor cells genetically modified with GDNF
Larry Goldstein UCSD; Salk Institute	IND	ALS	Allogeneic hESC-derived astrocyte precursors delivered into spinal cord



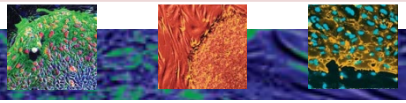
Neurodegenerative Disease

Award	Goal	Disease	Approach
Evan Snyder Sanford-Burnham; Howard Florey Institute (Victoria, AUS)	IND Candidate	Parkinson's Disease	The best of either hNSC derived from tissue, ESC, or iPSC; or hVM (ventral mesencephalon) precursors derived from ESC, NSC, or tissue
Xianmin Zeng Buck Institute; City of Hope	IND Candidate	Parkinson's Disease	Allogeneic hPSC-derived dopaminergic neurons
Capela/Stem Cells, Inc	IND	Alzheimer's Disease	Neural stem cell transplantation for neuroprotection
Frank LaFerla UCI; Monash University (Victoria, AUS)	IND Candidate	Alzheimer's Disease	Allogeneic hESC-derived NSC or hESC-derived NSC genetically modified with a beta-amyloid degrading enzyme or a transcription factor that promotes neuronal differentiation for transplant
Jan Nolta UCD	IND Candidate	Huntington's Disease	Allogeneic MSC engineered ex vivo to express siRNA targeting mutant huntingtin mRNA. Injected intracranially

Neurodegenerative Disease



Award	Goal	Disease	Approach
Leslie Michels Thompson UC Irvine	IND Candidate	Huntington's Disease	Allogeneic hESC-derived neural stem or progenitor cells for transplantation
Thomas Lane UC Irvine	IND Candidate	Multiple sclerosis	Allogeneic hESC-derived neural progenitor cells for transplantation
Peter Schultz Scripps	IND Candidate	Multiple sclerosis	Small molecules to remyelinate axons by stimulating the differentiation of oligodendrocyte precursor cells to oligodendrocytes
John Dimos iPierian, Inc.	IND Candidate	Spinal Muscular Atrophy	Small molecule that increases SMN1 gene product in patient iPSC-derived motor neurons
Philip Schwartz Children's Hospital Orange County	IND Candidate	Lysosomal Storage Disease	Immune-matched human neural stem cells transplantation subsequent to hematopoetic stem cell transplantation



For more information…

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