CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

Advancing Stem Cell Science– CIRM's Scientific Scope and Programs

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Executive Director, Scientific Activities

Presentation to ICOC Workshop

January 23, 2013

CIRM's Vision and Strategy

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)

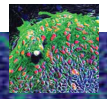
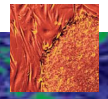
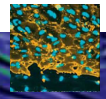
- Fund broad number of diseases and projects
- Establish foundation for leadership in stem cell research

Focus (2011-2016)

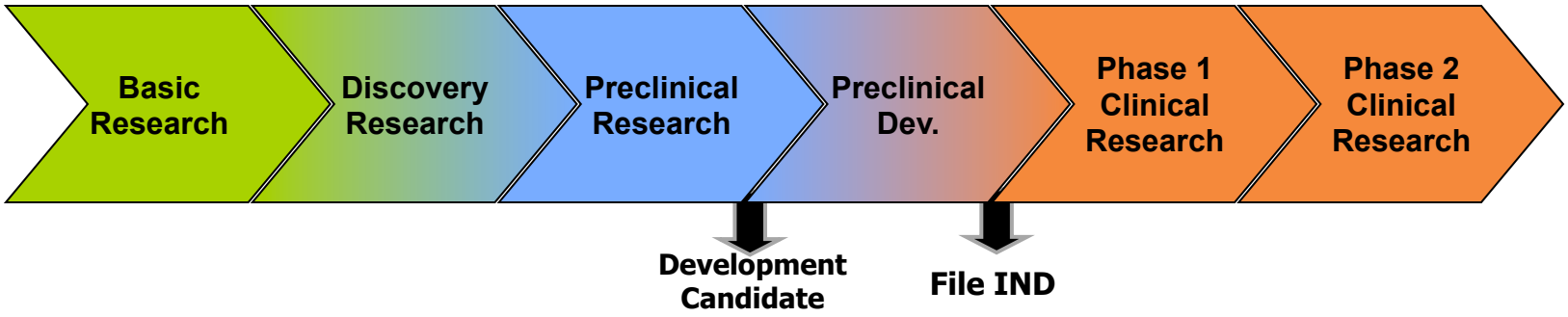
- Prioritize projects and investments
- Drive clinical trials for patients to generate preliminary evidence of therapeutic benefit
- Develop partnerships

Deliver (2016+)

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

Where have the $ been invested? CIRM's research funding commitment



Infrastructure: Facilities & Cores - $343.0 MM

Infrastructure: Intellectual - $379.0 MM

Pipeline: Foundational Research - $337.1 MM

Pipeline: Translational Research - $675.0 MM

CIRM's core programs provide a pathway spanning scientific advances to therapies

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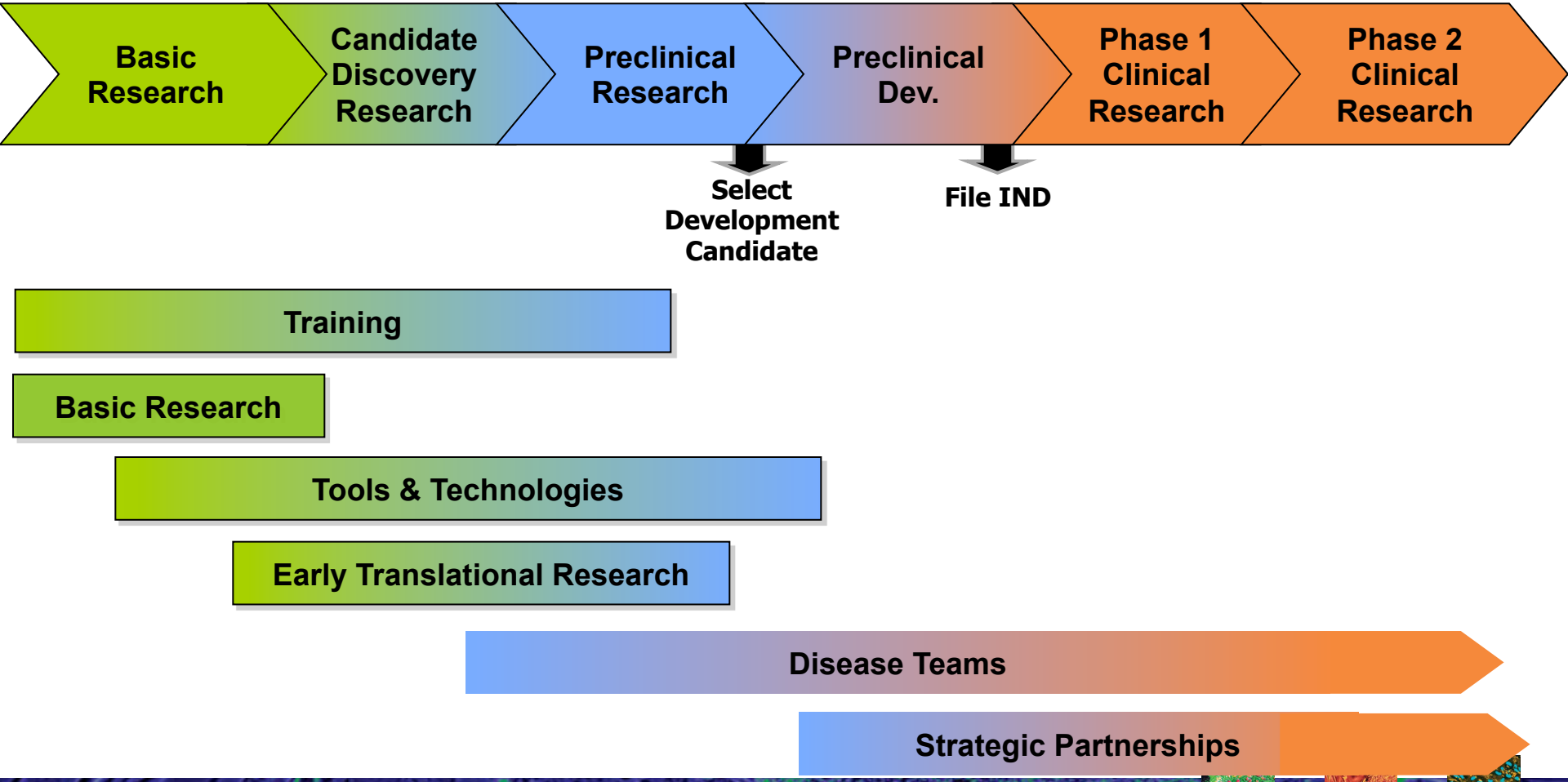

CIRM activities towards our mission

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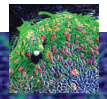
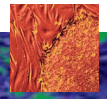
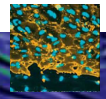
- Over 560 research and facilities awards to over 60 institutes and companies
- 12 new institutes and centers of regenerative medicine
- Over 1200 major scientific papers published
- Over 130 new major stem cell researchers in California
- 77 translational/development programs
  - 51 Early Translation programs, 24 Disease Teams, 2 Strategic Partnership programs
- $1.7 B awarded

Cumulative ICOC approved funding in core programs

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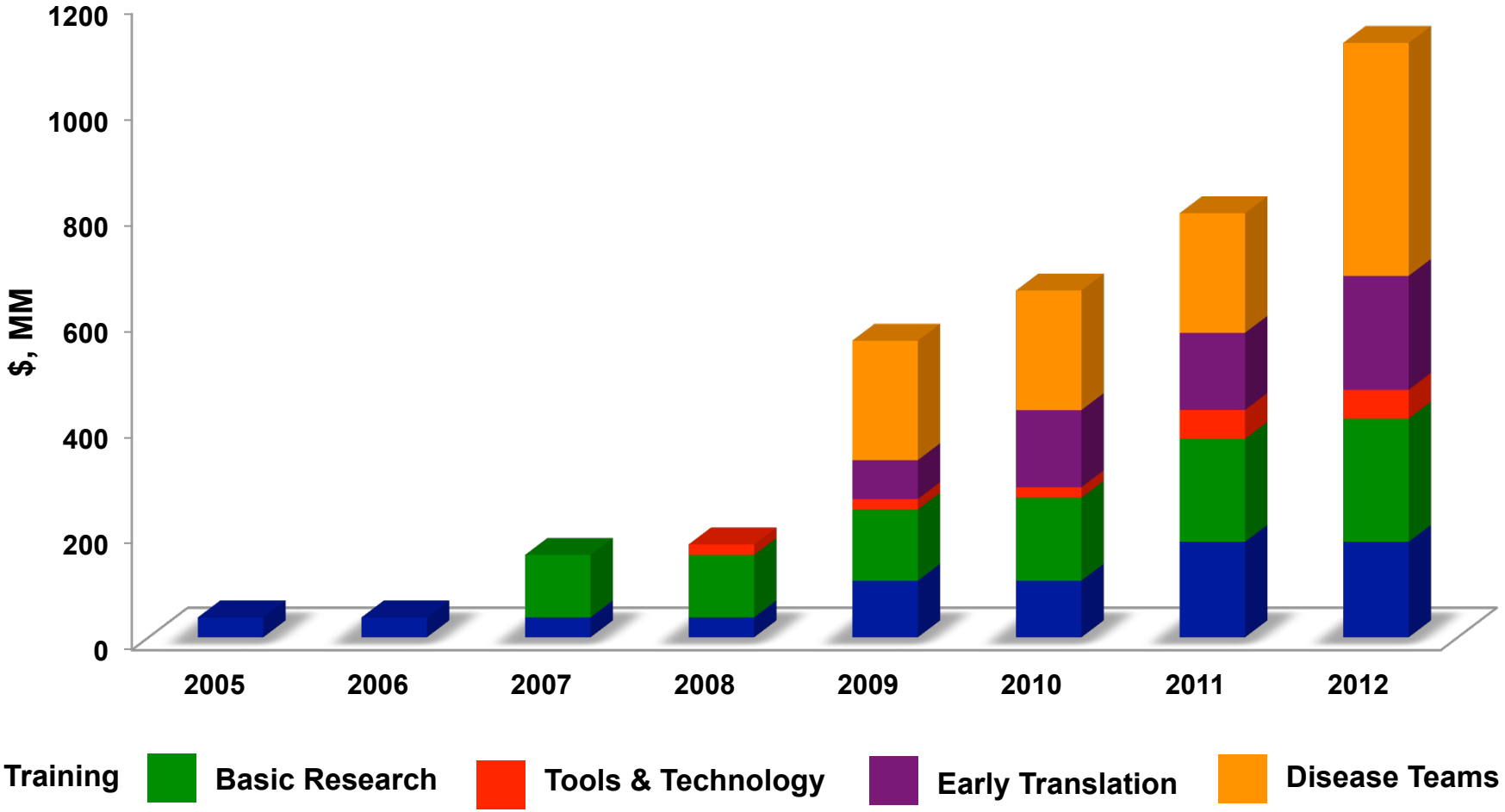


Breakdown: CIRM Training & Bridges Program Initiatives

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

RFA (Year Approved by ICOC)	# of Awards	Funds Approved by ICOC (MM)
Training	**33**	**$130.9**
Training I (2005)	16	$38.9
Training II (2008)	17	$45.2
Training Extensions (2011)	17 (from Training II)	$46.8
Bridges	**16**	**$50.6**
Bridges I (2008)	16	$24.0
Bridges Extensions (2011)	16 (from Bridges I)	$26.6
Totals	**49**	**$181.5**

CIRM Training & Bridges Programs

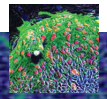
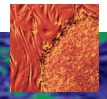
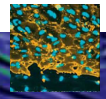
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Training: Predoctoral candidates , post doctoral and clinical fellows

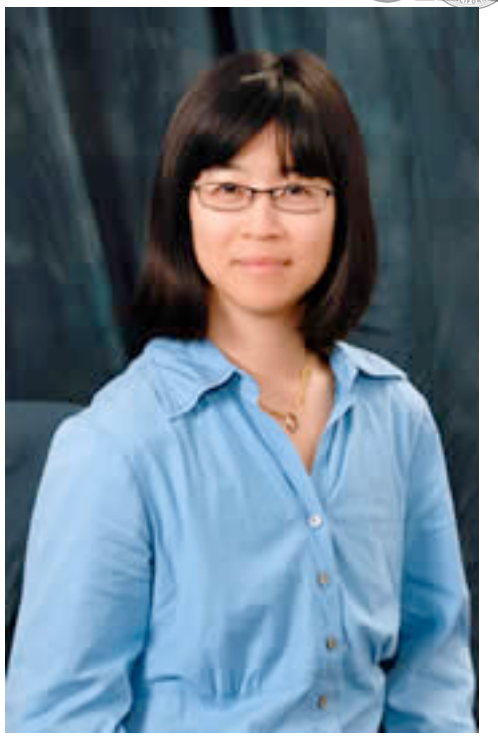
- Mentored laboratory stem cell research
- Course work: Stem cell biology – application to health and disease; ethical legal and social aspects of stem cell research
- To date: 635 CIRM Scholars at 18 institutions, 300 labs

Bridges: Undergraduate, Master's degree candidates especially from CSU and community colleges

- Shared Lab Stem Cell Techniques course
- Mentored internships stem cell research in laboratories in research-intensive universities and biotech companies
- To date: 482 interns from 16 institutions
- Survey 2011: 52% of 163 interns had jobs; 26% enrolled or accepted into graduate, professional programs

Training Program I: CIRM Scholar

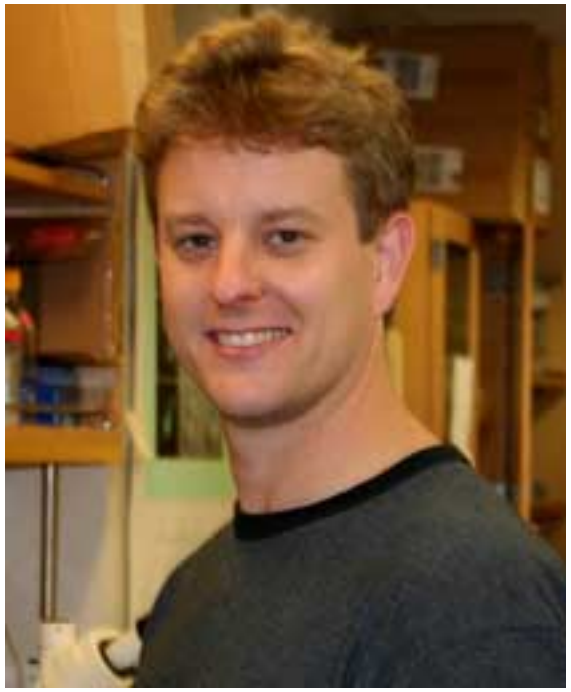


- Louise Laurent, MD, PhD
  - UCSD Training Program
  - Trained as a clinical fellow under Dr. Jeanne Loring from 2006-2007
  - Current Position: Assistant Professor, Department of Reproductive Medicine at UCSD
  - Published key paper reporting technique to determine ethnic origin of stem cell lines and profile of commonly used lines.

Training Program I: CIRM Scholar

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

- Mathew Blurton-Jones, PhD
  - UC Irvine Training Program
  - Trained as a postdoctoral fellow under Dr. Frank LaFerla from 2006-2007
  - Current Position: Assistant Professor Neurobiology and Behavior at UC Irvine
  - Published key paper showing neural stem cells can improve cognition in a mouse model of Alzheimer's disease.



Training Program I: CIRM Scholar

- Ann Zovein, MD
  - UCLA Training Program
  - Trained as a clinical fellow under Dr. Luisa Iruela-Arispe from 2006-2009

  - Current Position: Assistant Professor of Pediatrics and CVRI at UCSF
  - Awarded the Burroughs Wellcome Career Award for Medical Scientists

CIRM Bridges Program Intern

Ms. Laughing Bear Torrez

- CSU San Bernardino Bridges Program
- Bridges internship at UC Riverside with Dr. Duncan Liew
  - First author on a paper on the derivation of neural progenitor and retinal cells from pluripotent stem cells
- Earned Masters degree.
- Honored as college's outstanding graduating student
- Current Position: predoctoral student at Stanford University in the Stem Cell Biology and Regenerative Medicine Ph.D. program

CIRM Bridges Program Intern

Mr. Andrew Singh

- San Jose State University Bridges Program
- Bridges internship at Stanford University with Dr. Julian Sage
- Completed Master's of Biotechnology

- Current Position: research associate at iPierian where he is involved in work with iPSCs for modeling Alzheimer's and other diseases

CIRM Bridges Program Intern

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

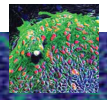
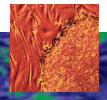
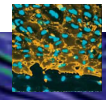
Ms. Kanomi Sasaki-Capela

- CSU Pomona Bridges Program
- Bridges internship at USC with Dr. Victoria Fox; research on standardization of human pluripotent stem cell cultures
- Completed Bachelor's degree, CSU Los Angeles
- Current Position: laboratory and training coordinator, USC Stem Cell Core Facility and investigator with the Core research and development program

Breakdown: CIRM Basic Research Initiative

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

RFA (Year Awarded by ICOC)	# of Awards	ICOC Approved Funding (MM)
SEED (2007)	**73**	**$45.3**
Comprehensive (2007)	**28**	**$72.0**
Basic Biology	**83**	**$113.5**
Basic Biology I (2009)	12	$16.3
Basic Biology II (2010)	16	$22.4
Basic Biology III (2011)	27	$37.8
Basic Biology IV (2012)	28	$38.0
Totals	**183**	**$231.8**

Basic Research Program

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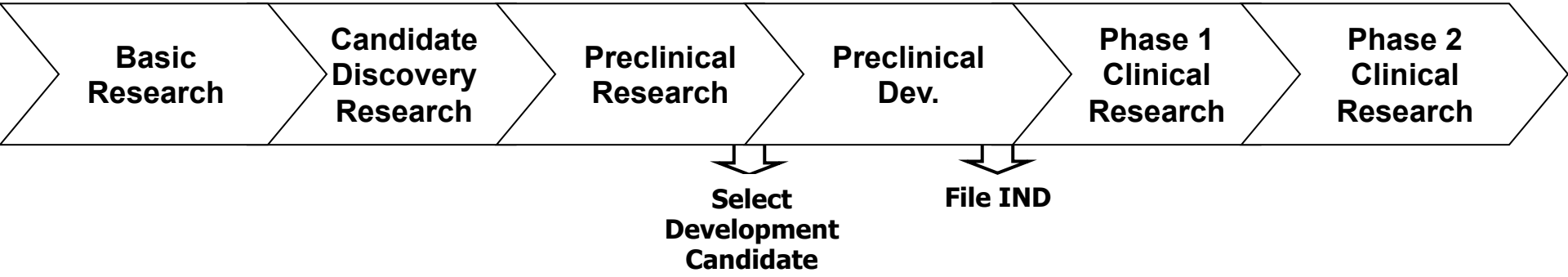
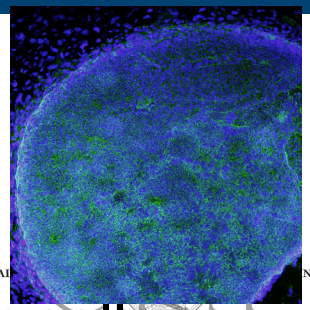


SEED Awards

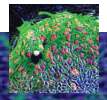
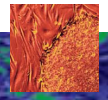
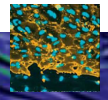
Comprehensive Awards

Basic Biology I, II,III, IV

Basic Research Program Focus: Human Stem Cells



- Supports basic research on **human** stem/progenitor cells
  - 164 Principle Investigators
- Attract researchers new to human stem cell research: SEED program:
  - Attract investigators new to embryonic stem cell research into the field to conduct research on the biology, derivation and application of hESC and their derivatives
  - 31/72 (42%) SEED investigators received 38 other CIRM research grant(s)
    - 12 received a Basic Biology award
    - 9 received New Faculty), New Cell Lines (2) or Stem Cell Transplantation Immunology (1) awards
    - 11 PIs received 14 ‘applied’ awards - 1 Tools and Technologies, 2 New Cell Lines, 9 Early Translational, 2 Disease Team Research awards

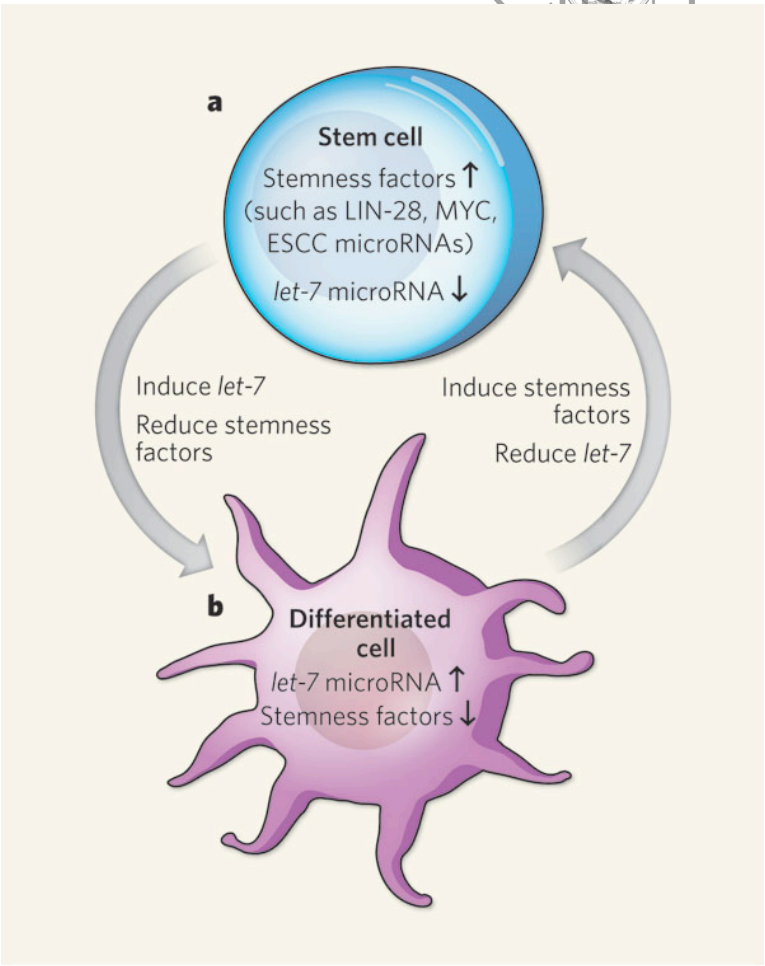




CIRM-Supported Research Highlights

PI: Dr. Robert Blelloch
(UCSF)
SEED grant

- Discovered that two distinct microRNA (ESCC and Let-7 families) play opposing roles in regulation of self-renewal genes

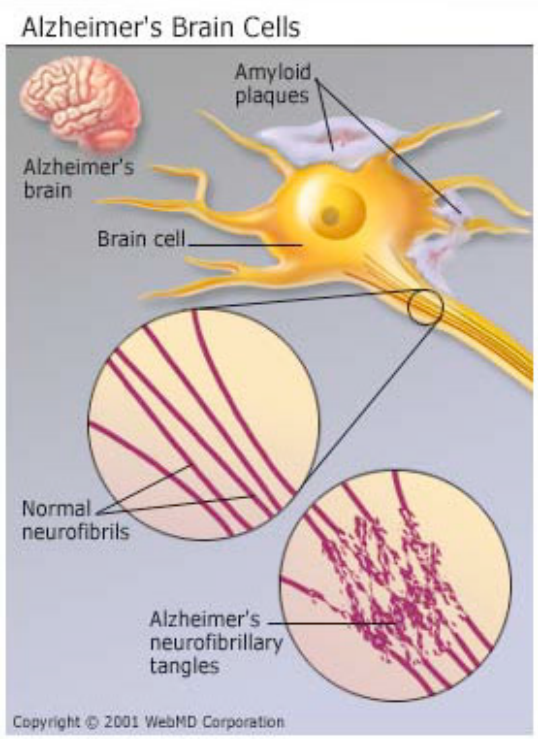
- Provided novel insights into cellular mechanisms that orchestrate stem cell self-renewal



Melton, C, Judson, R.L., Blelloch, R. (2010) Opposing microRNA families regulate self-renewal in mouse embryonic stem cells. **Nature** 463, 621-626.

CIRM-Supported Research Highlights

PI: Dr. Lawrence Goldstein
(UCSD)
Comprehensive grant



- generated iPSCs from Alzheimer's Disease patients and differentiated these cells into neurons
- derived neurons displayed aberrant properties typical of Alzheimer's Disease
- provides a novel system for studying the disease and for developing a platform for drug screening

Israel, M.A., et al. (2012) Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. **Nature** 382, 216-220.

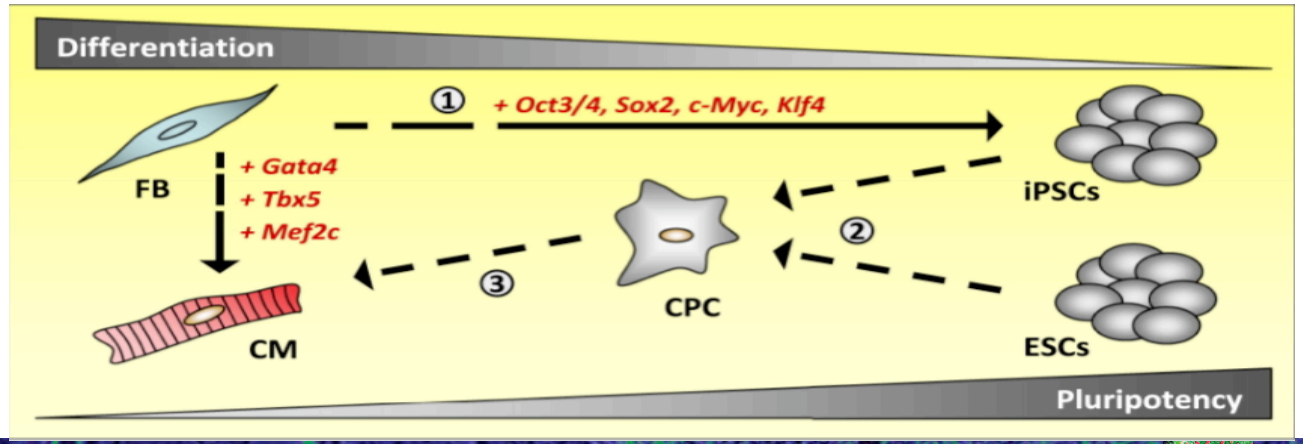
CIRM-Supported Research Highlights

PI: Dr. Deepak Srivastava
(Gladstone)
Comprehensive grant

- First report that committed fibroblasts can be directly reprogrammed into cardiomyocytes without passing through a pluripotent or progenitor state

- May provide a novel strategy for generating new heart cells for therapeutic use

Ieda, M., et al. (2010) Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. **Cell** 142, 376-386.



Breakdown: CIRM Tools & Technology Initiative

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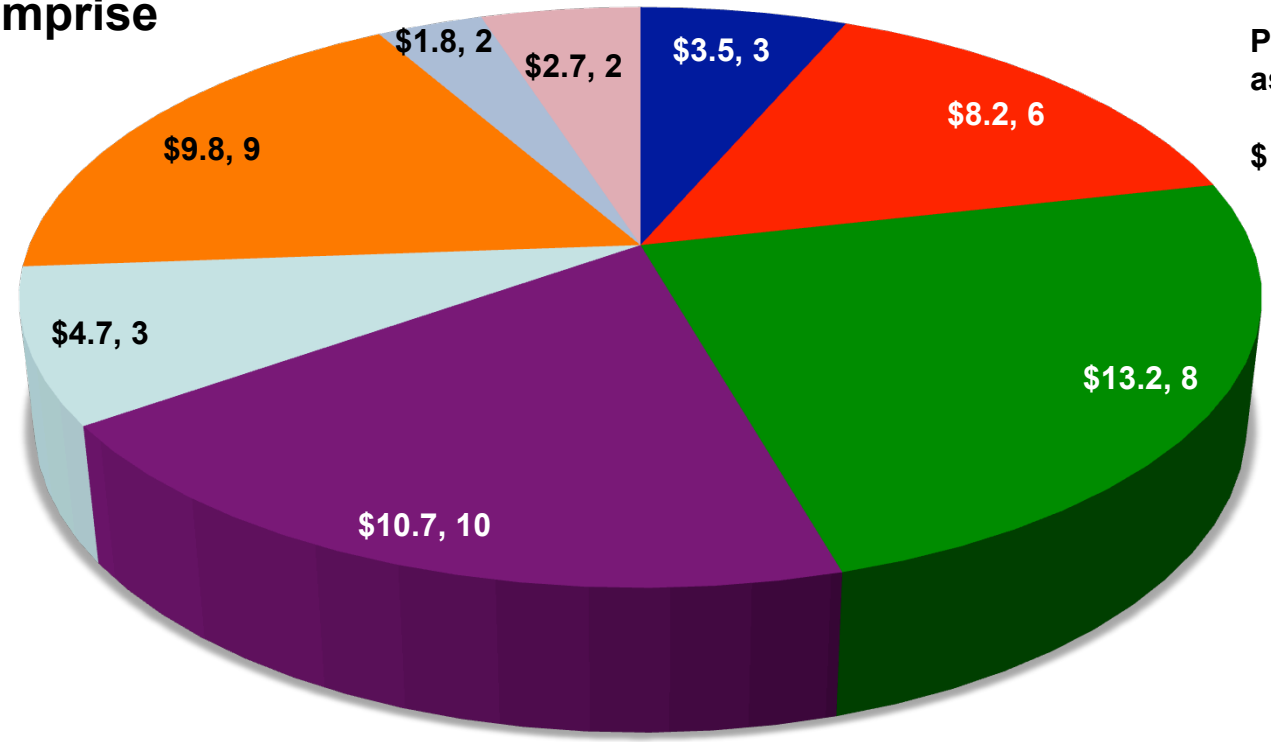
RFA (Year Approved by ICOC)	# of Awards	ICOC Approved Funds (MM)
Tools & Technology I (2008)	23	$19.8
Tools & Technology II (2011)	20	$34.7
Total	**43**	**$54.5**

Breakdown: CIRM Tools & Technology Initiative

43 Awards comprise $54.5 MM



Pie slices are labeled as follows:

$ MM, # of Programs

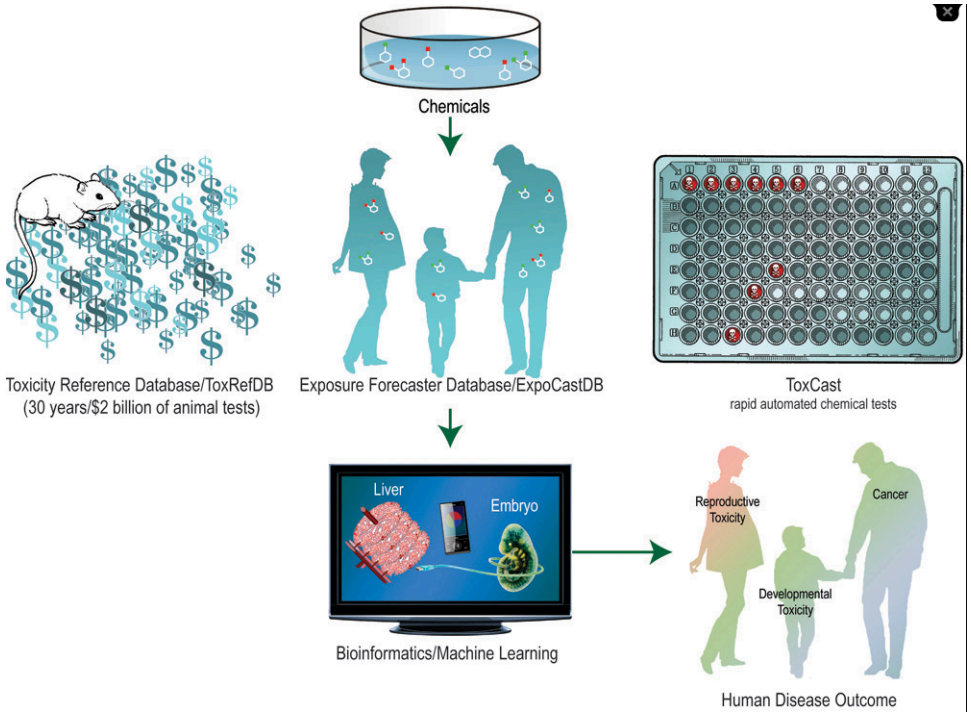
- Markers & Assays
- Screening
- Disease Modeling
- Cell Line Development
- Tissue Engineering
- Imaging
- BioProcess
- Cell Delivery Devices

Tools & Technologies Research Highlights
RT1-01143: McDonough, Vala Sciences Inc.

Contributed to the development of a technology and associated instrument (kinetic imaging cytometer, KIC)) that enables high throughput measurement of the electrical behavior of heart cells and subtypes in heterogeneous populations of cells.

- Won contract from EPA to screen up to 10,000 chemicals as part of their ToxCast program

- Collaboration with VistaGen: Vala will use its KIC platform in conjunction with VistaGen's human pluripotent stem cell derived cardiomyocytes for screening new drug candidates for potential cardiotoxicity



Tools & Technologies Research Highlights
RT1-01108: Loring, Scripps Research Institute

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Goal: Further develop the Stem Cell Matrix database and associated bioinformatics tools to define common features of pluripotent (and differentiated) cells. A potential bioinformatics “assay” replacement for the teratoma assay

Results:

- The Stem Cell Matrix database has grown from datasets on a few hundred lines to several thousand lines
- Publically available - over 1500 data uploads as of ~ 1 year ago

Impact: This large dataset and tool may replace the teratoma assay, particularly in some research settings

Tools & Technologies Research Highlights

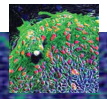
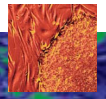
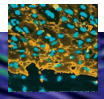
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

RT1-01057: Couture, COH

- Developed an efficient and cGMP-compliant suspension based culture system for hESCs (hPSCs). Generated hESC banks
- Potential Impact: Critical technology for development for clinical use and commercialization

RT1-01024: Unger, Fluidigm

- Optimized and scaled up a highly advanced microfluidic cell culture system compatible with manufacture, produced prototype instruments to drive these chips
- CIRM funding a catalyst for focus in the company, technology being further developed with TnT II award and company co-funding to produce 3 complementary commercial instruments
- Potential Impact: Enable less resource intensive way to screen for conditions affecting stem cell expansion and differentiation

Breakdown: CIRM Early Translation Initiative

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RFA	Program Period	Grants Awarded, #				Funds Committed, MM			
		B*	DCF	DC	Total	B*	DCF	DC	Total
ET I	2009 - 2013	7	---	9	**16**	$29.5	---	$43.9	**$73.4**
ET II	2011 - 2014	---	9	12	**21**	---	$16.7	$54.7	**$71.4**
ET III	2012 - 2015	---	11	10	**21**	---	$19.6	$49.8	**$69.4**
TOTAL		**7**	**20**	**31**	**58**	**$29.5**	**$36.3**	**$148.4**	**$214.2**

Early Translation Awards

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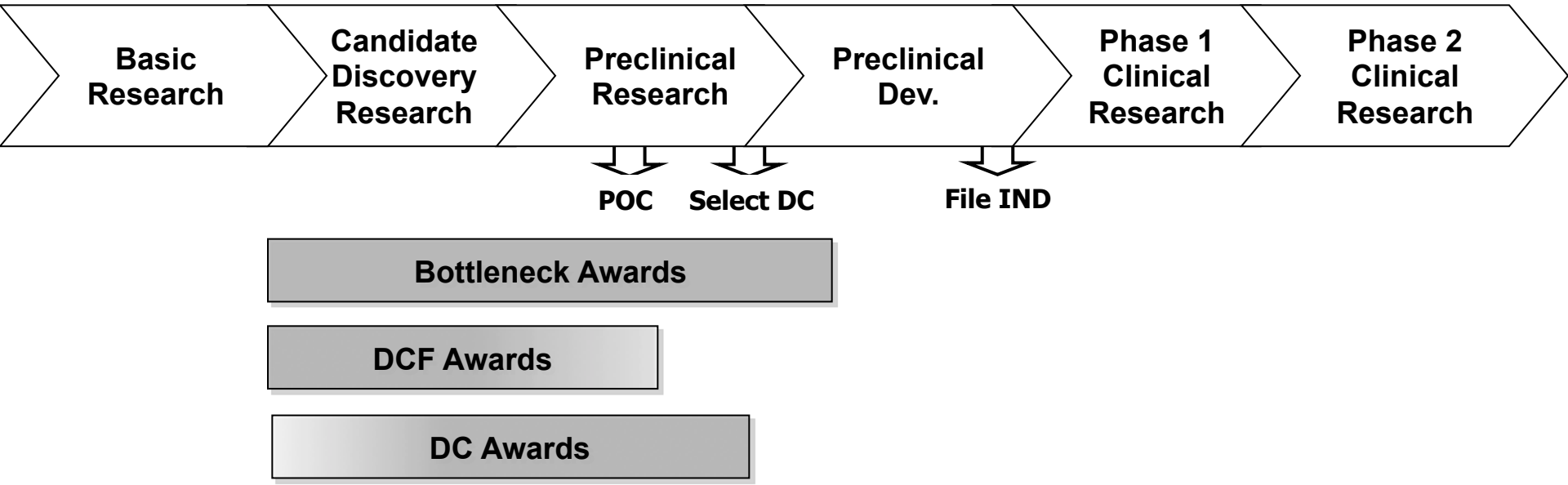
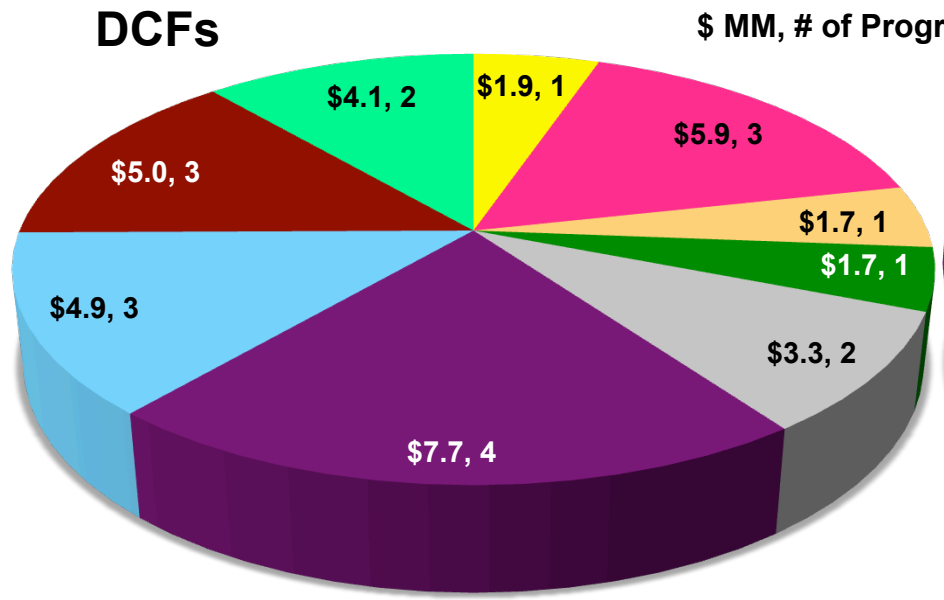


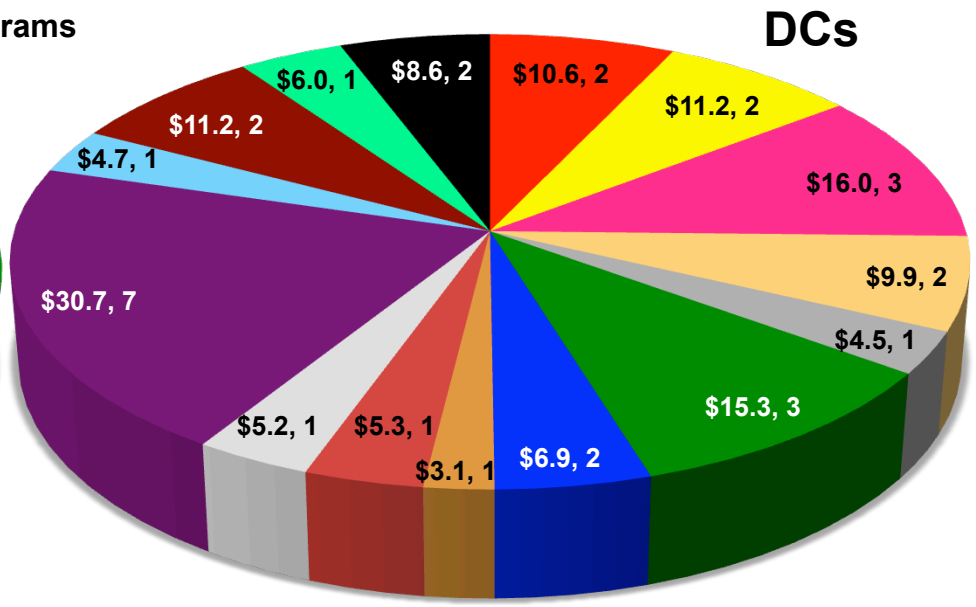
CIRM Early Translation Program

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

51 Early Translation Programs, funding commitment of $185.4 MM

Pie slices are labeled as follows:
$ MM, # of Programs





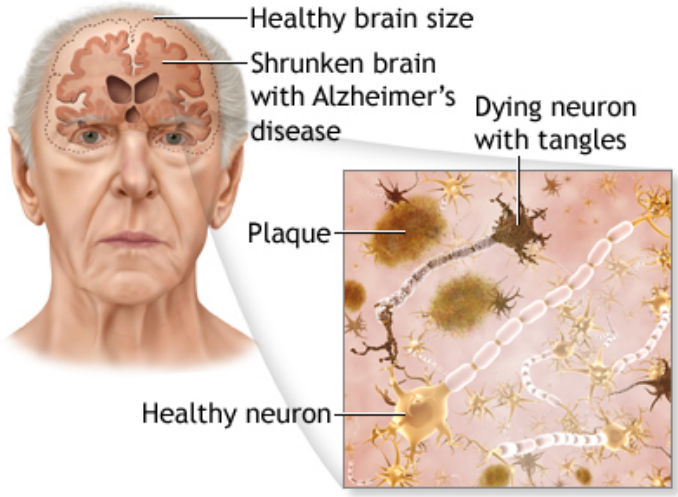
- Blood Disorders
- Bone Disorders
- Cardiovascular Disorders
- Cartilage Disorders
- Endocrine Disorders
- Eye Disorders
- Hematologic Cancers
- HIV/AIDS
- Kidney/Urinary Disorders
- Liver Disorder
- Neurodegenerative Disorders
- Neurologic Injuries
- Pediatric Neurological Disorders
- Skeletal Muscle Disorders
- Solid Cancers

Early Translation Research Outcomes
Early Translation ➡ Disease Team

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

TR-01245 ➡ DR2A-05416

- LaFerla, UCI; CFP- Boyd, Monash University Victoria, AS
- Alzheimer's Disease
- Allogeneic NSC



TR2-01272 ➡ DR2A-05739

- Klassen, UCI
- Disease: Retinitis Pigmentosa
- Approach: Allogeneic retinal progenitor cells

Early Translation Research Highlights:
TR1-01246: Langston, The Parkinson's Institute

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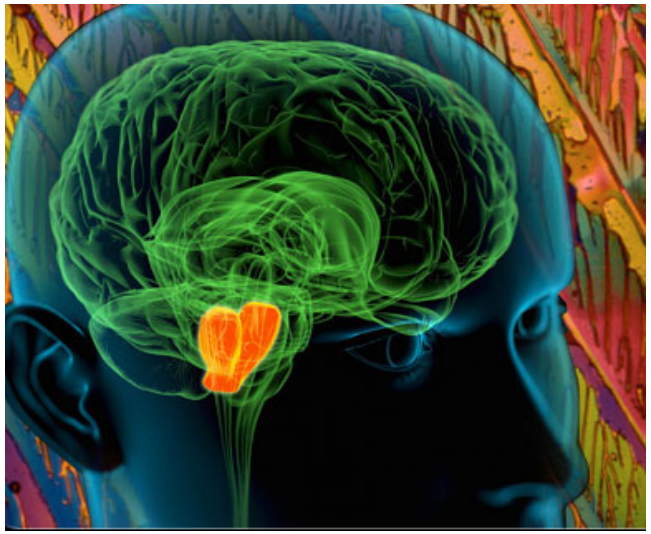
Goal : develop a model for PD is a dish using patient derived lines as a model to study disease mechanisms



Outcomes:

- iPS-derived neurons from a PD patients with causative mutations in either the LRRK2 or alpha synuclein genes show greater susceptibility to cellular toxins, exploring other readouts
- Resource for PD iPSC lines
- Has led to multiple new collaborations, industry and academic, public and private.
- Leveraged new funding both public and private (~$700,000 to date)

Early Translation Research Highlights:
TR1-01232: Hall, The Jackson Laboratory West

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Goal: Eliminate bottlenecks to translation of stem cell research by developing standardized mouse models in appropriate immune background

- Released mouse models for Parkinson's Disease, Type I Diabetes, and Multiple Sclerosis (2)

Impact: Standardized models will facilitate translation of human stem cell based therapies for these diseases

Disease Team Research Awards

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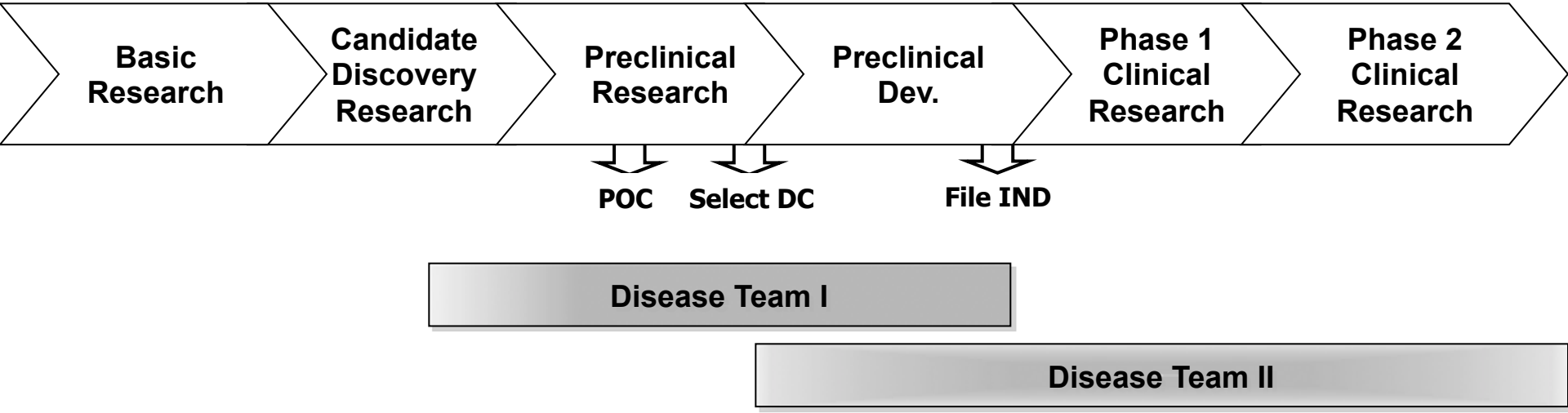

CIRM Disease Teams Initiative: Target End Goals

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RFA (Year Awarded by ICOC)	# of INDs	$ (MM) towards IND	# of Early Stage Clinical Trials	$ (MM) towards Early Stage Clinical Trials
Disease Team I (2009)	14	$228.0	0	$0
Disease Team II (2012)	3	$60.0	8	$148.1
TOTALS	**17**	**$288.0**	**8**	**$148.1**

CIRM Disease Teams Initiative

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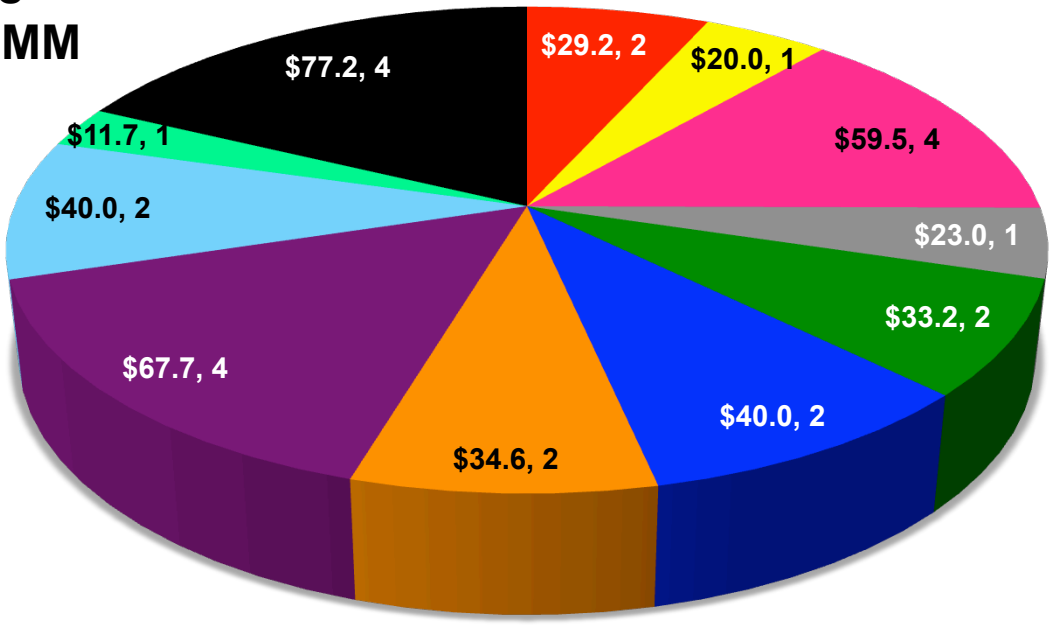
25 Disease Teams comprise $436.1 MM

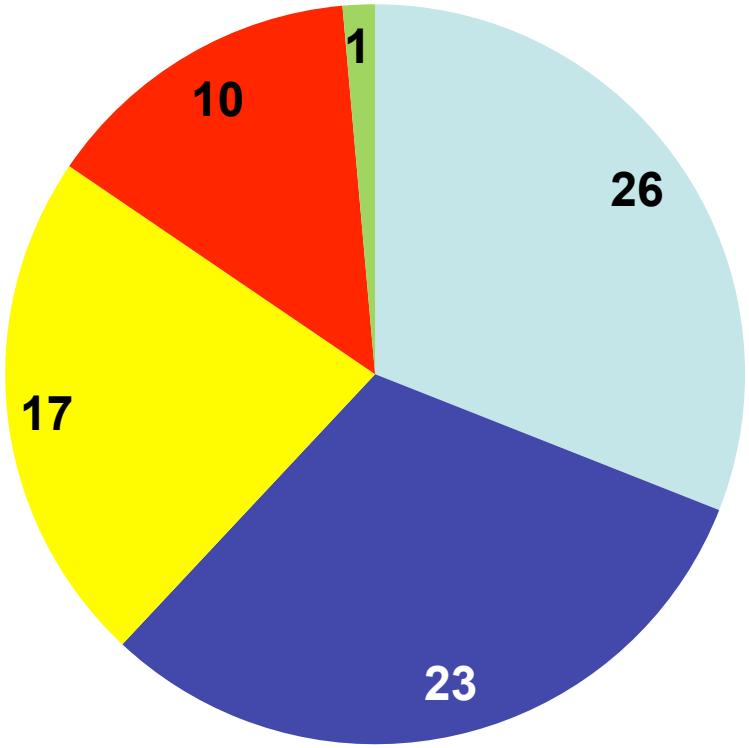


Pie slices are labeled as follows:

$ MM, # of Programs

- Blood Disorders
- Bone Disorders
- Cardiovascular Disorders
- Endocrine Disorders
- Eye Disorders
- Hematologic Cancers
- HIV/AIDS
- Neurodegenerative Disorders
- Skin Disorder
- Neurologic Injuries
- Solid Cancers

Therapeutic Modality



Therapeutic modality of CIRM translational portfolio current as of October, 2012
13 DTI – 5 allogeneic, 4 autologous (1 iPS), 2 Mab, 2 small molecules
11 DTII – 7 allogeneic, 2 autologous, 1 Mab, 1 small molecule
2 SPI – 1 allogeneic, 1 autologous

Driven by science and evidence needed on regulatory pathway

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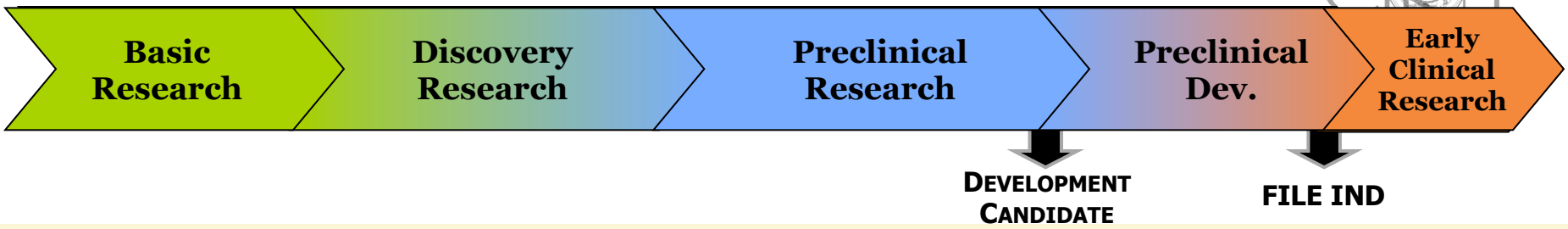
- Prior to award
  - mutually agreed upon Go, no go and progress milestones, success criteria
  - During the conduct of research
    - Interactive ongoing discussions between CIRM scientists and funded research team
    - Updates on interval progress on bi-annual to quarterly basis and overall annual progress updates
    - clinical development advisor meetings yearly/ key milestones (DT1s have been assessed in 2011 at 12-18 month milestone, now at 24-30 month milestone)
  - CIRM/FDA webinars, educational 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)

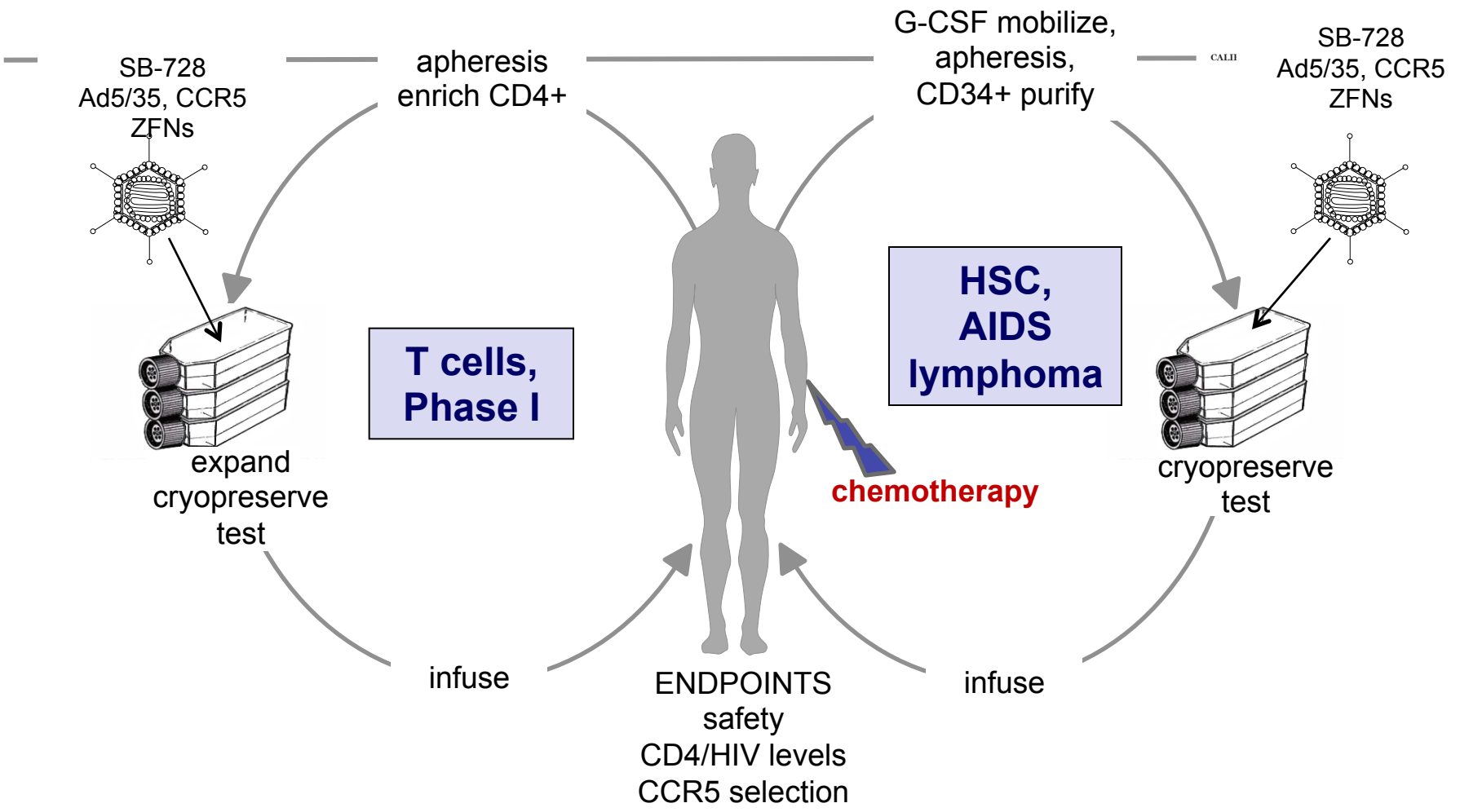
HIV/AIDS (2)

Cancer (4)

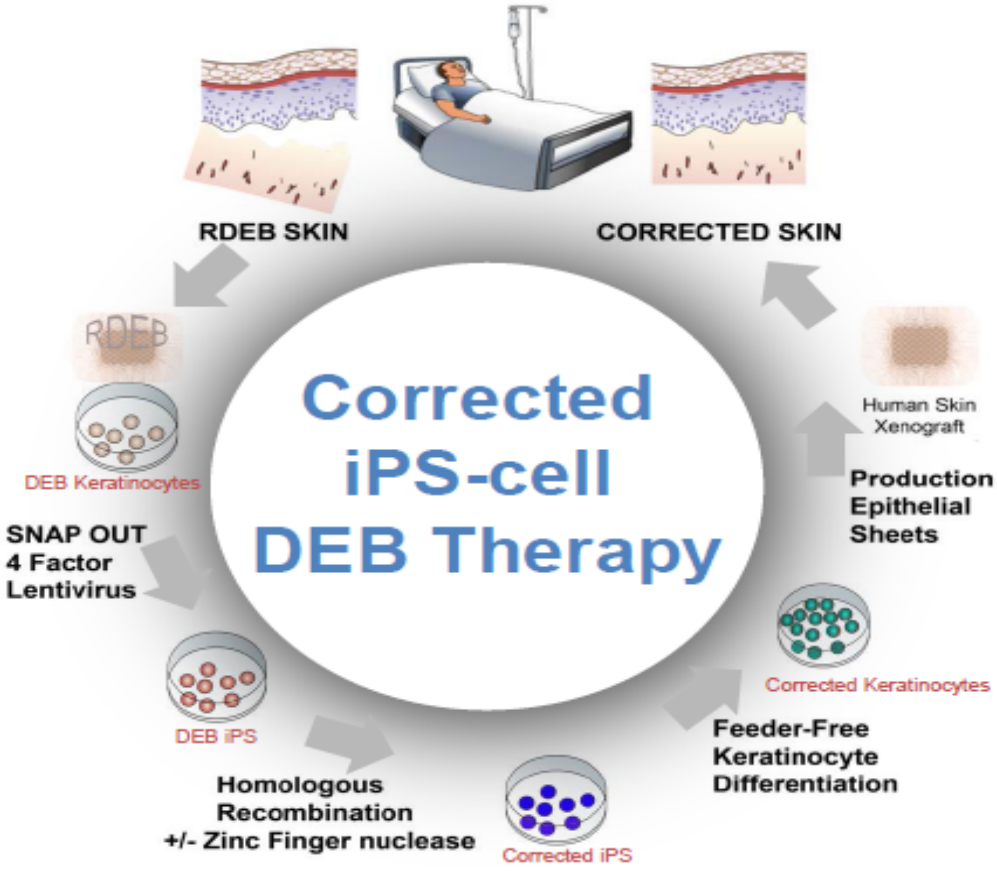
Blood Disorders (1)

Skin Disease (1)

Example – moving to the clinic in HIV/AIDS



Example: Moving to the clinic in rare genetic disorder dystrophic epidermolysis bullosa



Example: Moving to the clinic in cancer

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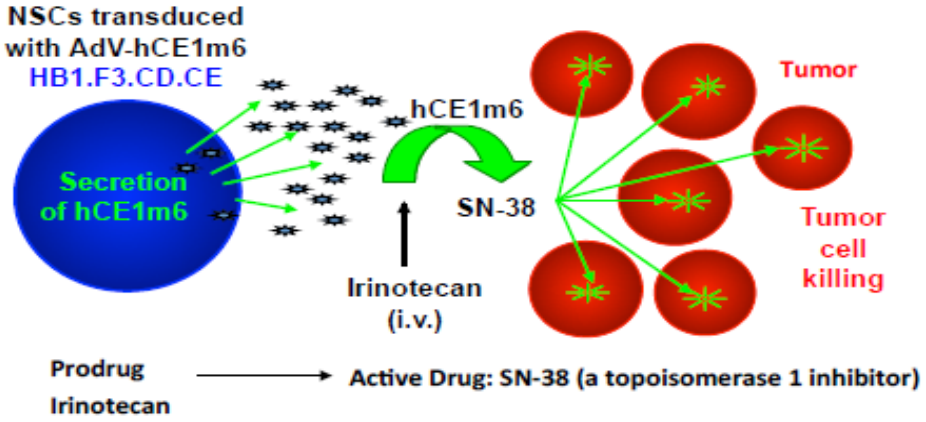
CIRM DT Cell Therapy/Therapeutic Candidate:
CE-expressing HB1.F3.CD NSCs to locally convert prodrug CPT-11 to SN-38 in recurrent glioma patients



Optimize NSC distribution to tumor cells

- ✔ NSC Delivery Route: intracerebral vs. intravenous
- ✔ NSC Dose: high/low
- ✔ NSC Tracking: SPIO labeling for MRI imaging

Optimize CE/CPT-11 efficacy

- ✔ CE variant selection: rCE vs. hCE1m6
- ✔ Optimize adeno transduction of NSCs
- CPT-11 dose regimens

City of Hope CIRM

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Example: Spinning out a company

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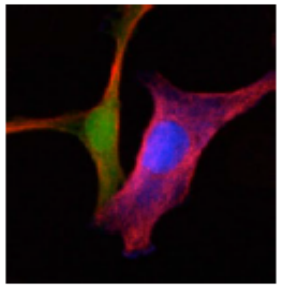

TheraBiologics Inc.

Karen S. Aboody, MD
Founder, Chief Scientific Officer & Director

A clinical stage biopharmaceutical company developing a neural stem cell platform for targeted cancer treatment

Cancer Targeted Drug Delivery™

Tom Smart, MBA
Chair, Board of Directors

Alexander J. Annala, PhD
Chief Operating Officer & Director

Rex Moats, PhD
Director

TBX-01: NSC.CD + 5-FC→ 5-FU active drug

TBX-02: NSC.CE + CPT-11→ SN-38 active drug

- **GMP Scale-up & Optimization**
- **Phase II – III Target Product Profile Development & Clinical Trials**

www.therabiologics.com

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Summary of DT highlights

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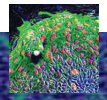
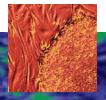
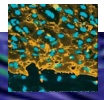
- Over half of the DT1s successfully advanced through their pre-IND meeting with FDA, towards an approvable IND
- 1 clinical trial to start in 2013, expect 1 to 2 more in 2013
- Anticipate 5 clinical trials by end of 2014
- 5 have collaborative funding partners; 1 has collaboration with disease foundation; 2 have companies as PI or co-PI; 2 have founded companies
- 21 invention disclosures, 24 active/pending patent applications
- 18 scientific publications

Clinical Investigation vs. Development?

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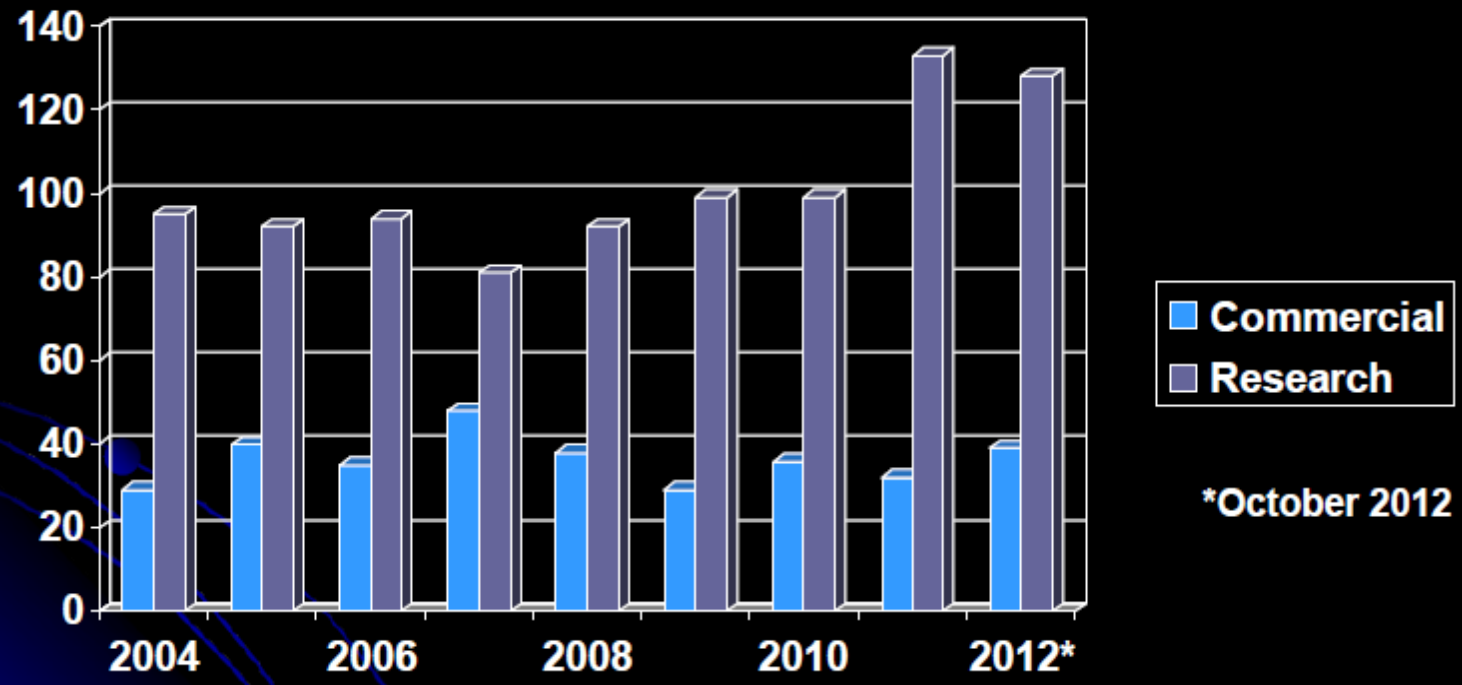
Regulatory Files Submitted to OCTGT: Commercial or Research Sponsors



FDA Experience cell-based products

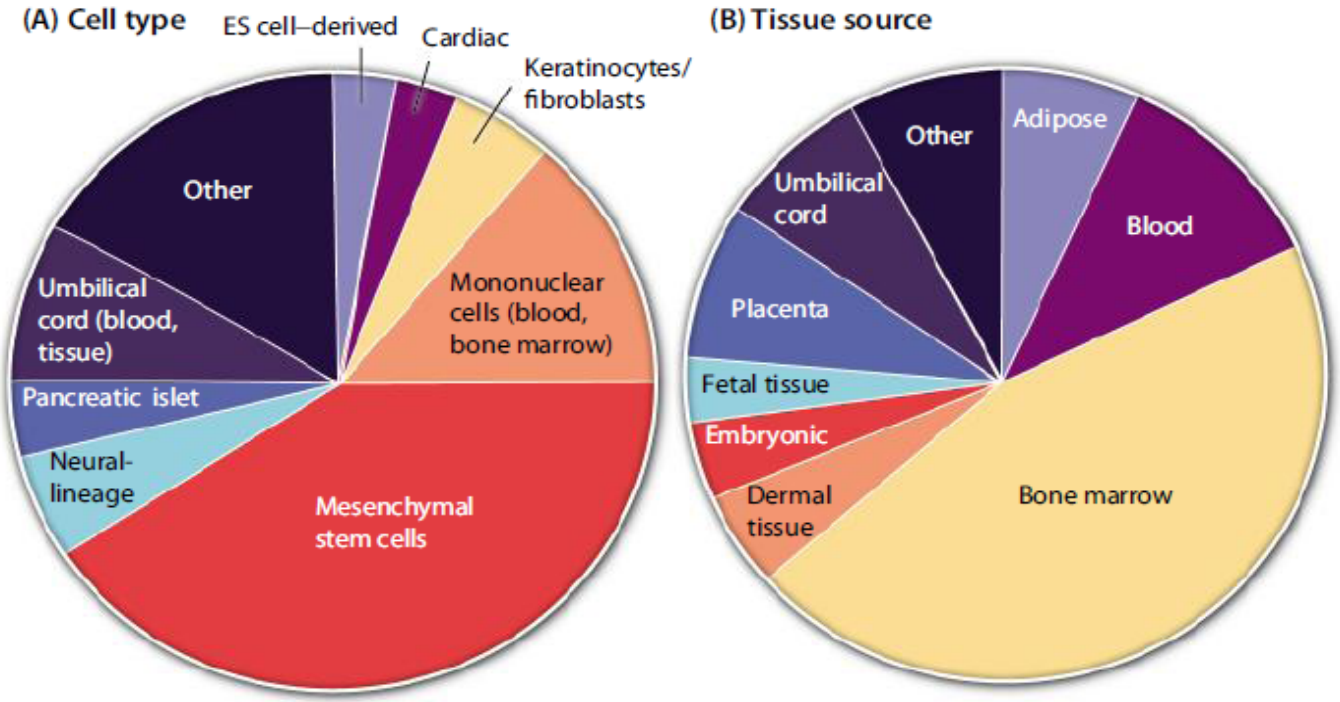


Fig. 1. FDA/CBER experience. Original submissions (~115) to initiate clinical investigations for cell-based RM products were submitted to FDA/CBER from 2007-2011. The cellular components of these products spanned a wide spectrum of (**A**) cell types and (**B**) tissue sources; ~70% of submissions were for new products and 30% were for new indications for previously evaluated (cross-referenced) products. Assessment of tumorigenicity risk was performed by direct testing of the product (in vitro or in vivo studies) (43%) or through consideration of product attributes, the scientific literature, and/or previous clinical experience (57%).

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