CALIFORNIA'S STEM CELL AGENCY

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Translation Program Update

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

Patricia Olson, Ph.D.
Executive Director, Scientific Activities

Presentation to the ICOC October 9, 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

Translational Portfolio RFAs cover product development spectrum

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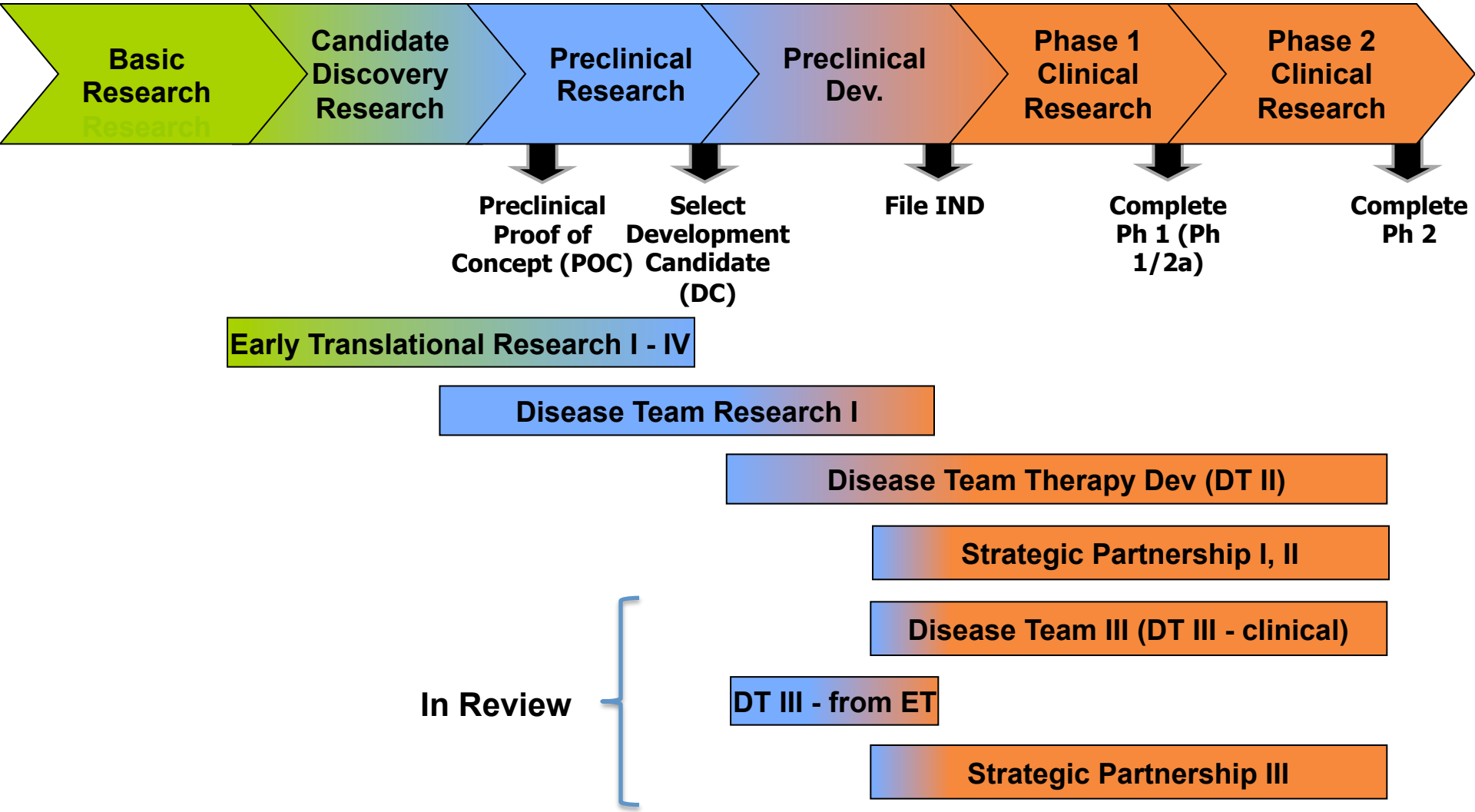
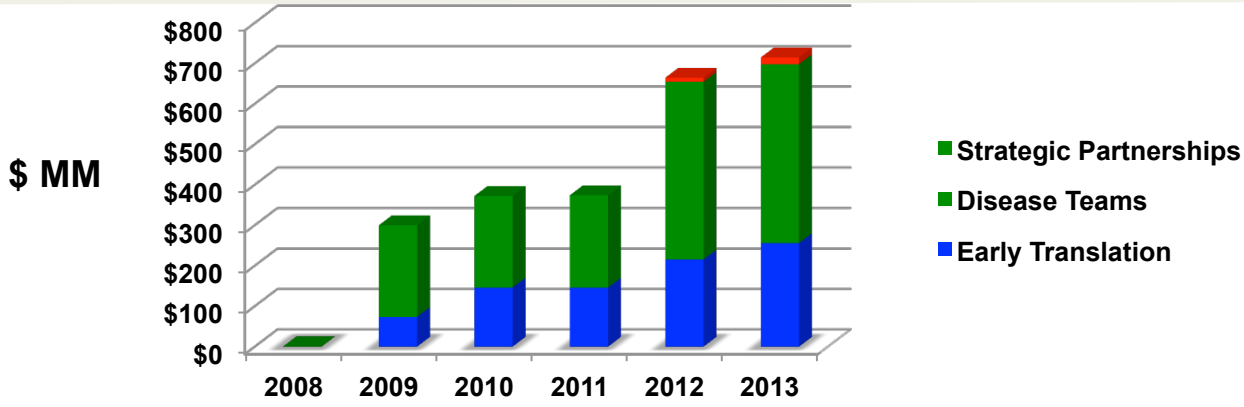
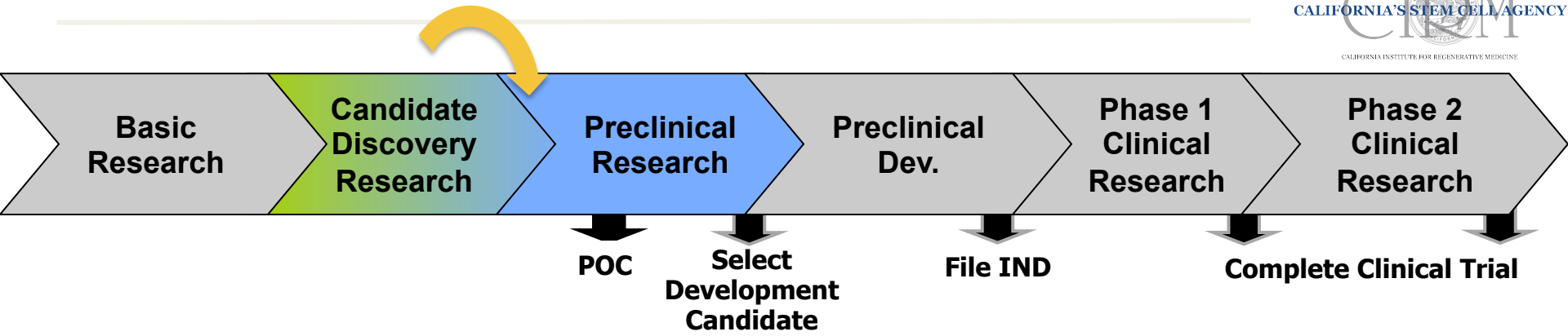


Annual Cumulative CIRM Translation Program-ICOC Awarded Funds *(as of Aug '13)*



		2008	2009	2010	2011	2012	2013
# Awards, Cumulative		***0***	***30***	***51***	***51***	***84***	***98***
	Early Translation	0	16	37	37	58	71
	Disease Teams	0	14	14	14	25	25
	Strategic Partnerships	0	---	---	---	1	2
$ MM, Cumulative		***$1.1***	***$300.0***	***$372.3***	***$374.1***	***$664.6***	***$714.6***
	Early Translation	---	$73.4	$145.7	$145.7	$215.1	$255.7
	Disease Teams	$1.1	$226.6	$226.6	$228.4	$439.5	$442.5
	Strategic Partnerships	---	---	---	---	$10.0	$16.4

Early Translational Program



Program Goal: Enable the early steps in the translation of promising, innovative stem cell discoveries

Rationale: Therapeutic hypothesis testing

Objective: Within project period,

- Achieve *in vitro* or *in vivo* proof of concept (DCF award), or
- Achieve a development candidate ready to move into IND-enabling preclinical development (DC award), or
- Address a translational bottleneck (Bottleneck award)

Early Translation Program: Summary

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RFA	Program Period	Grants Awarded, #				Funds Committed, $ MM				Funds, Awarded $ MM
		B*	DCF	DC	Total	B	DCF	DC	Total	
ET I	2009 - 2012*	8	-	8	***16***	34.7	-	38.7	***73.4***	***72.0***
ET II	2011 - 2014	-	9	12	***21***	-	16.7	55.6	***72.3***	***64.1***
ET III	2012 - 2015	-	11	10	***21***	-	19.6	49.8	***69.4***	***65.0***
ET IV	2013 - 2016		8	5	***13***		15.4	25.2	***40.6***	***≤ 40.6***
	Total	***8***	***28***	***35***	**71**	***34.7***	***51.7***	***169.3***	***255.7***	***≤ 241.7***

* 13 of the 16 ET I are closed or are being closed

Early Translation Program: Goal

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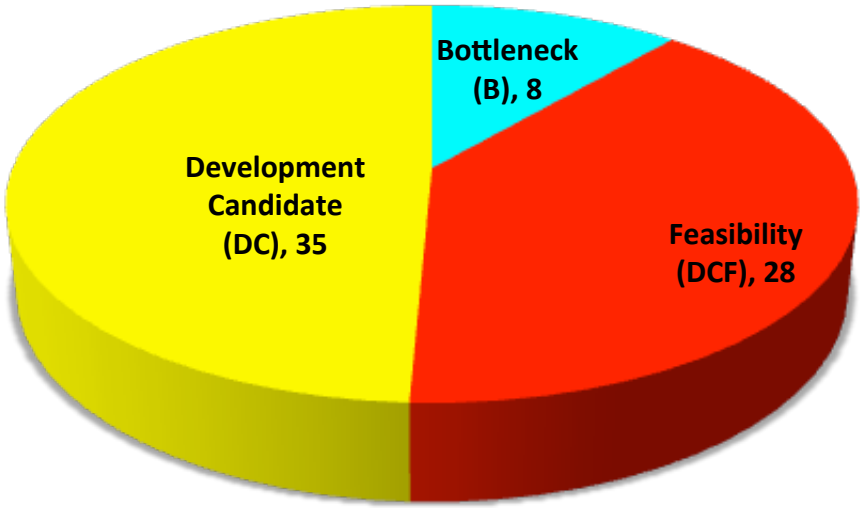
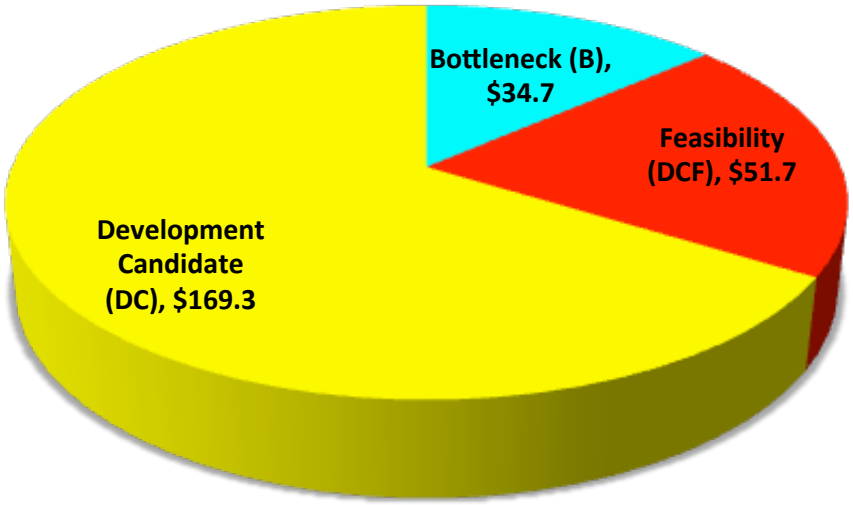
71 Awards *



$255.7 MM Committed^



* Excludes conversions
^ $241.7 actual

Early Translation Program: Priorities

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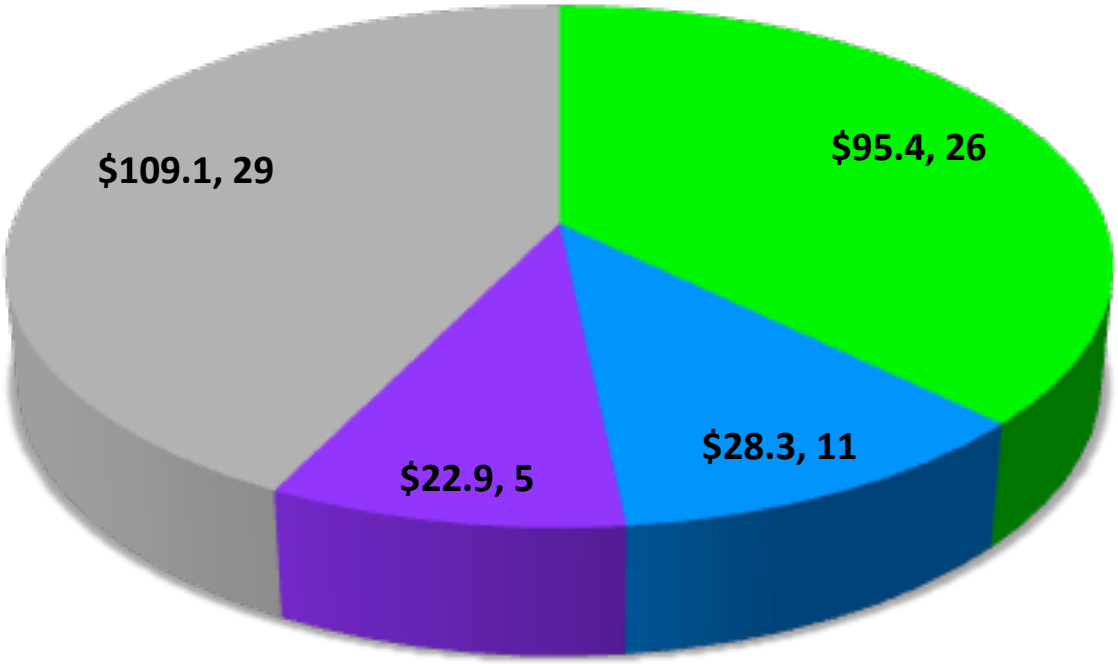
- Advance cell therapies derived from pluripotent stem cells
- Advance therapeutic candidates using cells derived from human pluripotent stem cells
- Address bottlenecks to advancement to the clinic of effective, novel cell therapies; particularly cell therapies derived from human pluripotent stem cells.

Early Translation Program: PSC Priority



Pie slices are
$ MM or # awards

PSC – Cell Therapy
PSC – DC Discovery
PSC – Translational Bottlenecks
Other

Early Translation Program: PSC Priority, Detail

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		ET 1	ET2	ET3	ET4	All ET	%, All ET
# Awards		**16**	**21**	**21**	**13**	***71***	
	PSC-derived Cell Therapy	6	8	7	5	26	37%
	PSC Derivitive for Therapeutic Candidate Discovery	-	3	4	4	11	15%
	Bottlenecks to PSC-derived Cell Therapy	5	-	-	-	5	7%
	Other	5	10	10	4	29	41%
$ MM		**$73.4**	**$72.3**	**$69.4**	**$40.6**	***$255.7***	
	PSC-derived Cell Therapy	$30.2	$24.1	$28.5	$12.4	**$95.4**	37%
	PSC Derivitive for Therapeutic Candidate Discovery	-	$9.6	$6.9	$11.8	**$28.3**	11%
	Bottlenecks to PSC-derived Cell Therapy	$22.9	-	-	-	**$22.9**	9%
	Other	$20.3	$38.5	$34.0	$16.4	**$109.1**	43%

Early Translation Program: Outcomes ET I, II to Date

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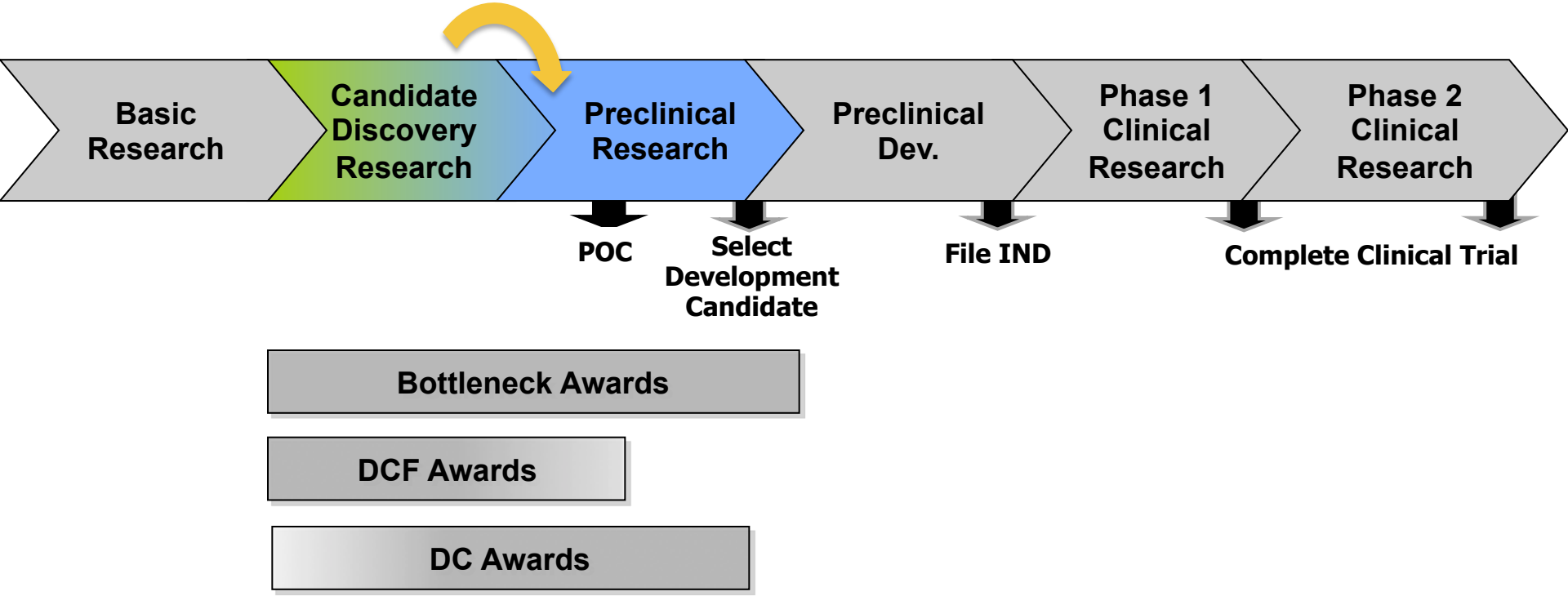
- 123 scientific publications; 31 in "high impact" scientific journals
- 23 invention disclosures, 14 active/pending patent applications
- Attracted co-funding – 5 Collaborative funding partners contributed $14.3 million to 14 funded ET projects, leveraging $55 million of CIRM funding

Early Translation Awards



Early Translational I: Bottleneck Awards

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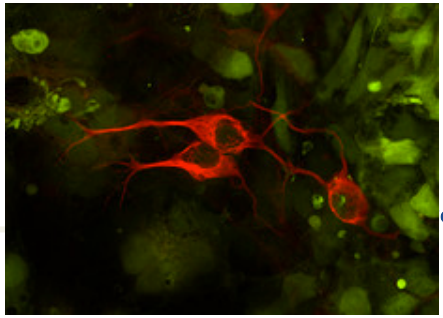
8 Awards focused on:

- Better models for developing/testing candidate therapies, 3 awards
- Characterizing, mitigating risks of PSC-derived cell therapies (teratoma/tumorgenicity, genetic instability, immunogenicity), 5 awards

Better models for developing/ testing candidate therapies

- TR1- 01232, Hall/Kaur, Jackson Laboratory West
  - Developed and released standardized mouse models for Type 1 diabetes, Multiple sclerosis, Parkinson's disease; models near release for myocardial infarction, stroke, spinal cord injury and traumatic brain injury
- TR1- 01246, Langston, Parkinson's Institute:
  - Derived over 50 iPSC lines from PD patients with causative mutations; defined phenotypic readout
  - Led to multiple new collaborations and new funding from both public and private (~$700,000)
- TR1- 01269, Tarantal, UC, Davis:
  - With a long term goal of treating inherited pediatric hematologic disorders, showed in a relevant preclinical model long term high levels of cord blood engraftment in in utero models with no adverse events. Showed imaging could be used for longitudinal monitoring of cell fate

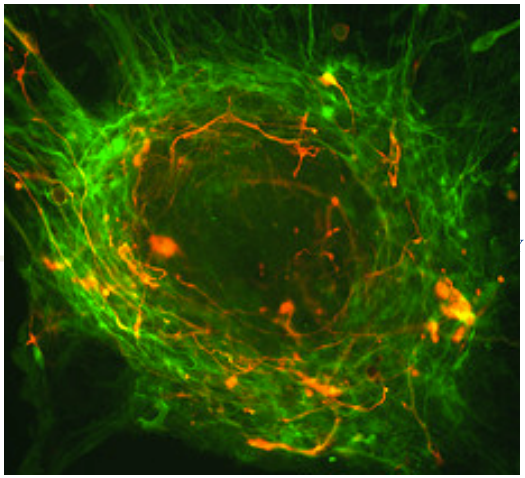
Mitigating risk of PSC-derived candidate therapies



- TR1-01227, Greene, Gladstone Institute
  - Developed assays and technologies to look at role of retro-element transposition in genomic stability during iPSC generation and maintenance. Published that reprogramming may be associated with increased endogenous retro-transposition
- TR1- 01277, Xu, UCSD
  - Developed and published an improved method for episomal (non-integrative) iPSC generation. Tested a suicide gene approach for residual PSC purging - may not be as effective as claimed by others; conducted and published the work that initiated useful debate on immunogenicity of autologous iPSC, further addressed in manuscript under review
- TR1- 01250, Loring, Scripps
  - In collaboration with Partner PI Laslett (CFP – State of Victoria), successfully generated and characterized novel live PSC reactive, antibodies at least one of which is better than the standard antibody used to detect residual PSC

Image courtesy of A. Ghosh lab, UCSD

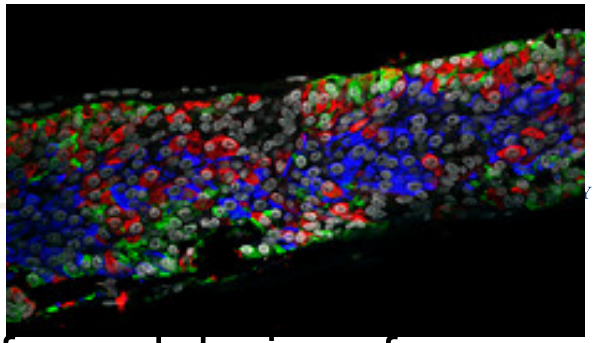
Mitigating risk of PSC-derived candidate therapies



- TR1-01276, West, BioTime
  - Characterized clonal embryonic progenitor lines (EPC) derived from hESC for differentiation to cartilage, bone and vascular endothelial cells. Identified and tested in a model of cartilage repair a chondrogenitor EPC line that showed articular cartilage formation. (publication)
  - Used EPC and phage display to identify peptides and antibodies specific for subsets of differentiating cell populations that can be used for monitoring hPSC differentiation and for purification of specific progenitor lineages (publication, patent application filed)

Image courtesy of G. Fan, UCLA

Mitigating risk of PSC-derived candidate therapies



- TR1-01215, Kelly, Viacyte
  - Developed and conducted in vivo studies that informed design of definitive IND enabling teratoma/tumorigenicity studies; functional and histological data were published in a paper describing scalable system for differentiation of pancreatic progenitors from hESC
  - Developed and established feasibility of an automated system and associated software for the in vitro immunocytochemical detection of residual hESC in the manufacture of the pancreatic progenitor cell component of combination product candidate VC-01. Reporter lines generated by Partner PI Ed Stanley (CFP – State of Victoria) have provided important corroborative data in the development of the this assay
  - Defined and establishing feasibility of assays for encapsulation device integrity.
  - Contributed to product development continuing in CIRM DT1 and newly initiated SP1 awards

Image courtesy of K. Kadoya. Viacyte

Early Translation I, II: DC, DCF Research Awards

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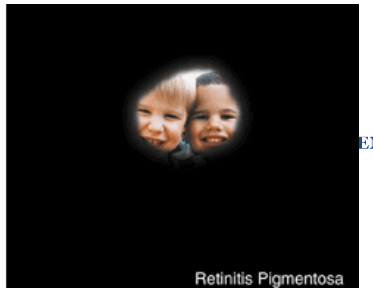
- 20 projects with a goal of achieving a therapeutic development candidate (DC awards) ready for IND-enabling development
- 9 projects with a goal of achieving proof of concept for a development candidate (DCF awards)
- Outcomes to date
  - 2 awarded DT II funding
  - 1 reviewed, recommended and approved for Bridge funding
  - 5 submitted eligible Letters of Intent for Disease Team III

Early Translation I, II Research Awards: Eye Disease

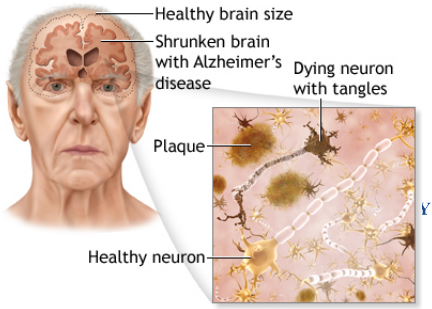


- TR2-01794, Klassen, UCI
  - Allogeneic tissue-derived retinal progenitor cells for retiniitis pigmentosa, DC award
  - Awarded DT funding (DR2A-05739)
- TR1-01219, Freidlander, Scripps
  - Autologous iPSC-derived RPE for atrophic AMD, DC award
  - Developed novel iPSC derivation method where replaced 3 out 4 Yamanaka factors with small molecules to generate 1-factor iPSC (1F-iPSC). Following extensive comparative in vitro and in vivo characterization, concludes that 1F-iPSC-RPE may be superior for clinical use. Published.
  - Conducting studies of technology with skin biopsies from AMD patients, the target population for therapy

Early Translation I, II Research Awards: Eye Disease

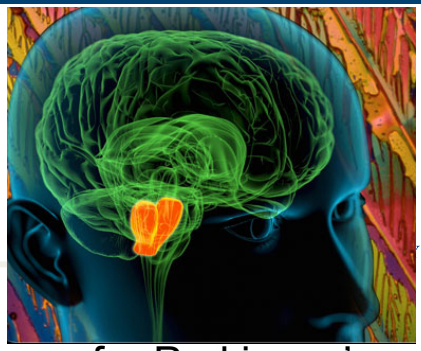
- TR1-01272, Travis, UCLA
  - PSC-derived RPE ± genetic modification to express negative regulators of complement for atrophic AMD. DC award
  - Defined a molecular signature for evaluating the fidelity of hPSC conversion to RPE; demonstrated that functional RPE cells can be derived from multiple lines of hESC and hiPSC with varying efficiencies (published).
  - Continued work to optimize iPSC-derived RPE
- TR2-01768, Deng, UCLA
  - Autologous tissue-derived limbal stem cells for corneal injury, DCF award
  - Developed xenobiotic-free culture conditions for the effective expansion of LSC based on markers and criteria previously demonstrated to be clinically relevant.

Early Translation I, II Research Awards: Neurodegenerative Disease – AD, HD



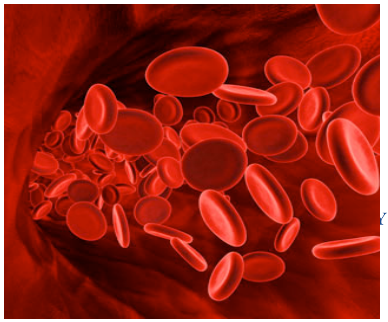
- TR1-01245, LaFerla, UCI
  - Allogeneic ESC or tissue-derived NSC for Alzheimer's Disease. DC award
  - Disease team funding awarded (DR2A-05416)
- TR1-01257, Nolta, UCD
  - Allogeneic hMSC engineered ex vivo to deliver siRNA to silence expression of mutant huntingtin mRNA for treatment Huntington's Disease. DC award
  - Showed, in an in vitro model system, reduction of mHTT protein in recipient cell population due to transfer of anti-HTT siRNA from NSC. Publication, patent application filed.
- TR2 -01841, Thompson, UCI
  - Allogeneic hESC-derived NSC, APC or NPC for Huntington's Disease. DC award
  - Selected NSC, successfully differentiated from GMP-compatible hESC line. Showed neurological and behavioral improvement in mouse model of HD. Full characterization, dosing studies in progress

Early Translation I, II Research Awards: Neurodegenerative Disease – PD



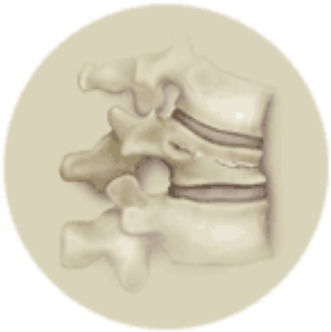
- TR1- 01267, Snyder, Sanford Burnham
  - Allogeneic committed neural progenitors derived from ESC, iPSC or tissue for Parkinson's Disease. DC award
  - Selected genetically modified hESC line based on comparative studies in a relevant preclinical disease model of differentiated committed neural progenitors from several PSC or tissue derived NSC. Made a research working cell bank; developing optimal cell preparation strategies
- TR2- 01856, Zeng, Buck Institute
  - Allogeneic hPSC-derived dopaminergic neural precursor cells (NPC) for Parkinson's Disease. DC award
  - Selected hESC line and a back-up hESC line as source for NPC. Made research working cell banks. Developed scalable GMP compatible process, and showed comparability to research process derived NPC
- TR2- 01778, Gage, Salk Institute
  - Patient iPSC-derived in vitro neurons + astrocytes co-culture model to identify anti-inflammatory small molecules against a proposed target that could be neuroprotective and correlate activity in assay with patient data from Partner PI, J. Winkler (CFP, BMBF). DCF
  - Fibroblasts received from clinically well characterized PD patients, iPSC lines derived, co-culture system under development, optimizing astrocyte differentiation

Early Translation I, II Research Awards: Blood Disorders



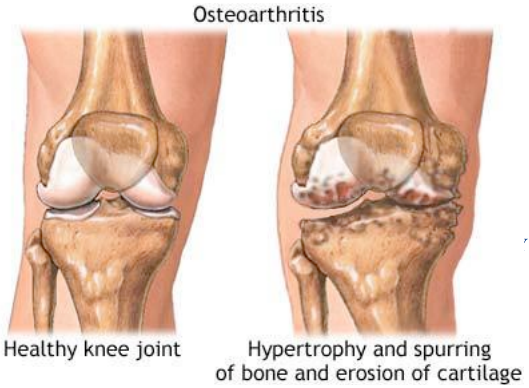
- TR1-01272, Verma, Salk Institute
  - Autologous iPSC-derived HSC genetically corrected ex vivo by homologous recombination to treat Fanconi Anemia, X-SCID
  - Derived iPSC lines from skin samples from patients with Fanconi Anemia and X-SCID; generated preclinical mouse models of X-SCID and Fanconi Anemia (SCID-X1 and FANCA-mutant mice with NOD-SCID backgrounds)
  - Developed and demonstrated a robust and reproducible method for efficient generation of multipotent hematopoietic progenitor cells from ESCs and iPSC in short term engraftment studies (published).

Early Translation I, II Research Awards: Bone Disorders



- TR1- 01249, Longaker, Helms, Stanford
  - Stable formulation of recombinant Wnt3A for ex vivo use, in combination aspirate/bone graft material (BMA/BGM), for autologous bone repair. DC award
  - Developed a cell line, methods and assays for research production and purification; demonstrated that treatment with stable recombinant Wnt3a was sufficient to stimulate osteogenic gene expression, to generate significantly more new bone in severalpreclinical models compared to available treatment option(s) and was not associated with any adverse reactions. Patent applications filed, publications
  - Reviewed, recommended and approved for Bridging funding
- TR2- 01821, Peault, Soo, UCLA
  - Autologous adult perivascular stem cells (aPSC) and an osteo-inductive protein on a FDA-approved acellular scaffold for bone repair. DC award
  - In preclinical model, showed improved capacity of combination product for high quality bone formation over controls. Developed process for reproducible isolation of aPSC and cell line and process for scalable GMP compatible isolation of osteoinductive protein.
- TR2- 01780, Gazit, Cedars-Sinai
  - Allogeneic MSC ± PTH for bone repair to treat osteoporosis- related vertebral compression fractures. DCF award
  - Developed bone defect models and systems to monitor homing and activity of MSC ± PTH in vivo. MSC + PTH showed enhanced homing and fracture repair compared to controls

Early Translation I, II Research Awards: Cartilage Disorders



- TR1-01216, D'Lima, Scripps
  - Chrondrocyte progenitors embedded in a scaffold implanted into chrondral defect or injected into OA joint
  - Optimized differentiation conditions, characterization assays, and scaffold components to enhance chrondrogenic potential and improved tissue quality. Selected ESC cell line source for chondroprogenitors based on histological criteria and function in in vitro and in vivo models. Conducted pilot safety assessment.
- TR2-01829, Schultz, Scripps
  - Optimized small molecule of lead molecule PRO1 that induces chrondrocyte differentiation of resident hMSC for osteoarthritis. DC award
  - Developed assays, performed SAR, made many Pro1 analogs, identified molecules with improved activity in cell culture and in relevant preclinical in vivo models. Synthesizing a final series of molecules to profile with respect to in vitro and in vivo chondrogenesis activity, pharmacokinetics and safety prior to candidate selection

Disease Team Program
Strategic Partnership Program

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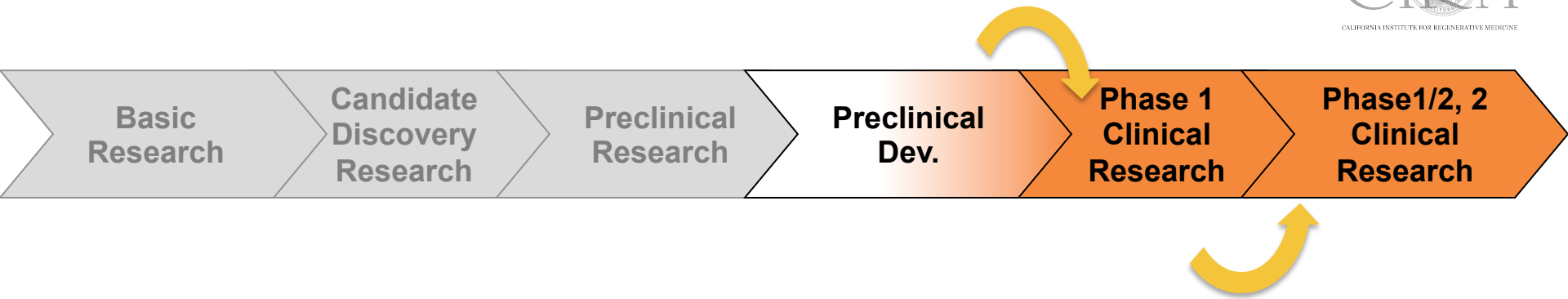

Program Goal: Enable preclinical dev to file IND to enter FIH and/or to complete clinical trial; for Strategic Partnership to attract industry engagement and investment

Outcomes: Within 4 years,

- Complete IND enabling studies to file IND to enter FIH and/or
- Complete clinical trial to establish feasible dose, delivery that is safe with evidence of biologic activity and/or clinical parameters of preliminary efficacy

Translational programs advancing to next stage

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Early translation preclinical research developing potential therapeutic candidates

ET Yr funded	#	DT awarded 2012	DT 2013 LOIs
2009	8	1	2
2011	21	1	3
2012	21		

Development teams successfully advancing through pre-IND FDA meetings, entering clinical trials

Year funded	#	Pre-IND	IND 2012	IND expected 2013/14	Clin Trials 2013
2010 DT	14	>50%	2	6	2
2012 DT	10				
2012/13 SP	2				

Outcomes of disease teams and strategic partnership programs

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- Disease Team 1 (DT1)
  - 14 projects funded with a goal of filing an approvable IND by the end of the project period (2014)
  - 2 DT1 projects filed INDs and are conducting CIRM-funded clinical trials in 2013 through continued DT1 (HIV) and awarded DT2 (recent heart attack and congestive heart failure)
  - Over half of DT1 projects successfully advanced through their pre-IND meeting with FDA
  - 1 approved for Strategic Partnership 1 funding
  - 1 received supplemental external funding
  - 2 were recommended and approved for CIRM Major Supplement Funding ($3 million each)
  - 6 submitted eligible Letters of Intent for DT3
- Disease Teams 2 and Strategic Partnerships starting

PI	Outcomes of Disease Teams – Heart Disease
Marban Cedars-Sinai Smith Capricor	**DT1** team completed IND-enabling preclinical safety/efficacy studies and **successfully filed IND** for their **allogeneic cardiac-derived stem cell** (CDCs) product **in 2012**. Capricor, a spin-out company obtained NIH funding to initiate a first-in-human phase 1 clinical trial (ALLSTAR) in **patients with heart failure following a heart attack.** CIRM **DT2** awarded to Rachel Smith, Capricor, will **fund the randomized phase 2 portion of the Phase 1/ 2 trial pending review of phase 1 data**. Phase 1 portion is designed to test 2 different doses of CDCs in 2 different patient cohorts, comprised of either recent or chronic heart failure patients after their heart attack, and is **on track to complete phase 1 component in 2013**, and after assessment of data, to enter phase 2 portion. To date, the trial has progressed smoothly. *ClinicalTrials.gov Identifier: NCT01458405*
Wu Stanford	**DT2** team in its first year, developing **hESC derived cardiomyocytes** for **end stage congestive heart failure**. After 3 months, **all activities for milestones are on target**. Stanford and Gladstone (Srivastava) labs are standardizing methods for preclinical surgical models, process development is ongoing to select manufacturing parameters to demonstrate preclinical proof of concept comparability of hESC-derived cardiomyocytes differentiated with improved manufacturing methods to cardiomyocytes differentiated using growth factors. Goal is to complete IND enabling studies to successfully file IND for FIH trial.

PI	Outcomes of Disease Teams – Vascular Dis
Laird UCDavis	**DT2** team in its first year, developing **allogeneic MSC engineered to express VEGF** delivered by intramuscular injection for patients with **critical limb ischemia**. Preclinical studies in progress; goal is to complete IND enabling studies to successfully file IND and complete phase 1 clinical trial.

PI	Outcomes of Disease Teams- HIV
Symonds Calimmune	**DT1** Filed/Approved IND to conduct first-in-human clinical trial with autologous cell therapy **attacking HIV entry/fusion**. The investigational product is LVsh5/C46(Cal-1) **modified CD34+ hematopoietic stem/ progenitor cells and CD4+ T lymphocytes**; IRB, RAC approved and **enrolling patients at California sites in 2013**, and no reports of serious safety events; share trial design & data from a second, planned future ex-US trial with same product in a different subgroup of HIV patients.*ClinicalTrials.gov Identifier: NCT01734850*.
Zaia CityofHope Sangamo	**DT1** team identified lead candidate autologous CD34+ hematopoietic stem cells gene modified at CCR5 locus with zinc finger nuclease-mRNA technology, to **disrupt expression of HIV co-receptor**; achieved preclinical proof of concept and disease-modifying activity in preclinical studies; completed pre-IND meeting earlier this year, and RAC review unanimously approved clinical protocol Sept 2013, and targeting 2014 for IND filing, with plan to enter FIH clinical trial for HIV patients

PI	Outcomes of Disease Teams - Cancer
Slamon UCLA Tak Mak Canada	**DT1** 1st **kinase (PLK4)** program completed CTA with Canada and cleared to do a clinical trial. FDA requested Certificate of Analysis (CoA) before approving the IND submission. Drug product manufacturing completed and CoA expected in October. Project is moving very well, has clinical supply (PLK4). 2nd kinase program has selected a development candidate, determined maximum tolerated dose in pilot toxicology studies and contracted to manufacture GMP batches for GLP tox studies. Team anticipates selection of backup to 2nd kinase program by end of 2013. Received CFP $ with Canada; planning FIH for **patients with solid cancers**
Aboody CityofHope	**DT1** Pre-IND meeting completed; IND enabling tox protocol vetted; passed RAC review Sept 2013; Preclinical POC prelim results show decreased tumor volume, prolonged survival in xenogeneic brain tumor model with human glioblastoma cell line, and studies with primary brain tumor pending;**IND filing** on track of **clinical trial for patients with brain cancer**. Developed in vivo iron-based cell labeling protocol, first 3 patients received it and images being analyzed; **founded company TheraBiologics** for dev of neural stem cell based treatments that home to brain cancer and deliver enzyme to enhance chemotherapy delivery; 6 publications acknowledge CIRM DT1 funding; awarded NIH-NINDS funds for preclinical studies of same product in another indication

PI	Outcomes of Disease Teams - Cancer
Weissman Stanford Vyas UK	Identified novel therapeutic candidate, an **inhibitor to CD47 a "don't eat me" signal on cancer stem cells**; achieved preclinical POC; pre-IND discussions completed and IND-enabling plan has been vetted; pilot safety studies competed; GLP/GMP manufacturing completed; pivotal safety studies initiated; IND filing planned for 2014; patent filed for the therapeutic candidate Mab which was characterized under the **DT1** award. CFP funding with UK; **planning FIH clinical trial(s) for patients with leukemia and other cancers**
Carson UCSD John Dick Canada	**DT1** Identified lead candidate, an **inhibitor to ROR-1 on cancer stem cells**; achieved preclinical POC;continuing work on GMP production of UC-961 (antiROR1 Mab), developing potency assays, formulation and continuing stability studies. In vivo dose response studies in preclinical models implanted with patient cancer stem cells are continuing; performing formal pharmacokinetic studies and tissue array studies in preparation for IND enabling studies. On track for IND-enabling studies to be completed by end of grant period; CFP funding with Canada; **planning FIH clinical trial for patients with leukemia**

PI	Outcomes of Disease Teams – blood dis.
Kohn UCLA	**DT1**, using **autologous bone marrow hematopoietic stem cells genetically modified to re-engineer** (**encodes anti-sickling beta-globin**) production of normal red blood cells **for patients with sickle cell disease (SCD)**; achieved preclinical POC, disease modifying activity, published in Journal Clinical Investigation July 2013; completed pre-IND meeting; cleared protocol from RAC; established clinical scale manufacturing process; GLP preclinical safety studies in progress;clinical protocol reviewed,approved by UCLA IRB, IBC and scientific protocol review committee; **on schedule to file an IND in 2014 for first-in-human clinical trial.**
Urnov Sangamo	**SP2,** in first year of award (currently in PFAR), developing **autologous hematopoietic cells that have been genetically modified with zinc finger nucleases (ZFNs) to re-activate the gamma globin gene**. During infancy, gamma-globin-containing fetal hemoglobin protects Beta-thalassemia patients from developing disease symptoms until gamma globin is replaced by adult-type beta-globin chains. **Completed pre-pre IND April 2013** in which preclinical, CMC,outline of clinical dev plan was discussed.
Shizuru Stanford	**DT2**, in first year of award to develop **monoclonal Ab** that **depletes blood stem cells and enables chemotherapy free transplants**. Assess safety, tolerability, pharmacokinetics and pharmacodynamics of humanized mAb as conditioning for purified hematopoietic stem cell transplants **in patients with severe combined immune deficiency**. Executed contract with company for rights to utilize the humanized mAb; **pre pre IND held in May 2013**.

PI	Outcomes of Disease Teams – Eye diseases
Humayun USC Coffey UK	**DT1** completed pre-IND meeting for product, **hESC derived retinal pigment epithelium (RPE) on a scaffold for patients with age-related macular degeneration**; pivotal safety/efficacy studies ongoing; **IND filing planned for 2014**; Regenerative Patch Technologies spin-out established; 5 publications referencing DTI award – describing the approach, methodology, differentiation to RPE and the matrix; **major novel advance is the design and composition of the matrix that supports the RPE monolayer**. Matrix designed to mimic permeability characteristics of the natural Bruch's membrane (which is defective in AMD) while being strong enough to enable surgical handling and transplantation; cells on a matrix approach allows transplantation of cells in their natural state as a polarized monolayer with top surface facing the photoreceptors as required for correct functioning of the RPE. **Developed a customized surgical tool to perform the transplant.** Multiple patent filings (IP licensed to RPT) cover the matrix and surgical tool. CFP funding with UK
Klassen UCI	**DT2** in first year of award, developing **retinal progenitor cells** to treat patients with **genetic disorder leading to blindness, retinitis pigmentosa**. Conducted activities required for initiation of IND enabling toxicology and POC studies; had pre-IND meeting; plan IND filing in 2014 to subsequently enter clinical trial. Published review in Clinical Investigation: Stem cell clinical trials: towards cell-based therapy for retinal degeneration. Spin-out company Jcyte

disease

Steinberg Stanford	**DT1** Preclinical studies to develop **allogeneic hESC-derived NSC therapy for stroke**. On-going studies to demonstrate: reproducibility of production process, efficacy in both an acute and chronic model of stroke, and preliminary toxicity in a model that supports cell persistence. Anticipated review of this data in Nov 2013; goal is to complete studies for successful filing of IND.
Svendsen Cedars-Sinai	**DT2** in first year of award, working on their manufacturing process, preclinical studies and device delivery for **allogeneic neural progenitor cells genetically modified with GDNF**; goal is to complete studies for successful filing of IND and completion of phase 1 clinical trial **for patients with ALS.**
Capela Stem Cells, Inc	**DT2** in first year of award developing **neural stem cell transplantation for neuroprotection in Alzheimer's disease**. After 3 months, all activities for milestones are on target, goal is to complete preclinical studies for successful filing of an IND.

PI	Outcomes of Disease Teams – Bone, Skin Diseases
N.Lane UCDavis	**DT2** in first year, **developing a synthetic molecule**, LLP2A-Ale, to **enhance homing of endogenous bone marrow MSCs to bone surface for patients with osteoporosis.** Working on a detailed plan to conduct IND enabling studies that includes a GMP, manufacturing program and a preclinical program to assess stability, toxicology and efficacy of the proposed drug. Manufacturing, and dev. of analytical assays to characterize and qualify the drug product in progress and subsequently will release material for toxicology, pharmacology and stability studies.They plan to successfully submit IND in 2014, followed by conducting a Phase 1 clinical study.
A.Lane Stanford	**DT1** developing therapeutic approach of **epidermal sheets** from **expanded autologous genetically corrected** (to express wild type COL7A1**) iPSC-derived keratinocytes for patients with rare genetic skin disorder lacking collagen type 7**, epidermolysis dystrophic bullosa; achieved preclinical POC; generated patient-derived gene corrected lines; **fostering regulatory path for patient-specific iPSC-derived therapies** for patients with rare skin dis; goal is to complete IND enabling studies to successfully file IND to enter clinical study.

PI	Outcomes of Disease Teams – Diabetes
Robins/Foyt ViaCyte	**DT1→SP1** Developing **allogeneic hESC-derived pancreatic cell progenitors in a device implanted subcutaneously for patients with insulin-requiring diabetes.** Completed pre-IND meeting; pivotal IND-enabling preclinical GLP studies in progress; **IND filing on track for 2014**; completed **$10.6M in private financing from investors, including J&J Development Corporation, for clinical development**; collaborative funding with JDRF; **SP1 award launched**, with goal to complete early phase clinical trial.

Disease Team 1 Status

Grant/PI	Disease	Award	Current Status
DR1-01461/Marban	Heart fail	5.6M	IND approved 6/2012; clinical trial PI Smith (Capricor) DR2-05735
DR1-01431/Chen DR1-06893/Symonds	HIV	20M	Chen converted to ET; Calimmune IND approved, clinical trial PI Symonds
DR1-01490/Zaia	HIV	14.6M	Continue
DR1-01477/Slamon	Solid ca	20M	Continue
DR1-01421/Aboody	Brain ca	18 M	Continue
DR1-01426/Berger	Brain ca	19.2M	Terminated NoGo milestone
DR1-01485/Weissman	leukemia	19.3M	Continue
DR1-01430/Carson	leukemia	20M	Continue
DR1-01452/Kohn	Sickle	9.2M	Continue
DR1-01454/A.Lane	Skin dis	11.7M	Continue
DR1-01444/Humayun	Eye dis	16M	Continue ICOC approved $3M supp
DR1-01423/Robins	Diabetes	20M	Continue ICOC approved $3M supp;SP1 with PI Foyt
DR1-01480/Steinberg	Stroke	20M	Continue
DR1-01471/Goldstein	ALS	11.5M	Converted to ET

Disease Team 2 and Strategic Partnership 1,2 Status

Grant/PI	Disease	Award	Current Status
DR2-05302/N.Lane	osteoporosis	20 M	Starting
DR2-05320/Svendsen	ALS	17M	Starting
DR2-05415/Wheelock	Huntington's	17.8M	Starting
DR2-05423/Laird	Limb ischemia	14.2M	Starting
DR2-05739/Klassen	Eye dis	17M	Starting
DR2-05735/Smith	Heart failure	19.8M	Starting
DR2-05394/Wu	Heart failure	20M	Starting
DR2-05365/Shizuru	immunodef	20M	Starting
DR2-05416/Capela	Alzheimer's Dis	20M	Starting
SP1-06513/Foyt	Diabetes	10M	Starting
SP2-06902/Urnov	Thalassemia	6.37M	Pre-funding admin review

CIRM works with investigators to avoid “bumps” in the development pathway

AP / Damian Dovarganes

CIRM science officer helps teams build product development experience in California

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Programs driven by science and evidence, and regulatory considerations needed on development pathway

- Prior to award
  - Set mutually agreed upon Go, no go, progress milestones, and success criteria
- During conduct of research
  - Discussions at least quarterly e.g., updates on interval and annual progress, review preclinical/clinical protocols, regulatory strategy, prep for interactions with FDA, attend team meetings
- Education and training of teams through CIRM/FDA webinars, roundtables, conferences, seminars

CIRM resources to guide product development for investigators

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http://www.cirm.ca.gov/sites/default/files/files/RFA13-01_DiseaseTeamIII_AMENDED11Feb2013.pdf

- CIRM Major Milestones Template
- CIRM Clinical Protocol Synopsis Template
- CIRM Manufacturing Plan Synopsis Template
- CIRM Target Product Profile (TPP) Template
  - CIRM workshop on preparing a TPP: http://youtu.be/QK_zPmarkws
- Communications with the FDA on the Development Pathway for a Cell-based Therapy: Why, What, When and How? Stem Cells Translational Medicine Vol 1, #11, November 2012
- www.fda.gov
- www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation
- www.fda.gov/ohrms/dockets/ac
- drugs@fda.gov

CIRM works with FDA on regulatory pathway for cell therapy

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- Webinars, roundtables and workshops
  - cell characterization, preclinical animal studies, imaging technology, immune response, scaffolding, clinical trials http://www.cirm.ca.gov/our-funding/regenerative-medicine-consortium

Regulatory Pathways: International Workshop on Cell Therapies

CIRM-led international regulatory workshop Sept 2013, focus on N. American, European, and Japanese regulatory frameworks for developing cell-based therapies

CIRM works with external Advisors on individual development projects at key milestones

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- Clinical Development Advisory Panel (CDAP) complements CIRM's interactions with development teams
  - Experts in product development, e.g., preclinical and clinical, cell process and manufacturing, regulatory, stem cell/disease-specific biology, disease-specific clinical expertise and commercial relevance
- Yearly meetings with each Development team to assess key milestones
- Advice helps informs CIRM decisions
  - Continue forward progress; refine approach e.g., modify milestones, timelines, budgets; convert the project to an earlier phase with reduced scope and budget, or terminate the project

Where to focus and prioritize to meet our strategic goals?

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- CIRM has a translational portfolio that is broad, often deep
- CIRM is advancing projects through the pipeline
  - What are the key criteria (characteristics, attributes) to consider for identifying which projects to select for more focused attention and funding?
  - Considerations for which types of platforms?
    - Within cell therapy, balance of autologous relative to allogeneic? pluripotent relative to tissue (adult) stem cells? Cell therapy relative to more standard e.g., biologics, small molecules?
  - Rare or common diseases?
  - High risk high impact vs nearer term?
  - Endogenous pipeline vs continued investment in external opps?
  - Continued early preclinical vs clinical trials?
  - In the early preclinical, which attributes to consider investing?

CIRM works with external Advisors on strategy for translational portfolio

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- CIRM convened meeting with external advisors in July 2013
- Identify attributes of what would constitute a competitive translational portfolio for developing effective therapies, and advice on strategies to get there
- Discussion on critical attributes separated by target diseases (therapeutic areas) and product characteristics; early endpoints and POC issues in clinical trials, and issues in commercialization
- CIRM in process of deliberating on recommendations