CALIFORNIA'S STEM CELL AGENCY

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Development Projects – Progress Update

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March 13, 2014 ICOC meeting
Agenda Item #10

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

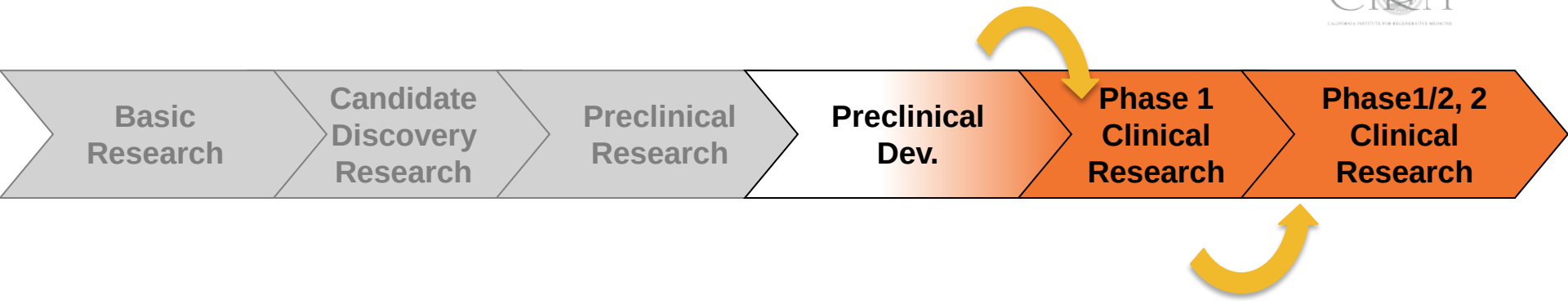
Deliver (2016+)

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

CIRM progress towards our mission

- Approx 600 research and facilities awards to over 60 institutes and companies
- 12 new institutes and centers of regenerative medicine
- Over 1800 major scientific papers published
- Over 130 new major stem cell researchers in California
- Approx 90 translational/development projects
  - 63 Early Translation projects - research (preclinical) to show preclinical proof of concept/identify potential therapy candidates
  - 27 Development projects - on regulatory pathway to patients in clinical trials
- >$600 M towards translational programs of $1.8 B awarded

Disease Team Program
Strategic Partnership Program



Program Goal: Enable preclinical development to file IND with the FDA to enter clinical trials in patients 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

CIRM helps development teams build product development experience

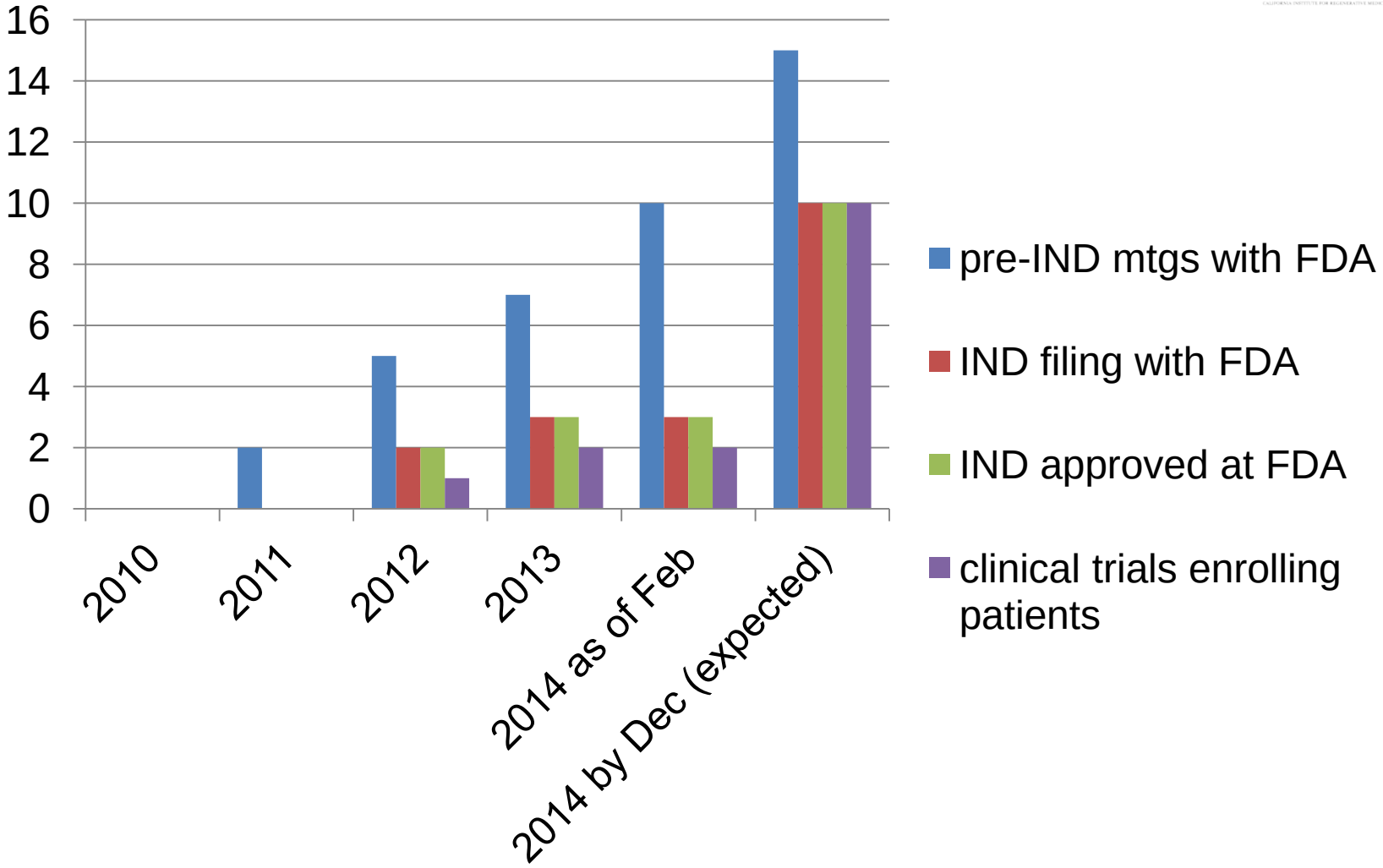
Programs driven by science and evidence, and regulatory considerations needed on development pathway

- Prior to award
  - Go, no go, progress milestones, and success criteria
- During research
  - review preclinical/clinical protocols, regulatory strategy, prep for interactions with FDA, attend team meetings, assess milestones
- Education and training of teams through CIRM/FDA webinars, roundtables, conferences, seminars

AP / Damian Dovarganes

Avoiding obstacles on the development pathway

CIRM's Development Teams are successfully advancing through milestones to enrolling patients



Development Team projects progressing to next stage

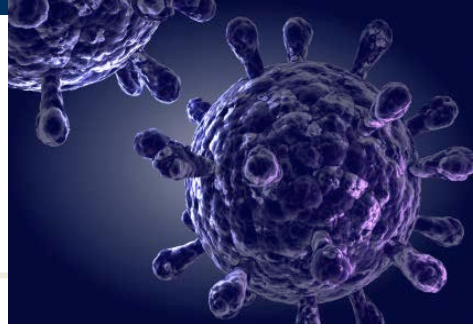
- Development teams successfully progressing through FDA meetings, enrolling patients in clinical trials
- 9 of first cohort of 14 disease teams successfully progressed and are either enrolling patients, or will be enrolling patients on clinical trials this year

Year funded	#	Pre-IND mtg	IND approved 2012/13	IND expected 2014	Clinical Trials enrolling 2013 expected 2014	Clinical trials awarded 2013/14
2010 DT	14	>70%	2/1	6	1 (2013)	8
2012 DT	10		1		1 (2013)	
2012/13 SP	2				1 (2014)	
2013 DT	6				5 (2014)	
2014	2			2	2 (2014)	

CIRM funded clinical trials – patients already enrolling or expected to be enrolling in 2014

- Patients with HIV/AIDS – enrolling now
- Patients with Congestive Heart Failure after a heart attack – enrolling now
- Patients with Cancer – solid tumors and leukemias
- Patients with Degenerative Eye Diseases – losing their vision
- Patients with Diabetes – impact on young and old, diverse ethnic background
- Patients with serious blood diseases – Sickle Cell Disease, beta-Thalassemia, particularly impacts at early age and in people with diverse ethnic backgrounds

CIRM funded clinical trials – patients with HIV/AIDS



- Burden of disease – medically, financially (CDC data 2010)
  - California 2nd highest of 50 states in reported AIDS cases
  - HIV/AIDS has claimed the lives of more than 550,000 Americans
  - About 1.1M Americans are living with HIV
  - Disproportionately affects Blacks/African Americans, and Hispanics/Latinos
  - $1.8 B lifetime treatment costs, based on new HIV diagnoses in California in 2009
- CIRM funded approaches
  - Calimmune team is blocking HIV entry by using RNA interference to re-engineer the patient's own blood stem cells/T cells to block the CCR5 gene from generating a protein. Patients with HIV/AIDS are enrolling on the clinical trial, assessing safety, feasibility, and exploring measures of activity
  - City of Hope team is mutating the CCR5 gene using zinc finger nuclease, which is essentially a pair of molecular scissors developed by Sangamo Biosciences that snips a spot on the CCR5 gene in the patient's own blood stem cells; clinical trial planned this year
  - 3 other approaches heading towards the clinic

CIRM funded clinical trials – patients with Heart Failure

- Burden of disease – medically, financially (CDC)
  - Approx 4.8M Americans have heart failure, most commonly caused by damage from a heart attack
  - Heart disease is the leading cause of death for most ethnicities in America
  - Estimated annual cost of heart failure in California is $1.5 B
- CIRM funded approaches
  - Capricor, California company, is injecting cardiospheres, derived from heart-specific stem cells from adult heart muscle, into blood vessels that feed the heart in patients with heart failure; enrolling patients onto phase 1/ 2 clinical trial. Completed phase 1 in 2013 with acceptable safety, now enrolling patients on the randomized phase 2, to determine if it reduces scarring of the heart and improves function
  - 8 other programs moving towards the clinic

CIRM funded clinical trials – patients with Cancer

- Burden of disease – medically/financially (NCI and CDC)
  - Approx 18.1M cancer survivors in 2020, 30% more than 2010
  - Costs of cancer care $157B; annual cost of cancer in California $15B
  - Growth and aging of American population is primary cause , affects all ethnicities, men and women
- CIRM funded approaches
  - Carson/Kipps team targeting Cancer Stem Cell with monoclonal antibody, ROR-1 in patients with Chronic Lymphocytic Leukemia – filing IND, clinical trial this year
  - Weissman team targeting Cancer Stem Cell with monoclonal antibody, anti-CD47, that impairs “don’t eat me” signal on solid tumors and blood cancers, filing IND, clinical trial this year
  - Slamon team targeting Cancer Stem Cell with small molecule targeting PLK4, in solid tumors, IND approved in US and Canada, clinical trial this year
  - 7 other approaches heading toward the clinic

CIRM funded clinical trials – patients with Degenerative Eye Diseases

- Burden of disease – medically, financially
  - Age related macular degeneration is a degenerative retinal disease
  - Affects the macula region of retina required for sharp central vision
  - Leading cause of blindness in people over age 55.
  - 1.8 M > 40 yo
  - AMD estimated to climb to almost 3M Americans by 2020
  - Annual costs to California exceed $4B; $1B from AMD
- CIRM funded approaches
  - Humayun team using human embryonic stem cells as a starting point to generate new retinal pigment epithelium on a synthetic scaffold, to replace cells that are lost and lead to vision loss in AMD; file IND and start clinical trial this year
  - 3 other approaches heading towards the clinic, including Klassen team developing therapy for patients with Retinitis Pigmentosa, rare genetic disease that leads to blindness in younger age group

CIRM funded clinical trials – patients with Diabetes

- Burden of disease – medically, financially
  - Diabetes affects 25.8M, 8.3% of Americans; disproportionately affects Hispanics/Latinos and Blacks/African Americans
  - Americans ≥ 65 yo, 10.9 M (26.9%) and <20 yo, 215K
  - Leading cause of kidney failure, amputations, new cases of blindness, and major cause of heart disease and stroke
  - Annual costs in California $13.8B
- CIRM funded approaches
  - ViaCyte replacing hormone producing beta cells of the pancreas from human embryonic stem cells within a device that protects against destruction from the patient's host defense system, and is implanted under the skin; IND filing and clinical trial this year
  - Other funded approaches focused on complications of diabetes, including wound ulcers, vision loss, critical limb ischemia, heart disease, and stroke

CIRM funded clinical trials – patients with blood diseases: Sickle Cell Disease

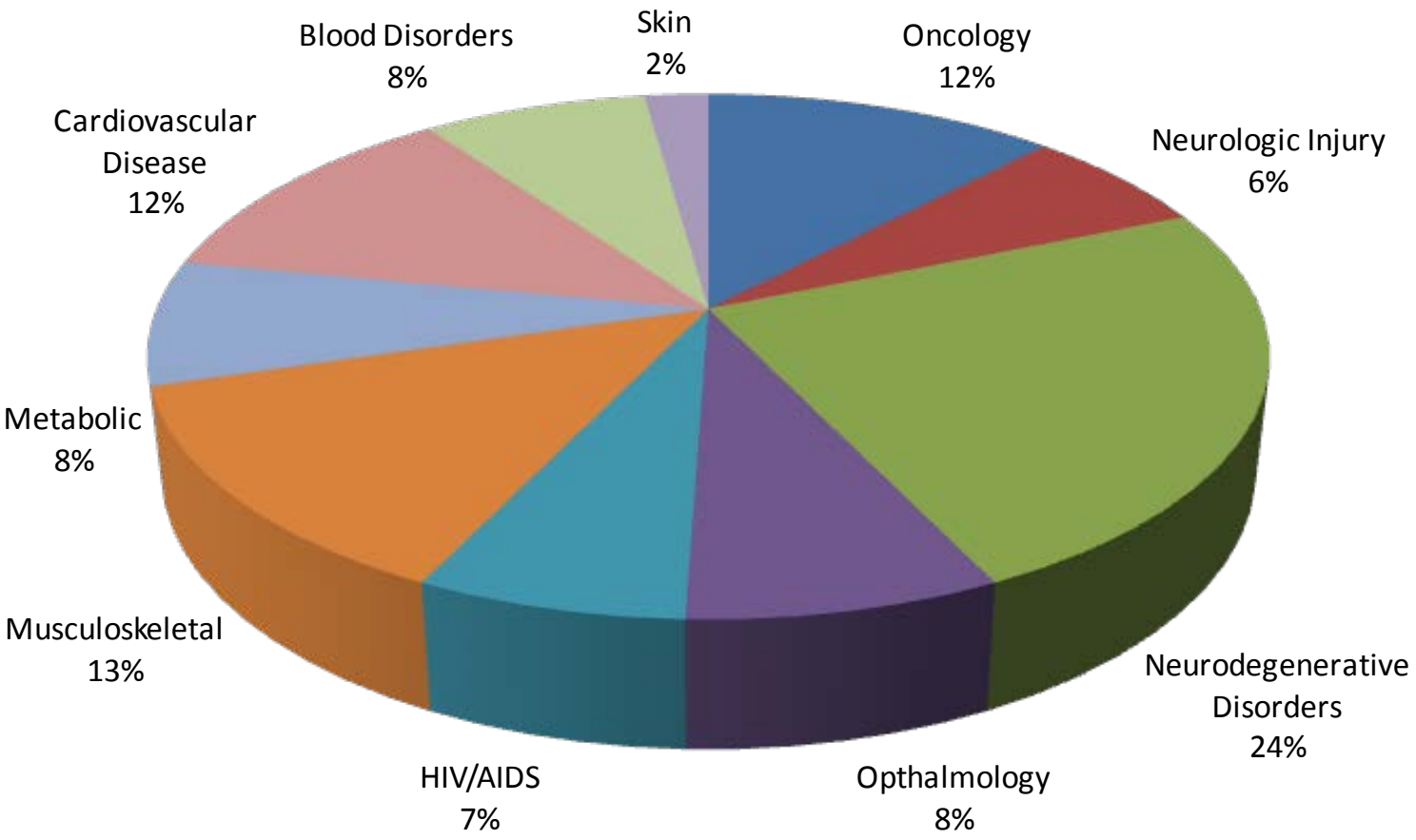
- Burden of disease – medically, financially
  - >80K Americans have Sickle Cell Disease
  - Predominantly affects Blacks/African Americans and to a lesser extent, Hispanics/Latinos
  - Sickle shape of the cells cause clogging of blood vessels and produce episodes of excruciating pain; leads to progressive organ damage
  - Costs to California – ave of 75K hospitalizations betw 1989-93, costing approx $475M
- CIRM funded approaches
  - Kohn team is correcting the beta-globin gene defect in the patient's stem cells and re-infusing the corrected blood stem cells back into the patient, IND filing and clinical trial this year
  - 1 other approach by Kohn earlier in development

CIRM funded clinical trials – patients with blood diseases: beta-Thalassemia

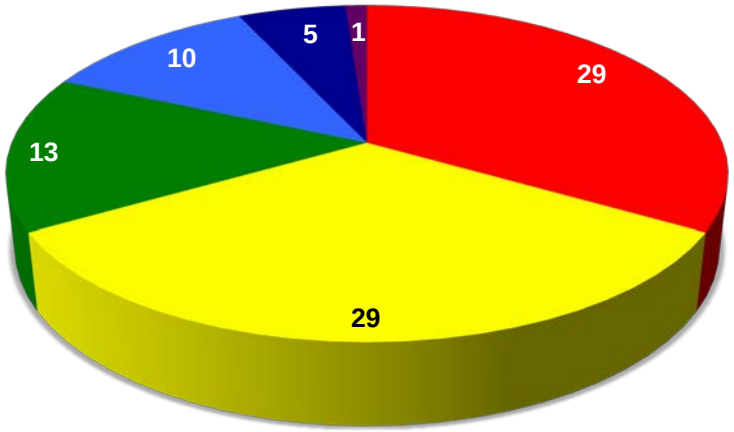
- Burden of disease – medically, financially
  - Incidence approx 1 in 100,000 in US, but more common in California due to immigration patterns, about 1/55,000 live births; prevalence in California about 696
  - Often fatal due to organ damage – the damage is a two-step process involving the disease itself and the therapy currently used to manage it. The frequent blood transfusions these patients receive can lead to a build up of iron in their blood, and if iron is not properly filtered out, it can lead to potentially lethal organ damage
  - Costs from UK data approx $800K per patient; direct annual medical costs in California approx $11M
- CIRM funded approach
  - Sangamo Biosciences is targeting the genome defect with zinc finger nuclease technology, and reinfusing the patient's corrected cells back into them; IND filing, clinical trial this year

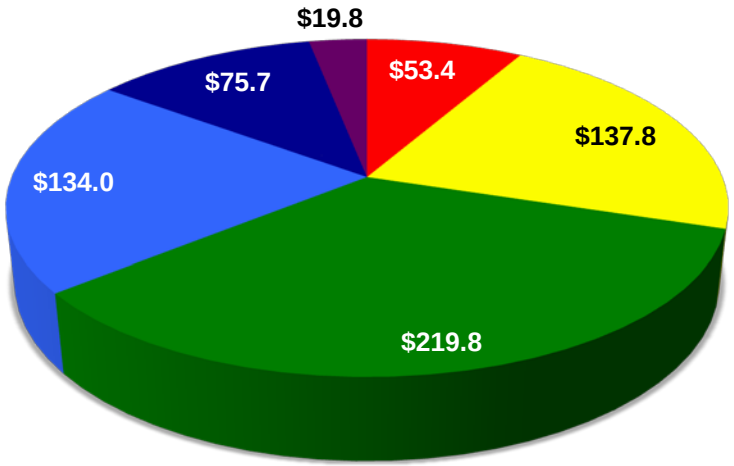
Therapeutic Areas and Goal of Projects

CIRM's Translational Portfolio: Therapeutic Areas



CIRM Translation Portfolio: Goals





87 Awards

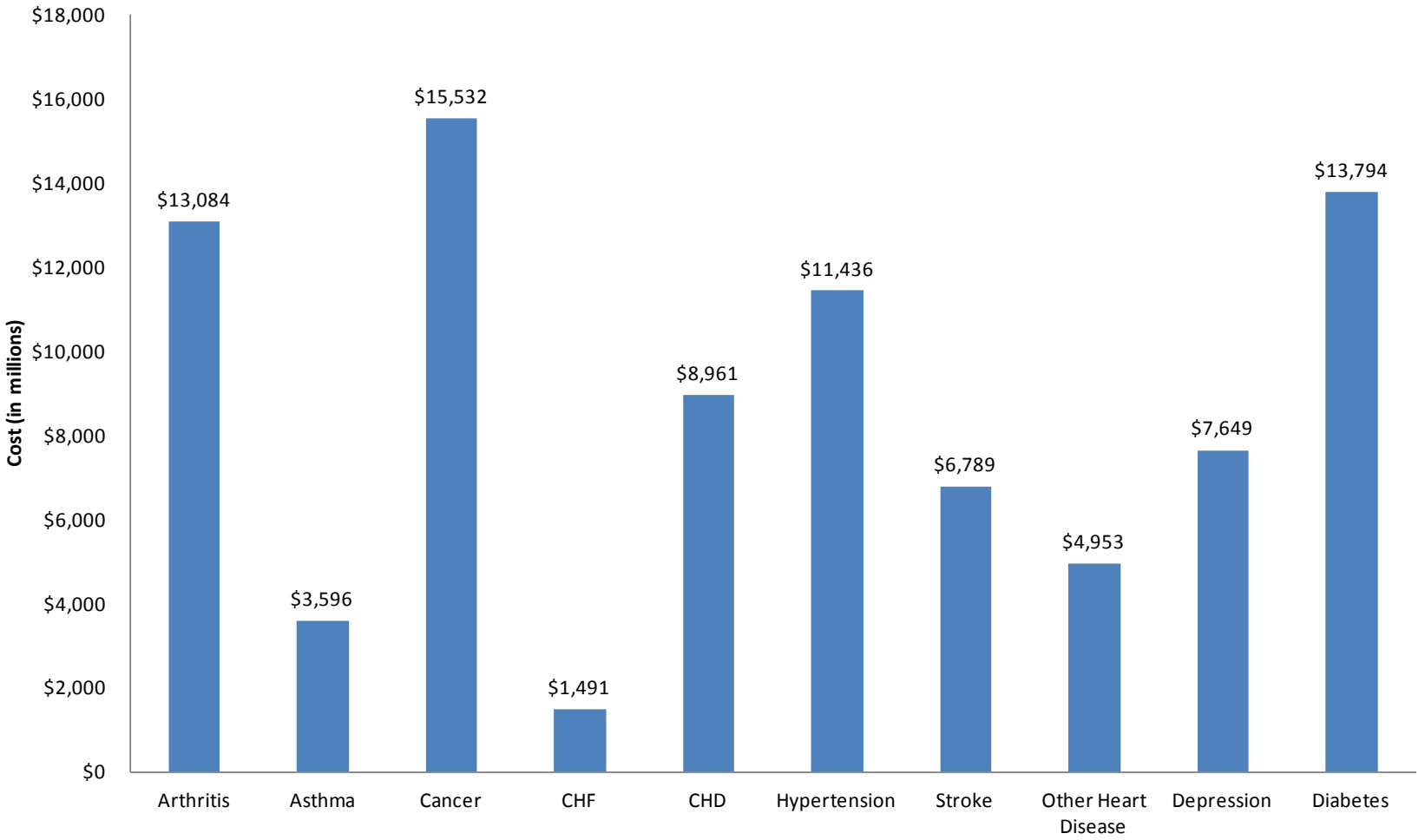
$640.5 MM of CIRM funds

- Preclinical proof of concept
- Preclinical dev't candidate
- IND filing to enter clinical trial
- Clinical Trial Phase 1
- Clinical Trial Phase 1/2
- Clinical Trial Phase 2

Pie slices are $ MM or # awards

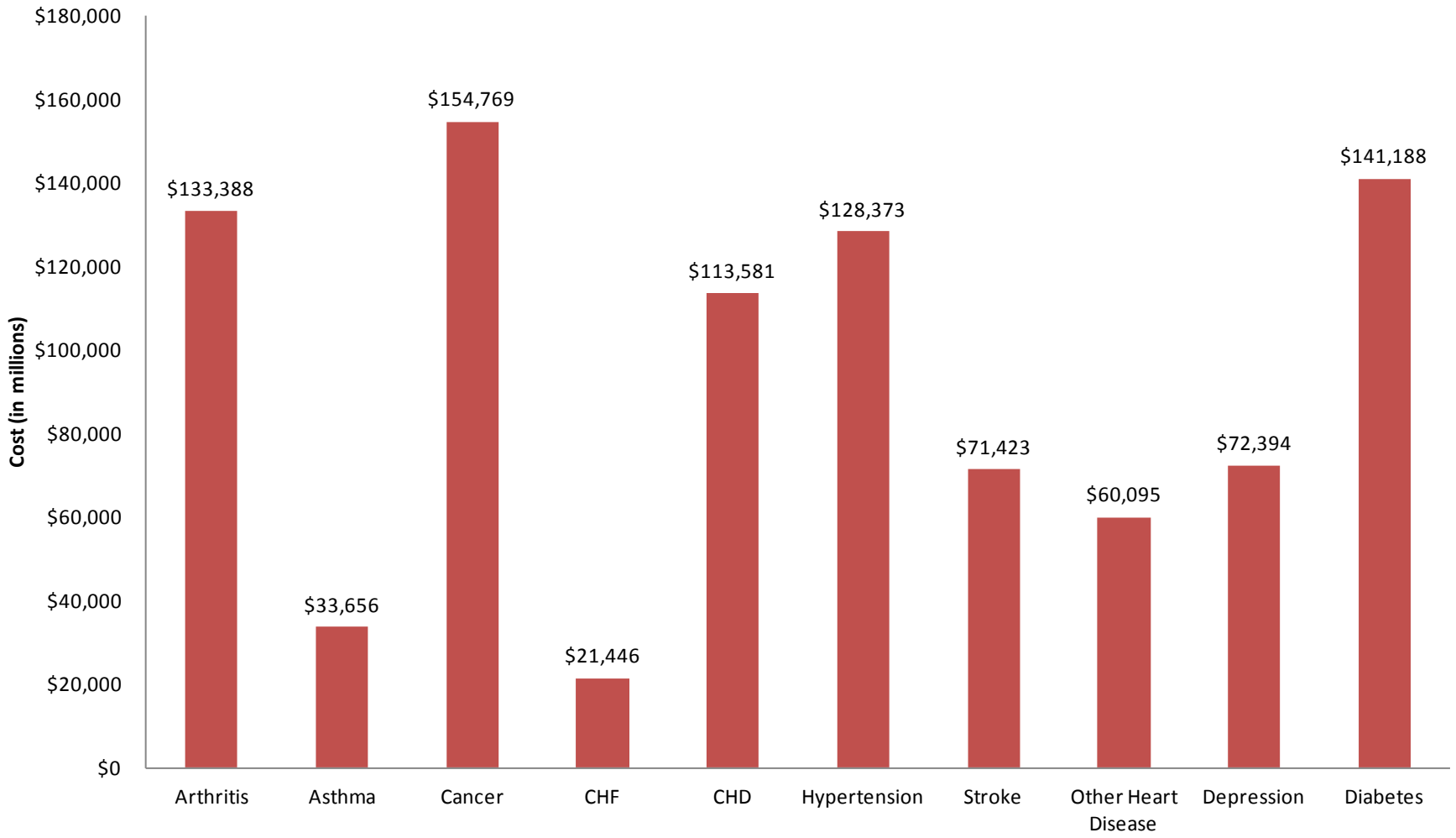
Projected and Expected Costs to California and U.S. of Chronic Diseases

Estimated Annual Cost of Chronic Diseases to California



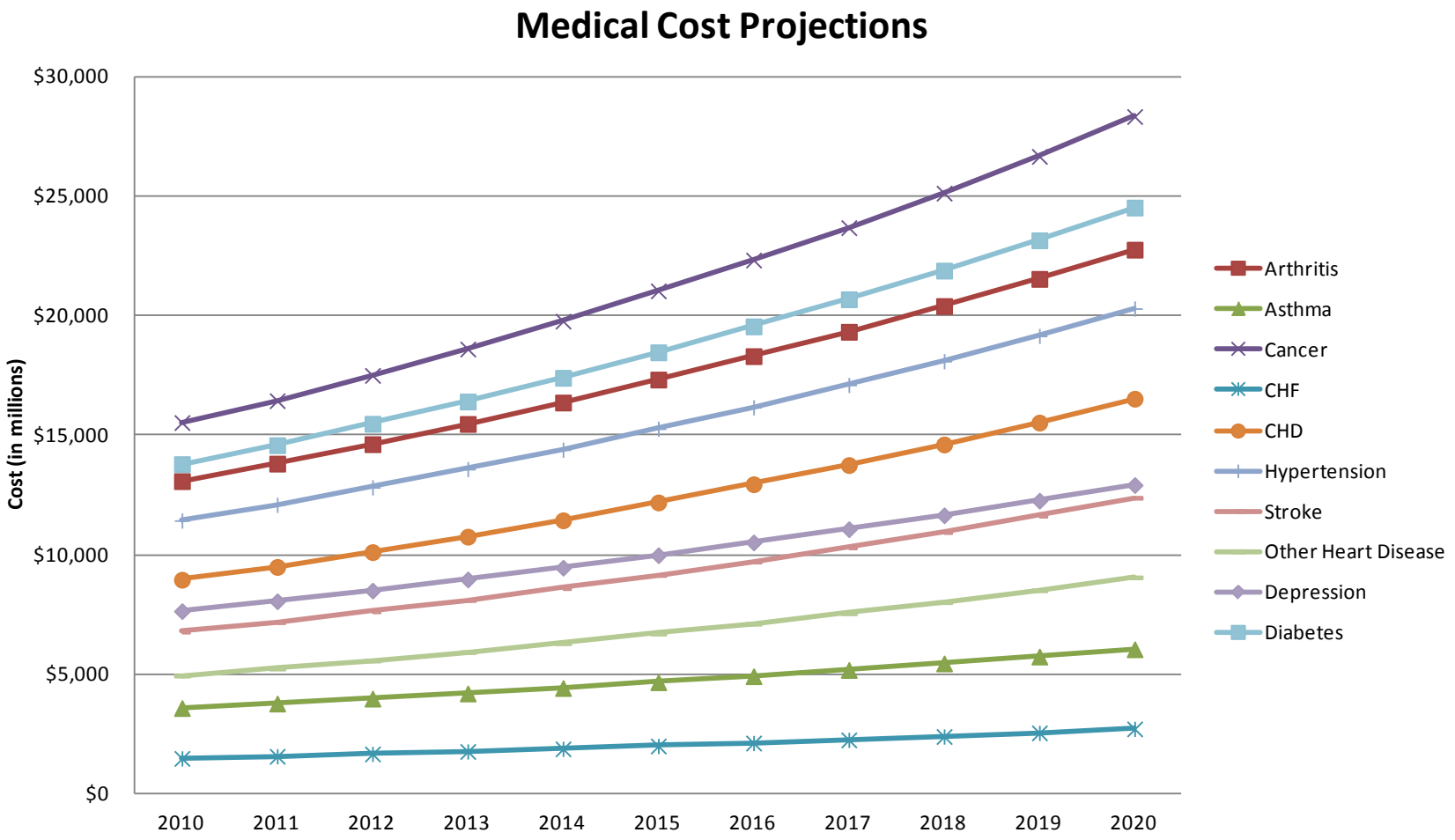
Source: Centers for Disease Control and Prevention and RTI International, CHRONIC DISEASE COST CALCULATOR.

Estimated Annual Cost of Chronic Diseases to US



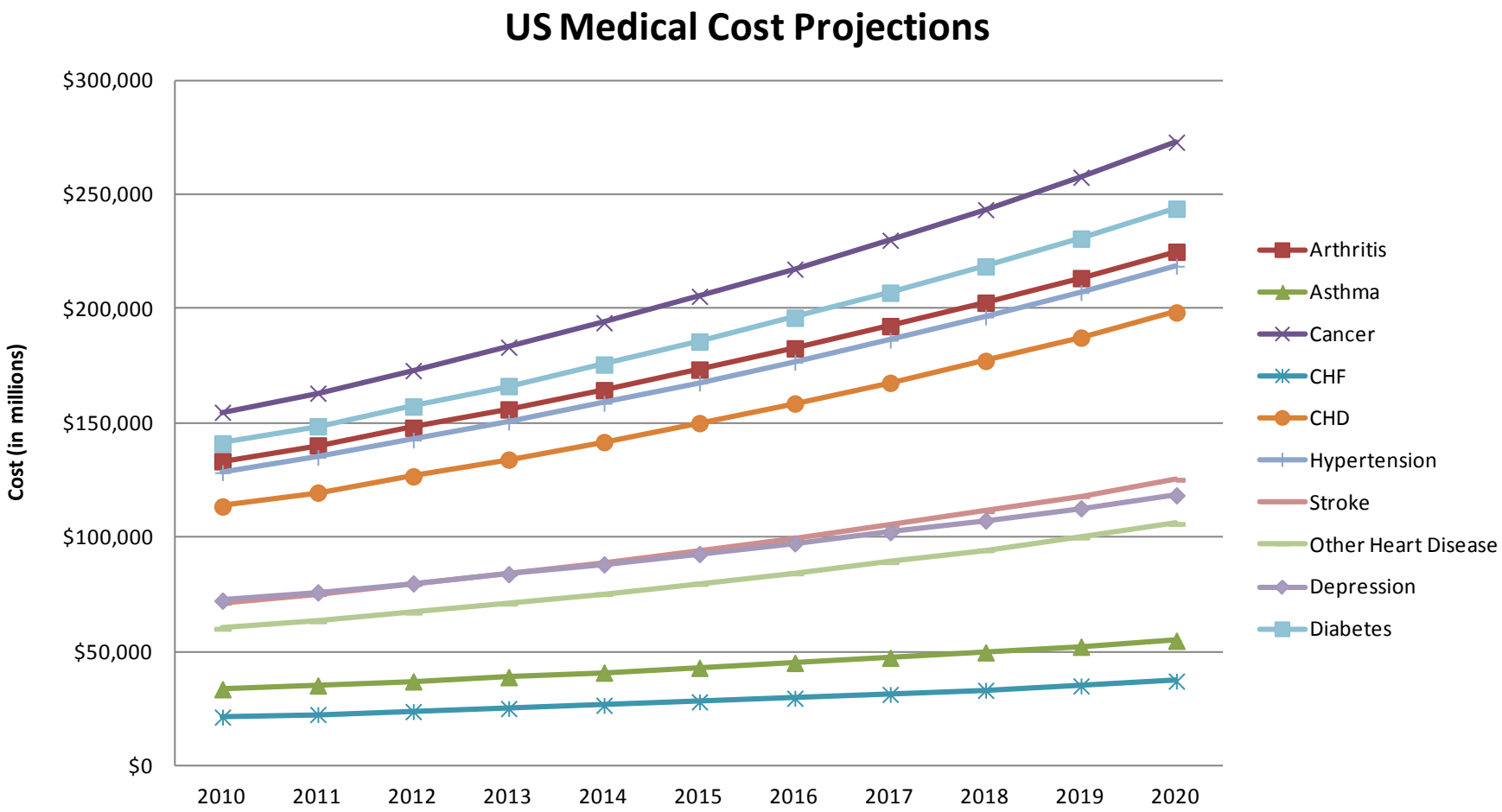
Source: Centers for Disease Control and Prevention and RTI International, CHRONIC DISEASE COST CALCULATOR.

Projected Costs of Chronic Diseases to California Through 2020



Source: Centers for Disease Control and Prevention and RTI International, CHRONIC DISEASE COST CALCULATOR.

Projected Costs of Chronic Diseases to US Through 2020



Source: Centers for Disease Control and Prevention and RTI International, CHRONIC DISEASE COST CALCULATOR.

CIRM works with FDA, external advisors, and investigators

CIRM works with FDA and other agencies on regulatory pathways for cell therapy

Regulatory Pathways: International Workshop on Cell Therapies

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

CIRM webinars, roundtables and workshops topics:

cell characterization, preclinical animal studies, imaging technology, immune response, scaffolding, clinical trials

http://www.cirm.ca.gov/our-funding/regenerative-medicine-consortium

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

- Clinical Development Advisors complement 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

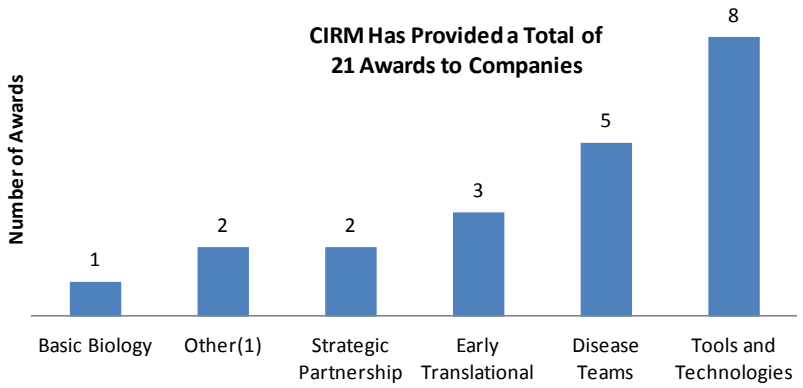
CIRM works with external advisors on strategy for translational portfolio

- July 2013 meeting to 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 proof of concept issues in clinical trials, and issues in commercialization
- CIRM implementing recommendations

CIRM's collaborations with companies

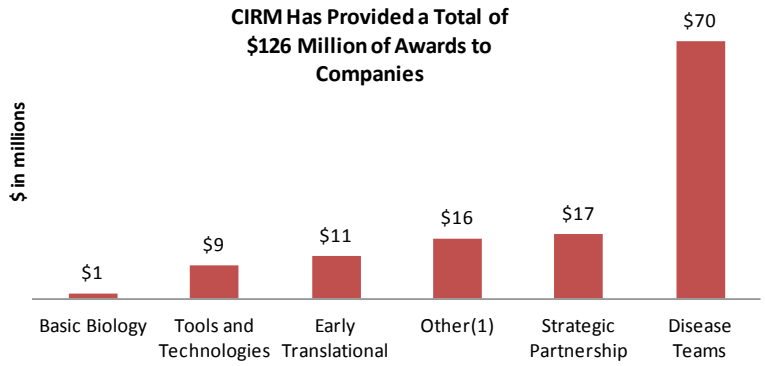
Summary of CIRM's industry engagement

Number of CIRM Awards to For-Profits



Note: Includes multiple awards to the same Company. Does not include terminated awards or Disease Team Planning Awards.
(1) "Other" includes: hiPSC Derivation and Transplantation Immunology.

Value of CIRM Awards to For-Profits



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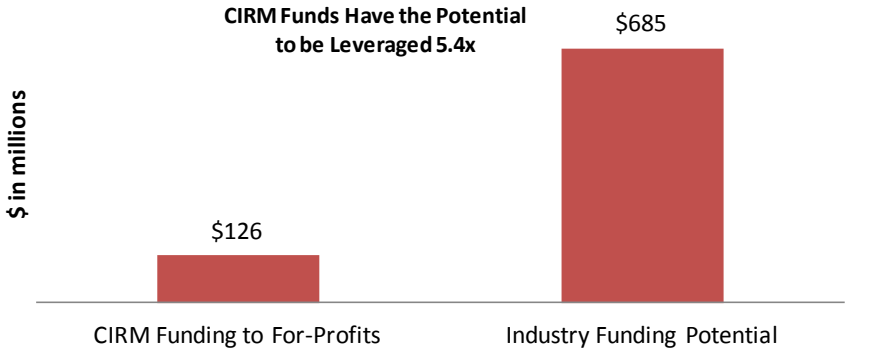
Industry Leverage



Note: "Industry Funding Potential" includes matching requirements associated with CIRM awards and payments associated with industry transactions which includes upfront and future milestone payments.

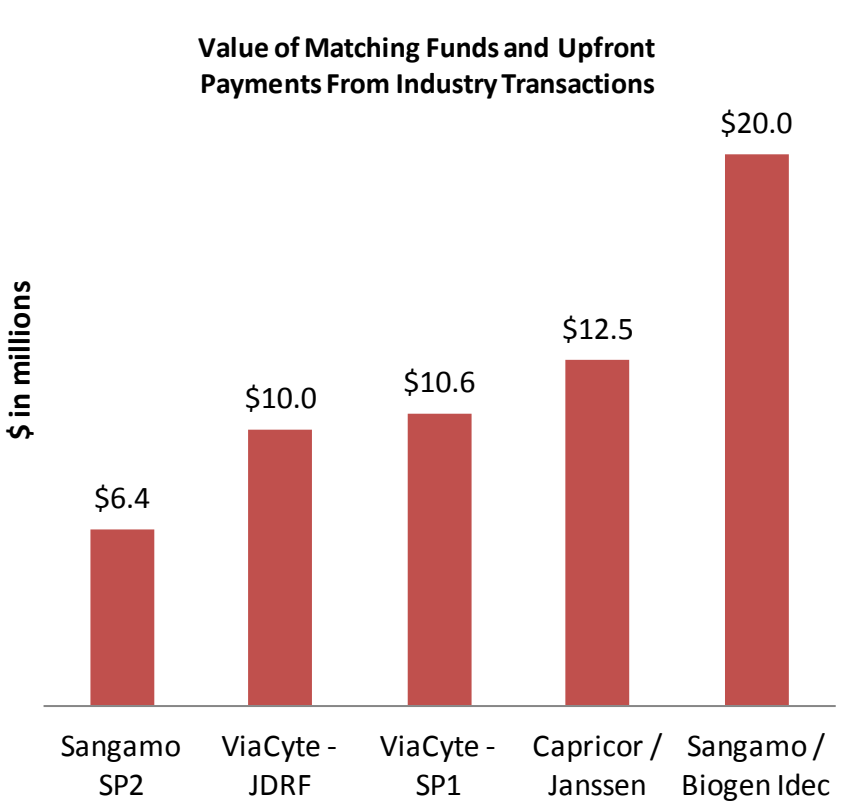
CIRM Teams with a company as the principal investigator

For-Profit Grantee	Total Amount	Number of Awards	Type of Award
BioTime, Inc.	$4,721,706	1	Early Translational I award - $4,721,706
Calimmune	$8,278,722	1	Disease Team Research I - $8,278,722
Capricor	$19,782,136	1	Disease Team II- $19,782,136
Cellular Dynamics International	$16,000,000	1	hiPSC Derivation - $16,000,000
Escape Therapeutics, Inc	$1,453,040	1	Transplantation Immunology - $1,453,040
Fluidigm Corporation	$2,693,424	2	Tools & Technology I - $749,520; Tools & Technology II - $1,943,904
GMR Epigenetics	$1,452,693	1	Tools & Technologies II - $1,452,693
iPierian, Inc.	$1,458,000	1	Basic Biology II - $1,458,000
Numerate, Inc.	$1,333,795	1	Early Translations Awards IV - $1,333,795
Sangamo	$6,374,150	1	Strategic Partnership II - $6,374,150
Stem Cells, Inc.	$19,300,000	1	Disease Team II (Alzheimer's) - $19,300,000
TriFoil Imaging, Inc. (Gamma Medical)	$2,478,347	2	Tools & Technology I - $949,748; Tools & Technology II - $1,528,599
Vala Sciences, Inc.	$906,629	1	Tools & Technology I - $906,629
ViaCyte	$39,356,426	5	Early Translational I - $5,405,397; Tools & Technology I - $827,072; Disease Team Planning - $48,950; Disease Team I - $19,999,937; Strategic Partnership- $10,075,070; Supplementary Funding to DT1 - $3,000,000
VistaGen Therapeutics, Inc.	$971,558	1	Tools & Technology I - $971,558
Total = 15	**$126,560,626**	**21**	

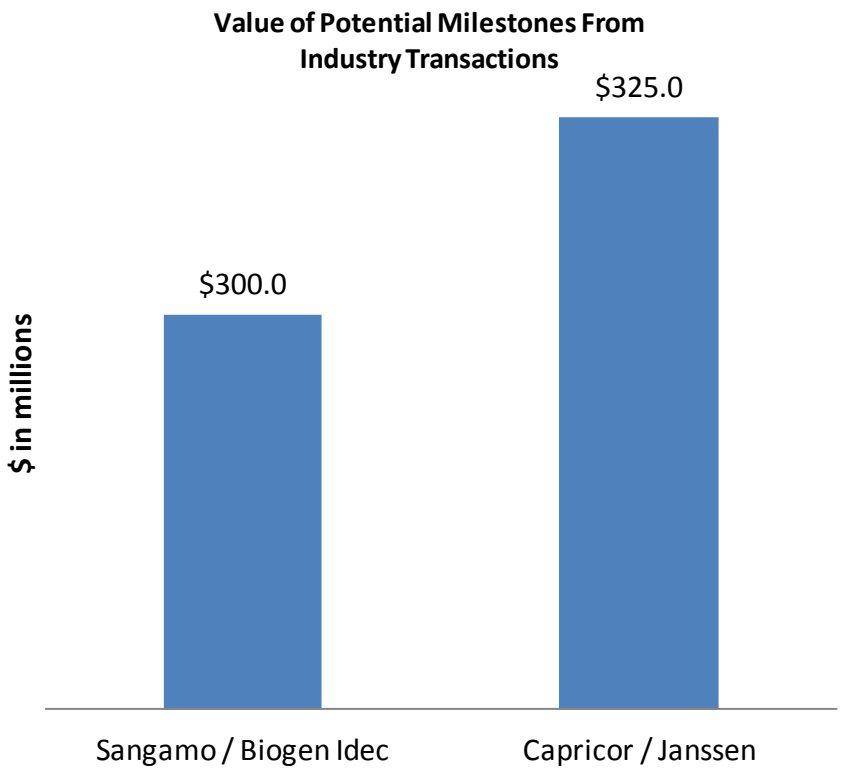
Note: Does not include terminated awards or Disease Team Planning Awards.

Industry Provides a Source of Leverage for CIRM Funded Technology

Matching Funding and Upfront Payments

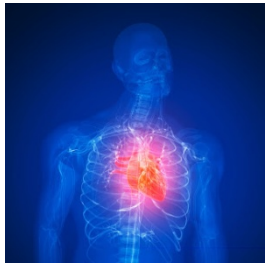


Potential Future Milestone Payments



Capricor and Janssen Enter Collaboration and Exclusive License Option

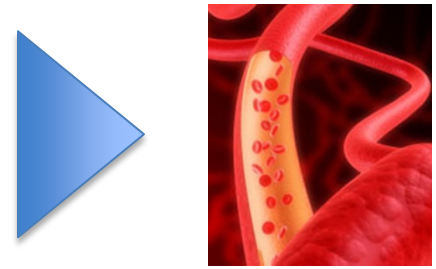
- Capricor was awarded a CIRM Disease Team award of $20 million for the completion of a Phase 2 clinical trial for patients who have suffered a large myocardial infarction
- Janssen has the right to enter into an exclusive license agreement for CAP-1002 following delivery results from Phase 2 ALLSTAR trial
  - $12.5 million upfront and up to $325 million in additional milestone payments
  - Janssen will collaborate on elements of cell manufacturing development



- CAP-1002, Capricor's lead product candidate, is an allogeneic adult stem cell therapy for the treatment of heart disease, derived from donor heart tissue

Sangamo BioSciences Collaboration with Biogen Idec for Hemoglobinopathies

- Sangamo was awarded a $6.4 million grant under CIRM's Strategic Partnership Award, and 1-1 required matching funds
- Announced collaboration with Biogen Idec for hemoglobinopathies (Beta-Thalassemia and Sickle Cell Disease)
  - $20 million upfront plus reimbursement of R&D-related costs; milestones of up to $300 million based on development, regulatory, commercialization and sales milestones



"Building upon emerging science related to fetal hemoglobin regulation, we intend to develop Sangamo's novel gene-editing technology to create a single approach that has the potential to functionally cure both sickle cell disease and beta-thalassemia."

– Douglas Williams, Ph.D., EVP of R&D, Biogen Idec

ViaCyte Successfully Matches $10 Million CIRM Strategic Partnership Award

- ViaCyte was awarded a $10.1 million grant under CIRM's Strategic Partnership Award
- ViaCyte successfully matched the funds with $10.6 million from a private financing from Johnson & Johnson Development Corporation, Sanderling Ventures and Asset Management Company

- Funds used to support clinical evaluation of VC-01, ViaCyte's encapsulated cell-therapy product being developed as a transformative therapy for patients with type 1 and insulin-dependent type 2 diabetes
- JDRF previously provided funding in conjunction with CIRM and also recently announced another $7 million investment to support development of VC-01

Inception 3 Created Based on CIRM Funded Technology from Stanford

- October 10, 2012 – Roche entered into an exclusive partnership with Versant Ventures and Inception Sciences to create a drug discovery incubator, Inception 3, for the treatment of sensorineural hearing loss
- ***Inception 3 will incorporate an innovative technology platform from Stanford University that was previously funded by CIRM***
  - Funding Type: Comprehensive Grant (RC1-00119)
  - Grant Title: Generation of inner ear sensory cells from human ES cells toward a cure for deafness
  - Investigator: Stefan Heller
  - CIRM Funds Committed: $2.5M
- Versant will provide equity financing and Roche will fund the research based on a series of milestones
- Roche retains an exclusive option to acquire Inception 3 upon a first lead compound reaching the filing stage of an IND

Elsevier BusinessIntelligence

"The Pink Sheet" DAILY

OCTOBER 10, 2012

Roche Enters Hearing-Loss Space In Risk-Sharing Venture With Inception, Versant

The newly formed Inception 3 will work to bring small molecule candidates for hearing loss, based on technology licensed from Stanford University, to IND-filing stage, at which point Roche will have the option to buy out the program.

A drug-hunting venture borne out of the Bristol-Myers Squibb Co./Amira Pharmaceuticals Inc. buyout in 2011 has resulted in a new opportunity for Roche. Under a novel collaboration structure involving big pharma, venture capital and biotech, Inception Science will create a third company – called Inception 3 Inc. – to discover and develop small molecule drug candidates for sensorineural hearing loss based on technology licensed from Stanford University.

Roche, which will fund Inception 3's work with milestone-based R&D payments, will hold an option to acquire the program upon the filing of the first IND based on the Stanford technology. Inception's backer Versant Ventures, meanwhile, will provide the equity financing for the new company, under an agreement announced Oct. 10.

Inception consists of two current small biotechs (Inception 1 Inc. and Inception 2 Inc.) focused on neurology and oncology, founded by former Amira execs after Bristol acquired Amira for $325 million upfront in July 2011 ("BMS Bets On Amira's IPF Drug In $325M Acquisition" — "The Pink Sheet" DAILY, Jul. 22, 2011). Bristol's focus was on idiopathic pulmonary fibrosis candidate AM152 and it spun out much of Amira's remaining intellectual property into new companies called FLAP LLC and Pannira Pharmaceuticals LLC[See Deal]. Meanwhile, backed by Versant, former Amira CEO Peggi Prasit, known around the biopharma industry for his "drug-hunting" acumen, established Inception ("After Complex Sale, Amira Scientist And VC Team Up Again For Discovery Start-up" — "The Pink Sheet" DAILY, Jul. 27, 2011).

Luca Santarelli, global head of neuroscience at Roche, said his company saw hearing loss as a significant untapped market but one in which its internal R&D personnel was not equipped to lead innovation. Meanwhile, Roche had prior positive experience with Versant from their work together after central nervous system-focused biotech Synosia Therapeutics Inc. was acquired by Biotie Therapies Corp. ("Biotie To Combine With Synosia To Form A "Global Leader" In CNS Drug Development" — "The Pink Sheet" DAILY, Jan. 11, 2011).

"There is only a limited set of targets and programs that we can [investigate] internally," Santarelli explained in an interview. "We are constantly looking for possibilities to access innovation on the outside in ways that enable us to eventually apply our strength of translational drug development at an appropriate time while at the same time tapping into areas that offer promise and unmet medical need, as well as areas where the mechanism of disease biology is better clarified."

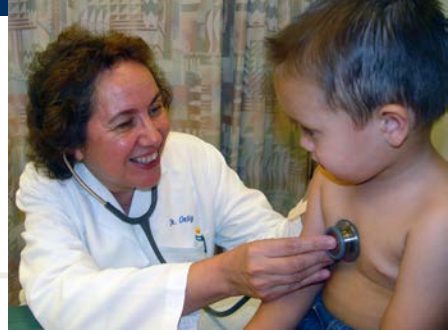
"The reason we didn't go for a straightforward collaboration with academia here ... is that the fact that it brings in a team of drug-hunters with a great track record of discovering drug candidates for intractable targets and then driving those to the IND stage," added Shafique Virani, head of neuroscience partnering at Roche. "We have the operational component of a drug-development team in addition to a major pharma and exciting best-in-class technology from Stanford."

Combined Capabilities Should Produce Rapid Progress

The various parties are not disclosing any financial details about the collaboration nor providing any sense of a timeline to the potential IND filing at FDA. However, Clare Ozawa, chief business officer at Inception and a

Looking Forward….

Building quality clinical capacity: Stem cell clinic network – June 2014



- CLINICAL TRIALS**:** Develop resources for effective, efficient design and execution of clinical trials for investigational stem cell tx
- DELIVERY OF THERAPIES: Become a center of excellence for delivering stem cell-based tx that have been proven safe and effective
- DATA AND INFORMATION: Centralize information about clinical trial experience and outcomes, and data to inform research, clinical, regulatory and reimbursement decisions
- INFORM THE PUBLIC: Education, outreach and training about clinical trials and available therapies, and potential dangers of unproven procedures
- HEALTHCARE ECONOMICS: Develop evidence base to support the development of sustainable business models, including reimbursement strategies

Continuing to progress the pipeline of therapies to patients

- Accelerated Development Pathway – March 2014 program announcement to teams already funded to complete clinical trials, that with access to additional expertise and financial resources could accelerate time to achieve evidence of clinical benefit for patients; expect future grantees to have future opportunities to compete into the pathway
- Development Teams – Continue to actively manage funded projects; new proposals to complete early phase clinical trials
  - Strategic Partnerships: Concept Today's ICOC; emphasis on industry, leveraging expertise and resources
  - Disease Teams: Researchers from academia and industry; concept Fall ICOC
- Preclinical Development Projects - Advance most promising preclinical projects in pipeline, and/or new preclinical projects with commercial partners, towards FDA interactions on development pathway – concept Today's ICOC

Thank You to the CIRM Staff – Science/Medical, Grants Management, Business Development

CIRM Science/Medical	Kevin Whittlesey, PhD
Arie Abo, PhD	**CIRM Grants Management**
Karen Berry, DVM, PhD	Gabriel Thompson
Rosa Canet-Aviles, PhD	Doug Kearney
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Pat Olson, PhD	Neil Littman, Ben Huang
Catherine Priest, PhD	**CIRM Portfolio Table (reference)**
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