Right now.

CIRM Update to CFAOC

November 20, 2020

Maria T. Millan, MD
President & CEO

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CALIFORNIA STEM CELL AGENCY

2004

CIRM created by Patient Advocates and California Stakeholders-Proposition 71

$3B

Committed to CIRM Mission

1027 Awards (200 under active management)

Cutting Edge Research & Transformative Programs funded

68 Clinical Trials

First in human, cell & gene medicine, some ready for final marketing approval

>2700 Patients

Patients enrolled in CIRM Funded Clinical Trials

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CIRM's Value Proposition:

Proven acceleration-based Funding Partnership Model

Robust portfolio of diverse technology platforms

"De-risk" early but promising science has resulted in industry pull >$12B in Industry Partnerships (most in the past 3 years)

Enable and enact the evolving FDA regulatory paradigm

Specialized Infrastructure- Alpha Clinics, Genomics Data Hub, Translational Hub

Education & Training Programs have seeded the new field

Patient & community advocate leadership shape the agency

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CIRM Investments

2019-2020 Investments

INFRASTRUCTURE	EDUCATION	DISCOVERY	TRANSLATION	CLINICAL
$5.7M	$500K	$11.1M	$49.4M	$123.8M

Total Investments since 2004

$479M	$218M	$907M	$357M	$730M

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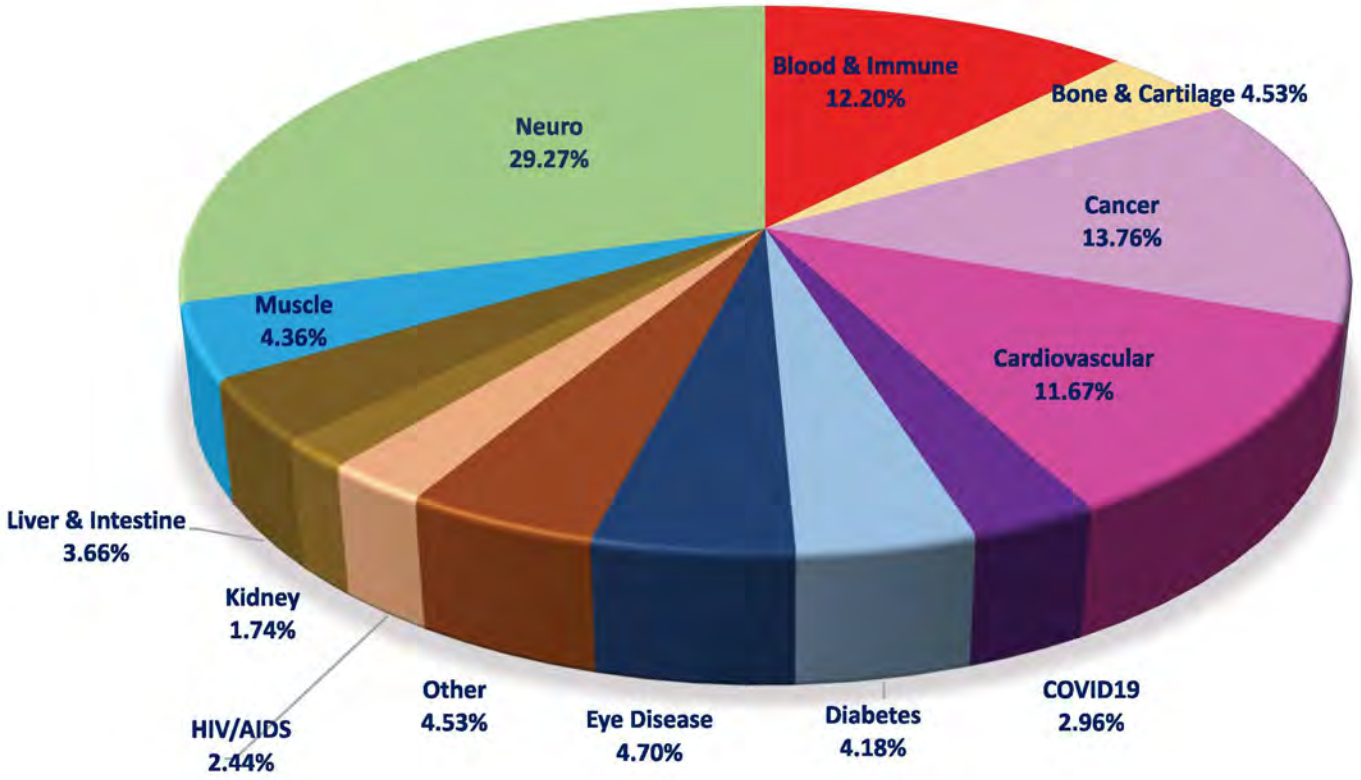
CIRM Research and Development Portfolio



N = 574 R&D Grants, excluding non-disease focused awards

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68 Clinical Trials & 25 Translational Programs:

Broad Disease Areas and Approaches to solve Unmet Medical Needs

Blinding Eye Disease
Lou Gehrig's Disease
Blood Cancers
Thalassemia
Brain Cancer
Colon Cancer
Heart Disease
HIV/AIDS
COVID
Genetic Diseases
Rare Pediatric
Spina Bifida
Epidermolysis Bullosa
Cerebral Palsy
Duchenne Muscular Dystrophy
Epilepsy

Traumatic Brain Injury
Parkinson's Disease
Huntington's Disease
Kidney Failure
Lung Cancer
Melanoma
Multiple Myeloma
Bone Disease
Immune Deficiencies
Sickle Cell
Metastatic Cancer
Paralysis
Stroke
Diabetes

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CIRM COVID-19 Program

- Special program approved by CIRM board March 2020
  - $5M allocation for Discovery, Translational, preclinical and clinical programs.
  - Leveraged CIRM's Acceleration & Funding Models
  - Research Plans address outreach and inclusion of underserved communities and account for disproportionately affected populations
- Bi-weekly grant review and board approval meetings
- 17 awards approved and launched

CIRM's COVID Project Portfolio

- **Stem Cells to discover drugs against COVID**
- **Vaccines**
- **Gene engineered cells (CAR NK cells)**
- **Biomaterial to combat COVID lung damage**
- **Novel cell therapy to fight the virus**
- **Epitope discovery tool**

- **Convalescent Plasma to provide immunity**
- **Immune Natural Killer cells to fight virus**
- **Cell Therapy (MSC) for lung damage due to COVID**

Multiplier Effect of Collaboration:

- CIRM and NHLBI MOU to jointly fund industry and academic cell and gene programs for the Cure Sickle Cell Initiative
- Leverages CIRM's Processes and Funding Infrastructure
- American Society of Hematology setting up registry & data capacity

Sickle Cell Disease

Sickle Cell Disease

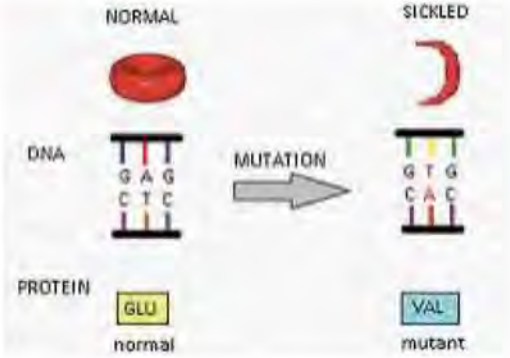
Point mutation in beta hemoglobin gene on Chromosone 11

100,000 in the U.S. & millions worldwide

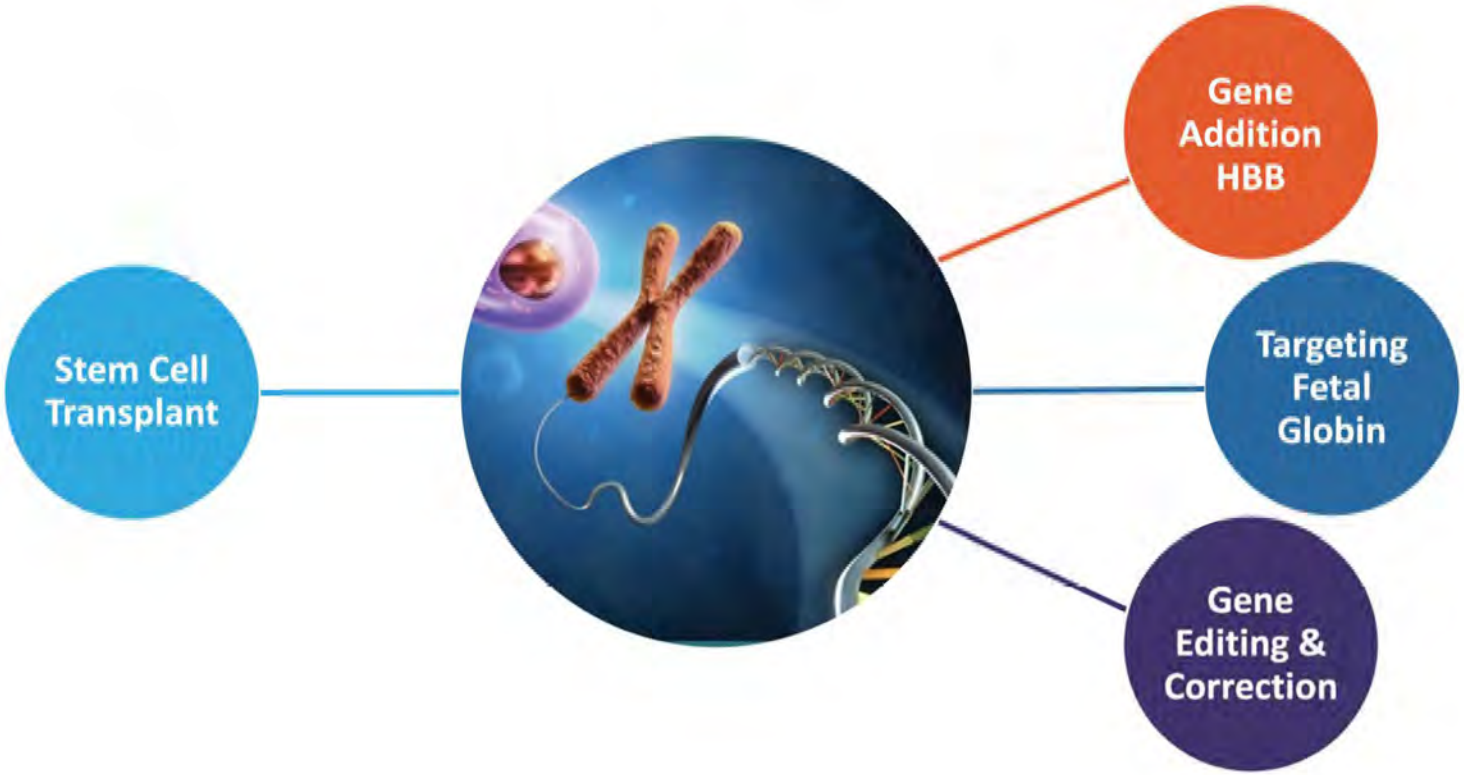
Average lifespan in U.S. ~ 40 years

30% growth in the number of globally by 2050

Debilitating pain, organ damage, strokes and hospitalizations



Stem Cell and Gene Therapy Approaches for Sickle Cell Disease



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Gene Editing of Patient's Stem Cells

Donald Kohn, MD
UCLA

Clinical Trial with genetic modification of patient's blood forming stem cells. Lentiviral delivery of an anti-sickling beta globin

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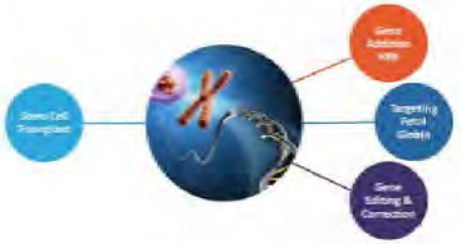
Converting hemoglobin to protective fetal version

David Williams, MD
Boston Children's (with California Sites)



Clinical Trial: Genetic modification of patient's blood forming stem cells to the more functional fetal version. Lentiviral delivery of shRNA that targets BC11A and increases the expression of fetal hemoglobin

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Gene Correction of Patient's Stem Cells

Mark Walters, MD
UCSF Benioff Children's Oakland

Pre-clinical: Genetic modification of patient's blood forming stem cells with CRISPR/Cas9 to correct mutation leading to Sickle Cell

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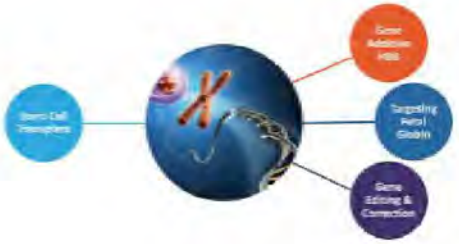
Gene Correction of Patient's Stem Cells

Matthew Porteus, MD
Stanford University



Pre-clinical : Genetic modification of patient's blood forming stem cells with CRISPR/Cas9 to correct mutation leading to sickle cell (uses different gene delivery than Walters' approach)

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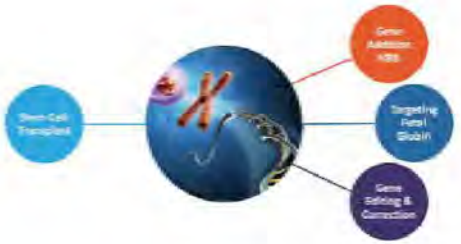
Blood Stem Cell Transplantation

Joseph Rosnenthal
City of Hope, Beckman Research Institute



Clinical trial to improve the results of blood stem cell transplantation from an immune matched donor using mild chemotherapy

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Blood Stem Cell Transplantation

Pierre Caudrelier, MD
ExCELLThera Inc.

Clinical trial with expanded umbilical cord stem cells to treat children and young adults with Sickle Cell

Patient Advocates as Advisors in Clinical Trials

Adrienne Shapiro
Patient Advocate

Study Endpoints

Patient Recruitment

Informed Consent

Study Design

SOMETHING BETTER THAN HOPE

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Gene Therapy for Parkinson's Disease

A Phase 1b Safety Study for MRI guided delivery of AAV2-GDNF for the treatment of Parkinson's disease

Proposed MOA: Survival and restoration of dopaminergic neuron function

Preclinical Data: Improved motor performance and restoration of dopaminergic function in relevant preclinical model *J Neuroscience 2010*

Phase 1a trial demonstrated safety and increase in [18F]Fdopa at 6 and 18 months *Mov Disord Jul 2019*

Clinical Design: Phase 1b trial,open label, single dose, bilateral putamen delivery, in patients with either early or moderate stage PD

Endpoints: Safety, preliminary clinical efficacy as assessed by motor function and quality of life

UCSF Brain Neurotherapy Bio

Krystof Bankiewicz, M.D., Ph.D., UCSF

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Translational Stage: Cell Therapy for Epilepsy

Stem cell-derived therapy for the treatment of chronic focal epilepsy

Off the shelf stem cell-derived cellular therapeutic comprised of inhibitory nerve cells

- Stem cell derived inhibitory neurons are delivered into the seizure focus, integrate, and secrete the inhibitory neurotransmitter GABA to rebalance neural electrical activity in the brain and eliminate or reduce seizures.
- Efficacy has been demonstrated in pre-clinical models of epilepsy.
- This work is a continuation of previous stem cell research started at the University of California, San Francisco by the company co-founders.

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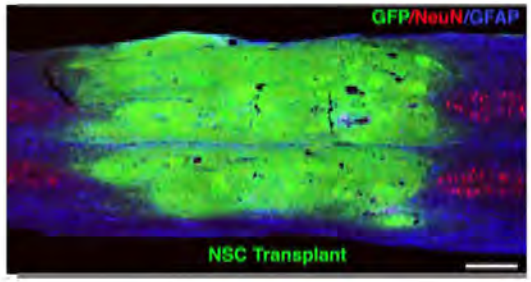
Translational Stage: Cell Therapy for Spinal Cord Injury

Human Neural Stem Cells (hNSCs) as a cell replacement that can form new neural "relays" across the injury to restore function.

PI: Mark Tuszynski, MD, PhD UC San Diego School of Medicine



- Transplanted hNSCs integrate in the injured spinal cord of rhesus monkeys
- Resulted in improved forelimb function
- Form “relays” and new connections
- Restore axonal transmission.
- c/w Efficacy signal in prior rodent studies
- Demonstrated that transplanted neurons overcome the inhibitory milieu of the adult injured spinal cord
- Transplanted cells extend axons over very long distances

Feb 26 2017, Nat Med

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On the Horizon: modified iPSC therapies

Autologous COL7A-1 gene corrected iPSC-derived epithelial sheets to treat dystrophic epidermolysis bullosa in patients with Colorado mutation

PI: Anthony E. Oro, MD, PhD; Stanford University

Paul Martinez, 32, a participant in Stanford's current clinical trial for EB patients.Picture from Stanford Medicine 2015

*

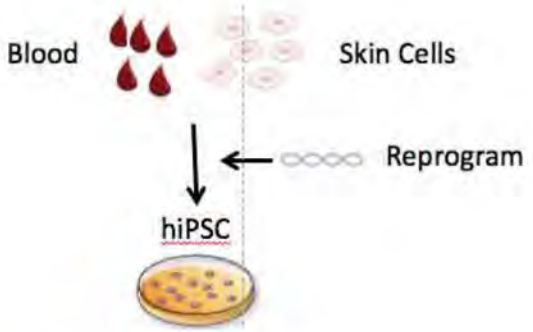
- Patient fibroblasts with mutations in the COL7A-1 gene are genetically edited and reprogrammed to iPSCs and differentiated into keratinocytes, which are prepared as epithelial sheets to graft onto patient wounds
- Developed and demonstrated successful production of gene-corrected skin sheets using a GMP compatible process for one patient and completing work for IND submission to go to clinical trials.

* Anthony Oro, Stanford University

CIRM hiPSC Repository- 2600 lines

World's largest repository*

- *Neurodevelopmental Disorders in Children*
- *Neurodegenerative Disease*
- *Inherited Dyskinesia*
- *Major Depressive Disorder*
- *Blinding Eye Diseases*
- *Lung Diseases*
- *Liver disorders*
- *Cardiomyopathies*



- Diverse Ancestries including including African, Admixed American (i.e. Hispanic, Native American), East Asian, European, and South Asian

- Broad Institute has developed "cell villages" with CIRM iPSC lines to study population genetics.

**Repository managed by FUJIFILM Cellular Dynamics*

UCSD UCLA pmsf UCI USC UCSF RARE science™ CIRM

CIRM Human Stem Cell Genomics Program

Over 20 labs supported by sequencing and bioinformatics COEs

Brain

Single Cell Atlas: cortical neurons
Single Cell Atlas: glioblastoma
iPSC brain organoids: autism donors
iPSC motor neurons: ALS donors
Dopaminergic neuron QC

Heart

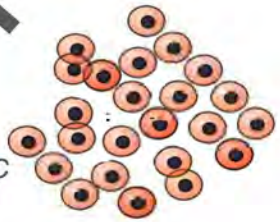
iPSCs from cardiomyopathy donors for drug responsiveness
Single Cell Atlas: atrial and ventricle cells
Single Cell Atlas: congenital heart disease iPSC

The Stem Cell Hub
Center for Excellence in Stem Cell Genomics

Pancreas

Single Cell Atlas: pancreas
Single Cell Atlas: pancreatic cancer

Blood



Single Cell Atlas: HSC
ESC-HSC differentiation
Sickle cell gene editing QC

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Education: Training the Next Generation

SOMETHING BETTER THAN HOPE

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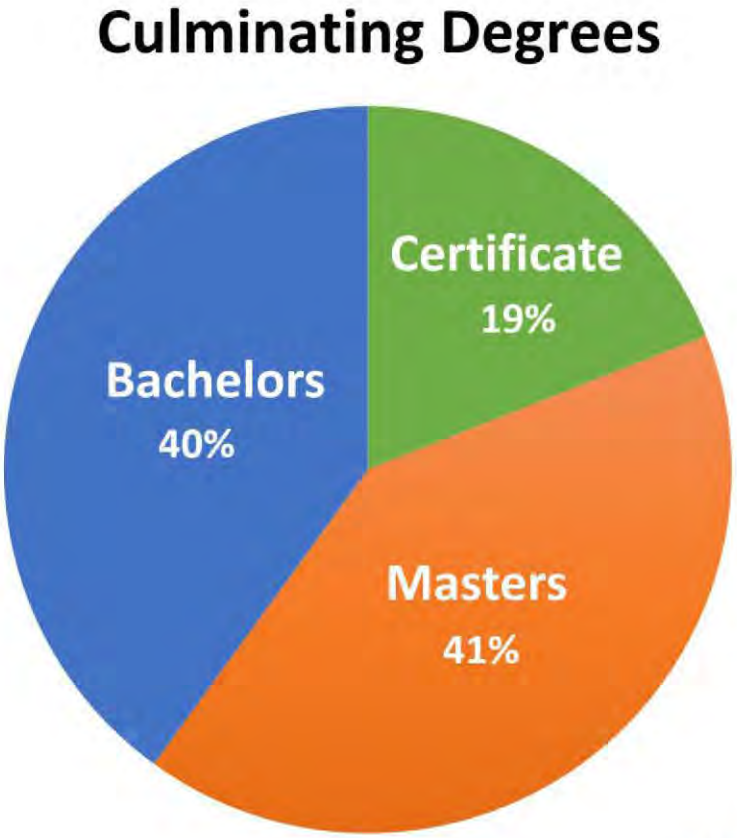
Bridges Program: 16 Home Universities Across California

- 14 currently active programs

- 1507 Alumni, 86 interns
- 51% first generation college students*
- ~ 200 mentors
- ~ 60 host institutions (and growing)
  - 33% are biotech companies
  - 67% academic/nonprofit



* Of those responding to survey

Every Moment Counts. **Don't Stop**

Bridges Alumni: Outcomes and Impact

- > 60% employed in R&D positions
  - 67% academic/nonprofit labs
  - 33% biotech/pharma
- About 35% in PhD, professional, or other graduate programs, including medical school
- Contributed to 274 publications in scientific journals while in program

10th Annual Bridges Conference
July 2019, San Mateo, CA

SPARK Program: Outcomes and Impact

- 482 students have completed internships since 2012
- Many trainees are still in high school, but of 76 recent of alumni who reported college attendance:
  - 50% are attending a UC
  - 18% attending another CA school (Stanford, Caltech, CSU)
  - 32% attend schools outside CA (Yale, Columbia, Harvard, Johns Hopkins, Duke, etc.)
  - Most pursuing biology or other STEM related fields

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CIRM 5-yr Strategic Goals

2016-2020

DISCOVER
46 of target 50
NEW CANDIDATES*

ADVANCE
73 progressing
THROUGH
DEVELOPMENT
100% increase

REFINE REGULATORY
8 RMATs
(first to receive and
15% of total
awarded to date by
FDA under
21st Century Cures)

SHORTEN TIME TO CLINICAL TESTING

73% CLIN1
achieved IND in 2
years

60% achieved IND
in <18 months

Time from TRAN to
CLIN1 4.4 years

EXPAND
51 of target 50
NEW TRIALS
68 Total
(>2700 Enrolled)

INCREASE INDUSTRY PULL
59% partnered
72 events

>$12B Industry Investment
$8.6B in 2020 ytd

*limited by remaining
Prop 71 funds

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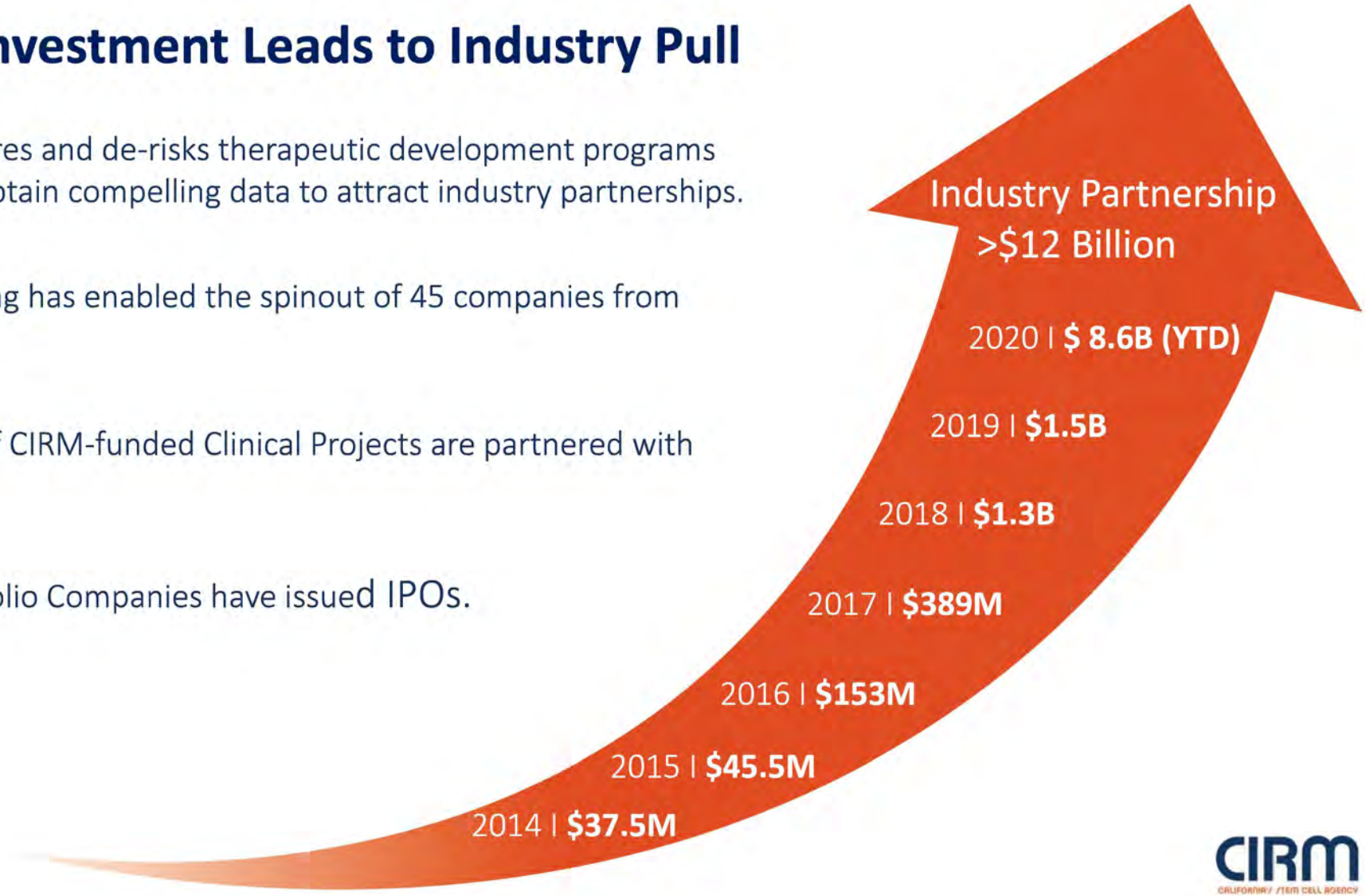
CIRM Investment Leads to Industry Pull

CIRM nurtures and de-risks therapeutic development programs until they obtain compelling data to attract industry partnerships.

CIRM funding has enabled the spinout of 45 companies from academia.

Over 50% of CIRM-funded Clinical Projects are partnered with Industry.

Three Portfolio Companies have issued IPOs.



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2019-2020: Highlighted Industry Partnering Events

Forty Seven, Inc.	Cancer Immunotherapy	**Acquired by Gilead Sciences for $4.9B (2020)**
VELOSBIO	Cancer Immunotherapy	**Acquired by Merck for $2.5B (2020)**
POSEIDA THERAPEUTICS	Cancer Immunotherapy	**$204.8M Initial Public Offering (2020)**
jCyte	Stem Cell Therapies for Retinal Diseases	**$252M Ex-US License to Santen Pharmaceutical (2020)**
TENAYA THERAPEUTICS	Gene Therapies for Heart Diseases	**Secured $92M Series B Funding (2019)**
Aspen NEUROSCIENCE	Stem Cell Therapies for Parkinson's Disease	**Launched (2019) and secured $75M Series A Funding (2020)**
GRAPHITE BIO	CRISPR Gene Therapies	**Launched with $45M Series A Funding (2020)**

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Highlighted Spinouts

Public/Acquired

ALKAHEST®

EPINOMICS

Forty Seven, Inc.

MUSTANGBIO

ONCTERNAL therapeutics

Orchard therapeutics

VELOSBIO

Venture Funded/Biopharma Partnered

4DMT

Ankasa

APPIA BIO

Aspen NEUROSCIENCE

CENTURY THERAPEUTICS

GRAPHITE BIO

jCyte

KHLORIS BIOSCIENCES

LOCANA

magnetic INSIGHT

NEURONA THERAPEUTICS

Regenerative Patch Technologies™

TENAYA THERAPEUTICS

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INDUSTRY ALLIANCE PROGRAM

CIRM's Industry Alliance Program (IAP): *A unique opportunity for the industry to partner with CIRM in accelerating clinical and preclinical stem cell, gene and regenerative medicine therapy programs to market.*

Launch Partners (2018)

VIVO CAPITAL

PANACEA VENTURE HEALTHCARE

BlueRock Therapeutics

Joined in 2019

novo nordisk

FREQUENCY THERAPEUTICS

vera therapeutics

elevatebio

Joined in 2020

BAYER

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Impact of CIRM Funding

68 Clinical Trials
>2700 patients enrolled
Specialized Infrastructure
Developed Specialists and Workforce for this new field
Robust Ecosystem- Hub for Partnership
1000 Programs toward Transformative Solutions

Economic Impact in CA*
$10.7 B Sales Revenue
$651M State & Local Tax
>56,500 New jobs

** 2019 Report from USC Sol Price School of Public Policy*

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CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Every Moment Counts. **Don't Stop** Now.

SOMETHING BETTER THAN HOPE

Thank You!

Maria T. Millan, M.D.
mmillan@cirm.ca.gov

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Every Moment Counts. **Don't Stop** Now.