SOMETHING BETTER THAN HOPE

Report from CIRM Scientific Strategy Advisory Panel

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Successful completion of 2016-2020 Strategic Plan

DISCOVER
46 of target 50
NEW CANDIDATES*
**limited by remaining*
Prop 71 funds

ADVANCE
74 projects progressed
100% increase

REFINE REGULATORY
8 expedited FDA RMATs
(21st Century Cures Act)

SHORTEN TIME TO CLINICAL TESTING

73% CLIN1 achieved IND in 2 years

Time from TRAN to CLIN1 4.18 years

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

INCREASE INDUSTRY PULL
63% development programs partnered
45 NewCo, 3 IPOs, licensing, acquisition, financing

Industry Partnership
>$13 Billion

2020 I **$ 9.6B**
2019 I **$1.5B**
2018 I **$1.3B**
2017 I **$389M**
2016 I **$153M**
2015 I **$45.5M**

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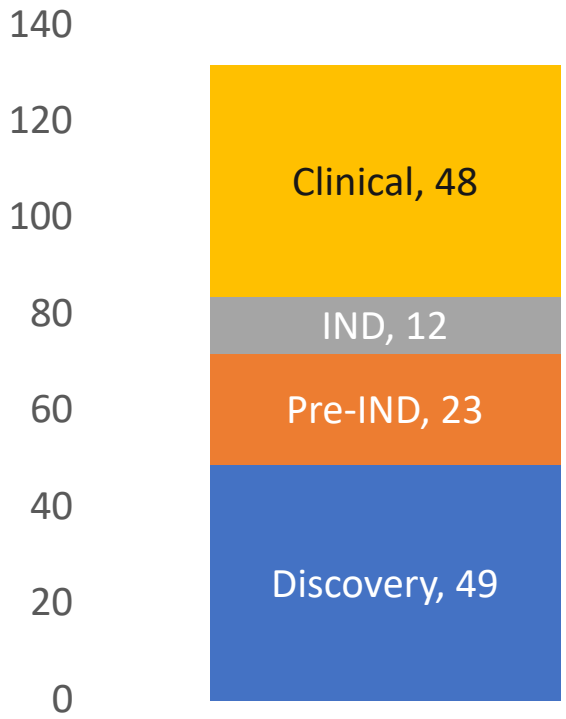
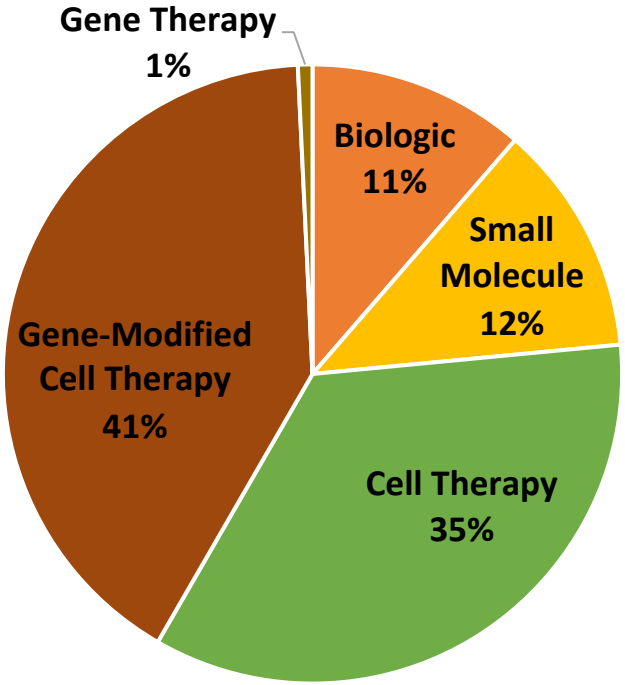
Active Portfolio of 132 Development Programs

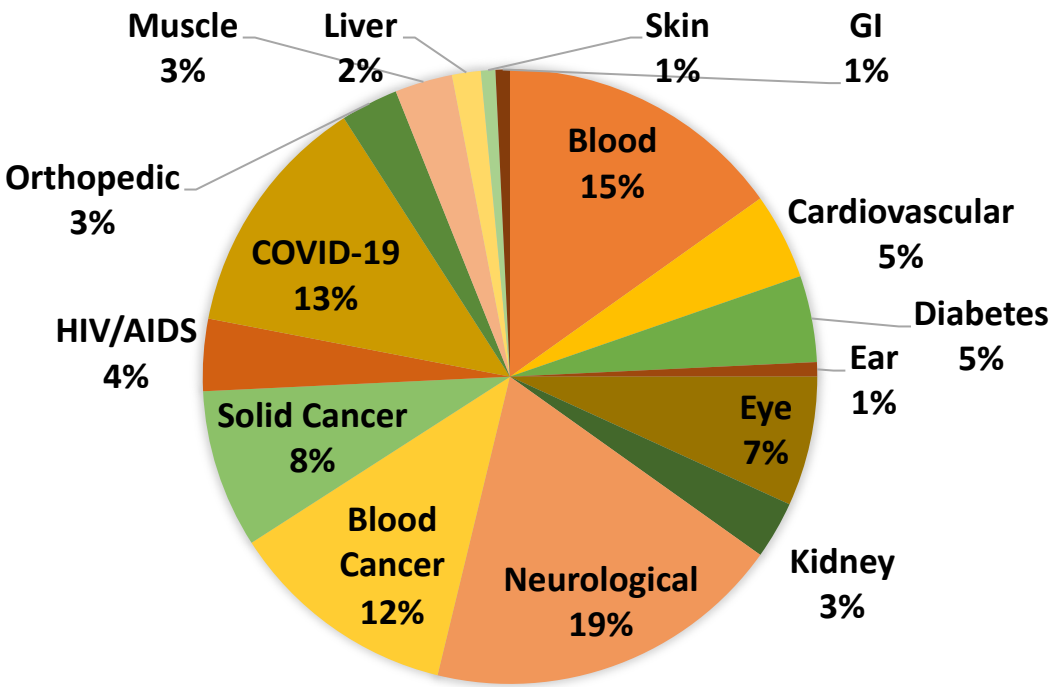
Development Stages



Therapeutic Modalities



Disease Areas



As of Dec 2020

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Current Portfolio of 68 Clinical Trials Across 35 Indications

Blinding Eye Disease
Lou Gehrig's Disease
Blood Cancers
Thalassemia
Brain Cancer
Colon Cancer
Heart Disease
HIV/AIDS
Genetic Diseases
Rare Pediatric

Huntington's Disease
Kidney Failure
Lung Cancer
Melanoma
Multiple Myeloma
Bone Disease
Immune Deficiencies
Sickle Cell
Metastatic Cancer
Paralysis
Stroke
Diabetes
COVID-19

51 Trials Funded from 2016-2020

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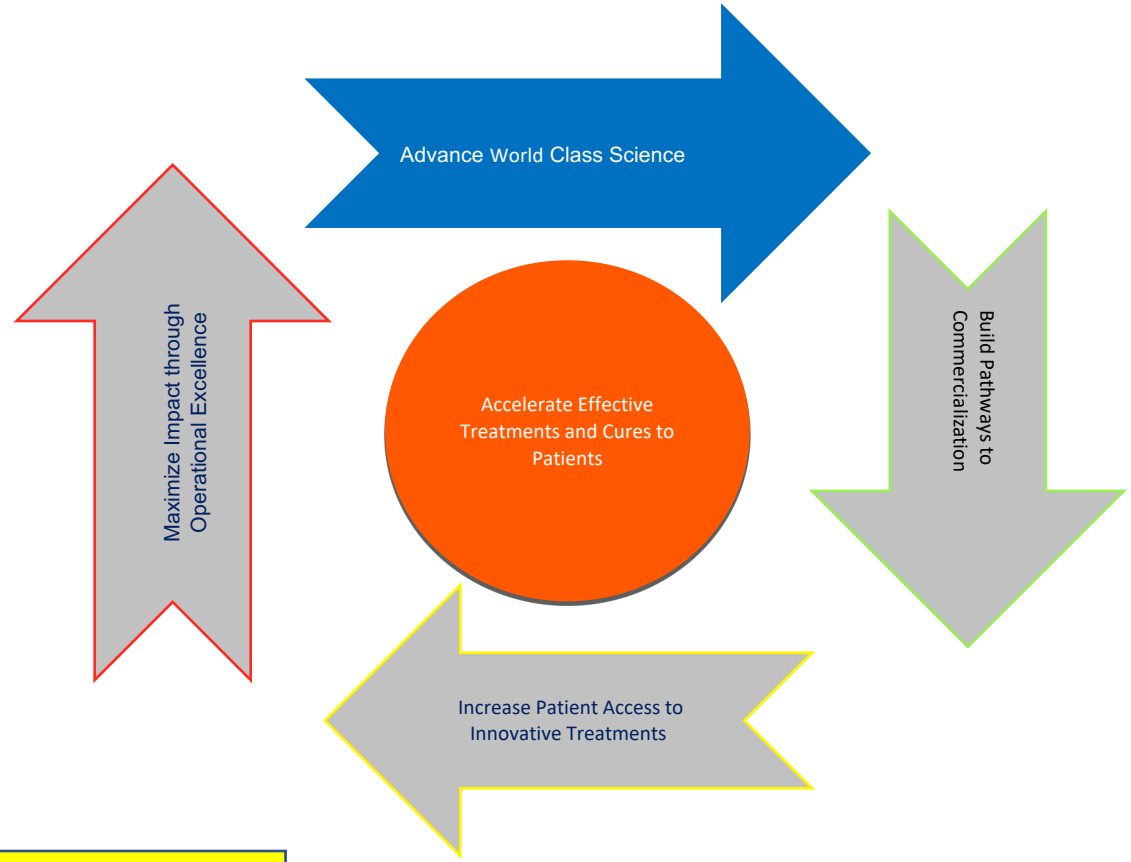
Strategic Themes for CIRM under Proposition 14

CIRM Today

Accelerating, Patient-Centric,
Funder, Partner and De-risker for
Basic, Translational, and Clinical Research
Infrastructure and Education Programs



Leverage & Build on Established Funding Model

Feb. 22, 2021 Scientific Strategy Advisory Panel:

Anchoring Questions:

- What is the greatest impact that CIRM could make in the next 10 years for stem cell research
- What types of vital research opportunities are in need of funding within the field of stem cell biology, genomics, gene therapy, particularly in the neuroscience field. Are there vital research opportunities that fall outside of these categories?
- Advantages and disadvantages of consortia
- What is the largest gap in stem cell research – in basic and translational research
- What key scientific & clinical research infrastructure gaps are there in the field? *(in addition to manufacturing)*

Representatives from the CIRM scientific community and Grants Working Group will introduce a variety of topic areas- 10-minute talks followed by 15 minutes of discussion (MM will moderate). No specific project proposals will be presented.

No project- or program- related feedback or funding recommendation is sought from the Panel

Neuroscience, specifically highlighted in Prop 14, will serve as an example for broader considerations in stem cell, genomics and regenerative medicine in non-neuroscience areas.

Strategy to Advance World Class Science

Accelerating Scientific Advancements	• Consortium approach • "Team Science" and built-in collaborations • Shared technology cores and infrastructure • Data & Knowledge Networks • DEI principles to address the "real world"
Clinical Paradigm	Next generation trial design (long-term studies, Real World Evidence, Patient Centric endpoints, consortia models, post-marketing)
Strategic Partnerships	Tangible deliverables from recently implemented demonstration cases: • NHLBI for Cure Sickle Cell • CZI for COVID genomics
Training Future Scientists and Workforce	"on-ramps" along educational and career stages, incorporate DEI & integrated into other CIRM pillars *(e.g. hands-on experience in CIRM funded research labs and infrastructure programs such as clinical research exposure Alpha Clinics Network and internships in future manufacturing initiatives)*

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Consortium Approach

- The SSAP strongly supported the development of consortia models for disease area (e.g. CNS), common biological mechanism or technology platform (CRISPR CAS 9)
- Disease-targeted consortia could be informed/build upon existing consortia such as Answer ALS and Stem Cells for Huntington's Disease that bring cross-disciplinary partners to advance knowledge and development for these indications. CIRM's Alpha Clinics Network and other CIRM infrastructure provides a solid foundation.
- Consortia would enable platform-based regulatory pathways for example for monogenic diseases and CIRM could take a lead in working with the FDA on these models.
    - for the 7000 known rare conditions, each monogenic disease can be caused by 100 different mutations. N=1 studies may be required with goal to combine data from a series of successful n=1 clinical gene therapy studies, each targeting a different mutation but all using the same gene transfer or editing approach. This may only be feasible in academic centers.
- The panel encouraged CIRM, through its existing and future collaborators, to lead an impactful international alliance to create patient registry and central data repository to longitudinally follow patients treated with cell and gene therapies.

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Data & Knowledge Networks

- Data sharing presents obstacles re. data ownership, business concerns, regulatory but these issues can be more easily addressed if a data repository is created as part of a newly formed project or consortium, where standard approaches to collecting and handling data can be implemented, and ownership and consent are clarified and harmonized from the start.

- Linkages in these networks would empower cross-cutting mechanisms (such as immunology) that impacts across projects, within and between consortia.

- Creation of iPSC (& organoid) based modeling consortia was considered a high impact direction if disease targets and molecular disease subtypes emerge.
  - They encouraged collaboration with NYSCF, NCATS and the Allen Institute.

- In addition, a consortium that marries iPSC technology with genomics and multi-omics approaches to systematically interrogate associations between biological and genomic variations
  - They recommended assembling a workshop of potential consortium participants would include data experts (e.g. CIRM's stem Cell Hub, Human Pangenome, Data Biosphere) & existing iPSC collections (e.g. CIRM iPSC bank, Answer ALS, NCATS) to develop concepts for potential consortium.

- Leverage existing models to support consortia
  - Example: Data sharing, developed and hosted at the CIRM funded UC Santa Cruz Genomics Institute, are the genome browser and other open-source genomics platforms. Multi-institution data are linked to the UCSC genome browser and coordinated with the Human Cell Atlas and allow users to perform metadata queries.

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Shared Technology Core Labs:

The SSAP repeatedly expressed the importance of Core facilities to accelerate scientific discovery and therapy development

- high quality, standardized approaches, tools or biological resources to stem cell and gene therapy researchers across California and their collaborators.
- access to high-cost and highly specialized technologies, not otherwise available to researchers.

These Core facilities would enable Consortia models, knowledge network and “continual learning” model:

Examples: validation core, biomarkers, development ready GMP vector & cell production,research and GMP grade iPSC, organoid models, clinical and research tissue biorepositories, animal model, specialized offerings (CRISPR CAS9).

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Education and Training Programs

- Strong support for DEI to be meaningfully incorporated into research plans and education and training

- Support for education and future workforce training

For ICOC Discussion

Scope of CIRM support for projects involving:

Small Molecules and Biologics

Gene Therapy

Vital Research Opportunities

Programmatic Evaluation

Priority for projects that are unlikely to receive funding from other sources

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Current Scope for CIRM Funding:

Current Scope for CIRM Funding:

Stem cell or progenitor cell-based projects

- Cell therapy development (e.g., hESC, hiPSC, MSC, HSC, and others)
- Projects directly studying stem/progenitor cells (e.g., mechanisms of differentiation)
- Projects using stem/progenitor cells as a tool (e.g., disease in a dish models)
- Directly reprogrammed cells
- Small molecules and other biologics that act on/depend on stem cells

“Genetic Research” or Gene Therapy (in scope under Prop 14)

- Current CIRM definition of gene therapy: “Is intended to replace, regenerate, or repair the function of aged, diseased, damaged, or defective cells, tissues, and/or organs”

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Challenges in CNS Research

SSAP indicated that the major reason for slow progress in neurodegenerative and neurodevelopmental condition is our rudimentary understanding of Disease Mechanism

In addition to funding "stem cell-based" projects, panelists felt that a broader investment in this area is essential to enable the rational development of stem cell and gene therapies. e.g. epigenetics, micro-environment, non-neuronal cells such as immune and inflammatory and vascular events (not currently in scope for CIRM Discovery RFA unless they include stem cells).

- Better understanding of disease progression, natural history racial and ethnic diversity is critical (these types of studies not currently in CIRM funding pillar).
- Areas such as neuropsychiatric diseases could be addressed in "disease in a dish" models (that may involve small molecule discovery- funding of development of small molecules are funded in limited cases)
- Reverse Translation- Learning from clinical trials
    - Data-driven meta-analyses to uncover hidden information and inform direction (Large Scale Data science not funded unless linked to a specific project, clinical trial or past genomics RFA)
    - This could be accomplished within the aforementioned Consortium Model.

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Gene Therapy:

- Advisors encouraged focused investment in the intersection of gene therapy and stem cells / regenerative medicine
- Target large indications as well as orphan and rare indications, the latter may rely on academic centers where industry does not pick up
- CIRM should pursue *in vivo* gene therapy projects both “More likely to succeed” as well as “hard problems”
- CIRM could support basic research that addresses the potential for genotoxic effects, through e.g., developing “in and out” approaches that allow genes introduced into humans to be turned off or be removed.
- One of the advisors raised the need for Non-human primate (NHP) studies in development of in vivo gene therapy approaches and pointed out the need for funding of this infrastructure (CIRM does not currently fund a NHP facility but NHP studies are eligible costs under funded research)

Genetic Research:

SSAP discussed promising approaches (specifically for CNS but also for other indications) that don't currently meet CIRM's eligibility criteria for "gene therapy"

> A gene therapy approach (i) that targets a stem cell for its therapeutic effect, OR any other somatic cell; AND (ii) is intended to replace, regenerate, or repair the function of aged, diseased, damaged, or defective cells, tissues, and/or organs; AND (iii) is being developed for a rare or unmet medical need unlikely to receive funding from other sources.
>
> Gene therapy means a human therapeutic intervention intended to: 1) alter the genomic sequence of cells or 2) alter the cellular lineage via gene delivery (i.e., direct lineage reprogramming). The intervention may include strategies to repair a disease-causing gene sequence, remove or inactivate a disease-causing gene, introduce new or modified genes that augment the therapeutic potential of the target cells.

" Genetics research is the scientific discipline concerned with the study of the role of genes in traits such as the development of disease. It has a key role in identifying potential targets for therapeutic intervention and also in understanding genetically based variations in response to therapeutic interventions." (from the journal Nature)

Guidance from ICOC: Should approaches such as those identified as promising approaches by the SSAP, e.g. epigenomic editing, anti-sense oligonucleotide, shRNA, mRNA, post/transcriptional regulation-based technology, be considered eligible for CIRM funding under "Genetic Research" as stipulated in Prop 14?

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Vital Research Opportunity

Prop 14 definition:

"Vital research opportunity" means scientific and medical research and technologies, including, but not limited to, genetics, personalized medicine, and aging as a pathology, and/or any stem cell research not actually funded by the institute under subparagraph (C)…which provides a substantially superior research opportunity, vital to advance medical science as determined by at least a two-thirds vote of a quorum of the members of the Scientific and Medical Research Funding Working Group and recommended as such by that working group to the ICOC, or as determined by the vote of a majority of a quorum of members of the ICOC.

Any research area that the ICOC deems worthy of CIRM funding but would normally not be funded by existing scope and eligibility of CIRM RFAs

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Vital Research Opportunities

- Small Molecule: Some SSAP embraced a broader approach (e.g. support the development of small molecules that expand mature cardiomyocytes or hepatocytes to repair, replace damaged tissues) while others advocated for CIRM to stay focused on stem cell-based approaches with small molecules.

- Disease prevention: panelists discussed the idea of CIRM funding prevention trials. e.g. Since replacing lost neurons may not address all disease manifestations, earlier targets may impact cell loss and maladaptive outcomes. Very long term and expensive trials but pharma will not pursue so CIRM could have an impact.

Small Molecule

At SSAP, the potential for small molecules in regenerative medicine that rely on more complex stem cell and genomics research that are more likely to be conducted at academic center

- Potential for small molecules in regenerative medicine
- Development may rely on more complex stem cell and genomics modeling that are best accomplished within academic centers

Current Eligibility for small molecule:

> A small molecule or biologic (i) that acts on or is dependent on endogenous stem cells for its therapeutic effect, that is dependent on targeting cancer stem cells for its therapeutic effect, that modifies a stem cell product, OR where a stem cell is necessary to manufacture the therapy, AND (ii) is being developed for a rare or unmet need unlikely to receive funding from other sources.
>
> Not eligible for phase 2 or phase 3 clinical trials and limited eligibility for CLIN1/TRAN*

**Previous rationale for limiting eligibility: fiscal considerations and that this platform has a more well-established regulatory path and funding for late-stage projects is easier to obtain than novel cell therapies*

Guidance from ICOC: Should we make eligible small molecule projects for the full spectrum of CIRM funding--DISC/TRAN/CLIN including late stage and registration trials?

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Minimally Manipulated Cells

Current eligibility

> Minimally manipulated bone marrow, minimally manipulated cord blood or unmodified hematopoietic stem cells (HSCs), are eligible only if being developed as a novel method of addressing a rare or unmet need unlikely to receive funding from other sources.

Rationale for limiting eligibility is the wealth of projects already in clinical trials using minimally manipulated cells which generally do not offer a novel therapeutic approach and are more likely to have financial support.

Guidance from ICOC: Should CIRM continue with this eligibility criteria to prioritize novel approaches over more established ones?

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Critical Research “unlikely” to be funded by others

- Federal restrictions on hESC research funding are subject change with political winds, but CIRM’s funding provides stability to the field
- Areas where funding sources are sparse or do not exist with restricted or “at risk” federal funding
  - human fetal tissue - important validation, diagnostic and research tool
  - human embryos - knowledge for human reproduction, pregnancy loss and birth defects
  - human gametes - knowledge for fertilization and infertility
  - human mitochondrial replacement – potential for curative approaches

CIRM remains well positioned to provide platforms for policy discussions related to stem cell research.

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Critical Research “unlikely” to be funded by others

Current requirement

> …a rare or unmet need unlikely to receive funding from other sources.

Prop 71 and Prop 14 state:

> “In order to ensure that institute funding does not duplicate or supplant existing funding, a high priority shall be placed on funding pluripotent stem cell and progenitor cell research that cannot, or is unlikely to, receive timely or sufficient federal funding, unencumbered by limitations that would impede the research. In this regard, other research categories funded by the National Institutes of Health shall not be funded by the institute, unless such research funding is not timely or sufficient.”

Aside from some clear cases such as embryonic stem cell and fetal cell research, the review team has not been able to provide clear review criteria to GWG on how to evaluate “research that cannot, or is unlikely to, receive timely or sufficient federal funding” in a scientific review

Guidance from the ICOC regarding how this requirement should be addressed

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