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COMMENTARY

Boldly De-Risking Development of Impactful Cell and Gene Therapies: The California Stem Cell Agency's $3B Funding Model

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The California Institute for Regenerative Medicine (CIRM) is California's Stem Cell funding agency [1]. Since its inception in 2004, CIRM has deployed $2.7B to advance development of stem-cell based regenerative medicine therapies for patients with unmet medical needs. This perspective highlights 3 elements of CIRM's funding model that have enabled California academic researchers and companies to de-risk development of novel regenerative medicine therapies and attract biopharma industry support. To date, CIRM has funded over 1000 projects including 64 regenerative medicine clinical trials; over half the clinical trial projects have secured biopharma industry support. Overall, CIRM funding has enabled the launch of 44 companies and CIRM-funded projects have drawn in a cumulative $9B in industry investments.

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The California Institute for Regenerative Medicine is a unique state agency tasked with deploying $3B in California state funds to support research of regenerative medicine treatments and cures based on pluripotent stem cell, progenitor cell and other vital medical technologies. Since its inception in 2004 after voter approval of Proposition 71, CIRM has allocated $2.7B in grant funding to over 1000 projects that have supported basic biology research, development of novel stem cell-based technologies and therapies, stem cell education, workforce training and strategic infrastructure development. CIRM currently supports over 132 active projects and expects to fund several more before fully allocating its research funding.

The active portfolio consists of 118 active therapeutic development projects that span all disease areas including oncology, cardiovascular disease, diabetes, ophthalmology, neurodegeneration, rare immune disorders, sickle cell disease and, most recently, COVID-19 [1]. While a majority of the projects are cell therapies and gene-modified cell therapies the portfolio also includes small molecules, biologics and gene therapies (Figure 1). To date, CIRM has directly funded 64 clinical trials and has enabled an additional 31 non-CIRM funded clinical trials through its support of earlier stage research in those programs. This perspective will describe how CIRM's unique public funding model has de-risked the discovery and development of stem cell-based treatments until they are ready to be partnered by the biopharma industry.

Over the years, the CIRM de-risking model has attracted robust biopharma industry investment into CIRM-funded projects including: partnering of 50% of CIRM-funded clinical trials, spinout of 44 companies, and overall commitment of $9B.

Over 50% of CIRM-funded clinical trials are backed by venture capital, public capital markets and/or strategic biopharma partners. CIRM funding of California academic R&D projects have enabled the launch of at least 44 spinout companies. Recent company launches include Jasper Therapeutics with $50M in Series A funding to enable antibody-based bone marrow conditioning for cell and gene therapies and Aspen Neurosciences with $70M in Series A funding to develop induced pluripotent stem cell-based therapies for Parkinson's Disease. CIRM has tracked a total of $9B in industry funding committed to CIRM-funded projects since 2014. The industry dollars cover the entire spectrum from angel investments to public offerings and biopharma acquisitions. Over the past 2 years, three CIRM-funded companies have issued IPOs including Forty Seven, Inc., Orchard Therapeutics & Poseida Therapeutics, and two CIRM-funded companies have been acquired including Forty Seven's acquisition by Gilead Sciences and Asterias Therapeutics' acquisition by Biotime, Inc. (now Lineage Therapeutics). In addition, a recent economic impact report [2] prepared by University of Southern California researchers estimated that CIRM funding has generated 56,000 jobs and added $10B to the California economy.

Based on CIRM's experience, the three critical elements of CIRM's de-risking approach are:

1. Ensuring that funding mechanisms bridge the entire translational "Valley of Death"
2. Constantly optimizing funding models to meet the needs of a rapidly evolving industry
3. Championing the portfolio and proactively engaging potential industry partners

BRIDGE THE ENTIRE VALLEY OF DEATH

At the time of Proposition 71 approval in 2004, the field of human embryonic stem cells was in its infancy with just over 132 scientific publications comprising the collective knowledge. The discovery of human induced pluripotent stem cells, which overcame several of the ethical and practical challenges of embryonic stem cell research, wouldn't be

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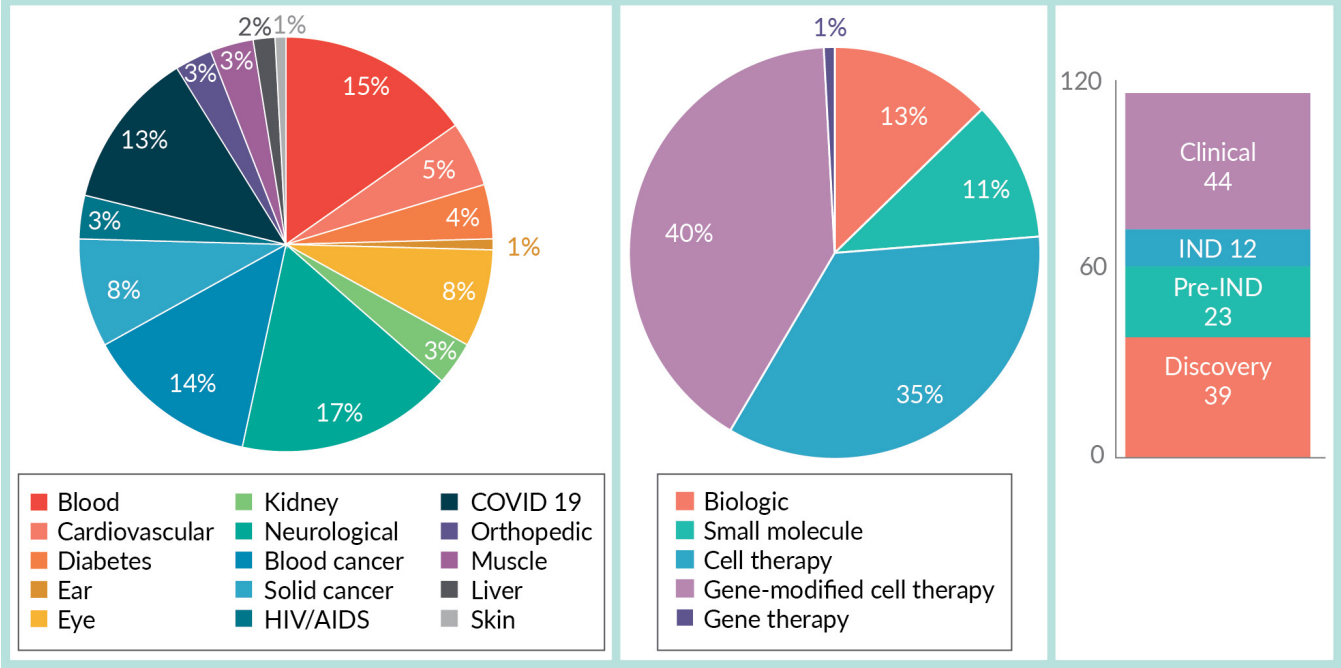
FIGURE 1

CIRM currently supports 118 active therapeutic development projects across discovery, pre-IND, IND and clinical trial stages.



A majority of the projects are developing cell therapies or gene-modified cell therapies but small molecules, biologics and gene therapies are also represented. The 118 active projects cover a broad range of disease areas including COVID-19.

published for another 3 years [3]. The seminal preclinical proof of concept of genetically engineered CD19 CAR-T cells had been published just a year earlier [4]. The field of gene therapy, a core pillar of regenerative medicine today, was still struggling to learn the ethical, scientific and clinical lessons from the tragic death of Jesse Gelsinger in a gene therapy clinical trial just a few years prior [5]. Suffice it to say, when CIRM first became operational and started allocating grant funding in 2006, the immediate focus was on seeding the field to build a critical mass of expertise, resources, and infrastructure for fundamental pluripotent stem cell and regenerative medicine research in the state [6].

Having said that, CIRM's foray into translational research and development occurred relatively early in the agency's lifecycle when it launched a funding initiative to support candidate discovery of stem cell-based therapies in 2008. From 2008-2013, CIRM issued two sets of funding initiatives encompassing the entire pathway of therapeutic development from candidate discovery, IND-enabling preclinical studies as well as clinical trials. Early stage research on candidate discovery and translational bottlenecks was supported by the Early Translational Research funding initiative. The bulk of the translational research pathway from late-stage candidate discovery research through clinical trials was covered by Disease Team funding initiatives. The Disease Team awards were envisioned as collaborations of multi-disciplinary teams including scientists, clinicians, manufacturing experts and regulatory advisors to tackle development of disease-modifying therapies for a particular disease.

A crucial hallmark of both initiatives was commitment of substantial long-term funding to support the research and development activities. For example, the Early Translational Research awards provided up to $6.7M over 3 years and the Disease Team awards provided up to $20M over 4 years. Contrast these funding levels to the National Institutes of Health's (NIH) Small Business Innovation Research (SBIR) funding programs, which collectively represent the largest source of

seed funding in the country. The two phases of SBIR awards, which are roughly analogous to CIRM's aforementioned funding initiatives, currently provide up to $250K for 6 months of initial R&D and up to $1.7M for two years of later stage R&D.

CIRM's Early Translational and Disease Team initiatives were offered a combined 7 times between 2008-2013 and committed $643M in research funding. The Early Translational awards resulted in the discovery of at least 7 therapeutic candidates that would go on to clinical studies and at least 18 candidates that are currently in preclinical development. The Disease Team initiative helped progress at least 14 preclinical candidates to clinical trials. Combined, both initiatives helped launch 17 spinout companies.

Both these initiatives uniquely enabled California academic researchers to de-risk their therapeutic candidate deep into the development pathway at their own academic institutions thereby setting them up to attract significant industry investments. In several instances, CIRM funding supported preclinical discovery and development in a California academic institution followed by successful launch of a spinout company. The company then leveraged CIRM, industry and other funding sources to progress the therapeutic candidates through clinical studies. For example, a combined $19M in Early Translational and Disease Team award funding enabled Dr. Henry Klassen's team at UC Irvine to discover, develop and complete a phase 1 study of a retinal progenitor cell therapy for the rare blinding disease retinitis pigmentosa. The UC Irvine team launched the spinout company jCyte, which went on to secure an additional $8M in clinical trial award funding from CIRM to complete a phase 2b study. On May 8th, 2020, jCyte entered an ex-US licensing and commercialization agreement with Santen Pharmaceutical and will receive up to $252M, which includes $62M in up-front cash. CIRM Disease Team award funding also enabled Dr. Irving Weissman and the Stanford University team to discover, develop and obtain first-in-human clinical data for the innovative anti-CD47 antibody immunotherapy approach to cancer. The spinout, Forty Seven, Inc., then leveraged CIRM funding as well as venture and public market financing to progress clinical development of the lead candidate until its acquisition by Gilead Sciences in April 2020 for $4.9B.

These funding initiatives also enabled small companies to de-risk truly novel stem cell technologies such as Viacyte, Inc.'s, embryonic stem cell-derived cell replacement therapy for diabetes. In fact, Viacyte has utilized $72M in CIRM funding to drive two generations of its cell-device combination therapies to the clinic and to initiate early stage research of a universal cell therapy. In 2018, the company reported strategic collaborations with Gore & CRISPR Therapeutics as well as an $80M Series D venture financing round to support progression of all three pipeline programs.

CONTINUAL OPTIMIZATION OF THE FUNDING MODEL

Over the last decade the cell and gene therapy industry has undergone rapid growth. Both biopharma investment and venture capital investment have grown steadily year over year between 2010 and now. Analyses by Smith, et al. of large biopharma investments between the period of 2010 and 2016 showed that almost every major biopharma company had committed capital to cell and gene therapy development [7]. Similarly, venture capital investment in regenerative medicine saw 34% year over year growth between 2011-2016 [8]. The 2019 annual report from the Alliance for Regenerative Medicine (ARM), an industry advocacy group, showed that global venture capital investment in regenerative medicine had reached $4.9B in 2019 [9]. This same period saw the groundbreaking US Food and Drug Administration (FDA) approvals of chimeric antigen receptor T (CAR-T) cell therapies such as Kymriah,

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Yescarta and Tecartus and gene therapies such as Luxturna and Zolgensma. Along with the multibillion-dollar acquisitions of late-stage companies such as Kite Pharma and Avexis, there were also billion-dollar acquisitions of preclinical stem cell companies such as Semma Therapeutics and Bluerock Therapeutics suggesting robust biopharma appetite for these advanced technologies.

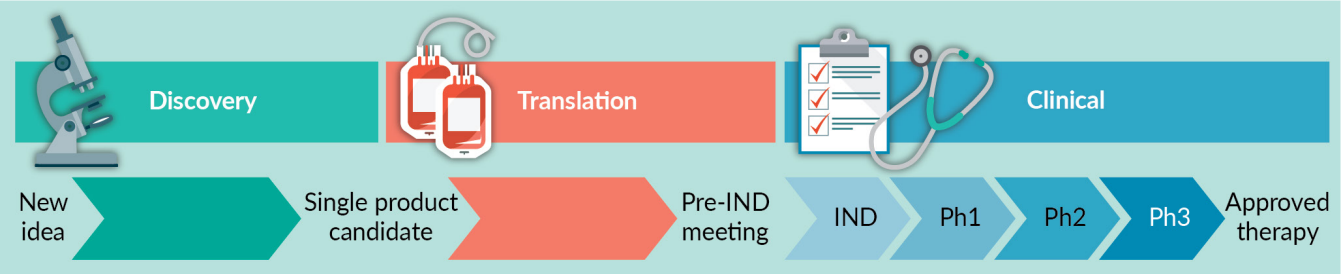
After assessing the state of the industry in 2015, CIRM overhauled its entire operational model to better serve cell and gene therapy development and to anticipate the industry's future needs. CIRM innovated a systems-based funding approach to move projects efficiently and rapidly through the development pathway from candidate discovery to phase 3 clinical trials (Figure 2). The systems-based approach was designed to overcome several limitations of the previous initiatives-based model such as slow, discontinuous funding opportunities and the financial and project risks associated with large denomination, multi-year awards. The former was addressed by three always-on funding programs covering candidate discovery (DISC), translational development (TRAN), and clinical trials (CLIN) that rapidly reviewed and approved scientifically meritorious projects for funding. By gating the funding to well-established regulatory milestones such as pre-IND meeting, IND clearance, etc., both the expected outcomes and eligibility criteria were clearly defined. The financial and project risks were mitigated in two ways:

1. By adopting a milestone-gated disbursement model similar to that utilized by the venture capital community and
2. By requiring all for-profit grantees and late-stage non-profit grantees to have "skin in the game" through commitment of co-funding to the project.

Combined, these were designed to promote timely execution of project tasks in a capital efficient manner.

CIRM envisioned these awards as true partnerships between CIRM and the grantee. As such, it also established strategic infrastructure and advisory services to further accelerate achievement of project milestones and outcomes. The strategic infrastructure funding programs established the Alpha Clinic Network and the IQVIA Cell and Gene Therapy Center. The Alpha Clinic Network comprises six leading California medical centers that have utilized CIRM funding to establish specific expertise in cell and gene therapy clinical trials. The network works collectively to implement solutions such as rapid trial startup, efficient patient recruitment, broader patient access and coordinated manufacturing support [10]. The Alpha Clinic Network has supported over 130 trials, both CIRM-sponsored and industry-sponsored, in more than 40 disease indications. The cell and gene therapy trials supported by the network range from phase 1 trials for small companies such as Angiocrine Biosciences to Kite Pharma's ZUMA-9 study. The CIRM-funded

FIGURE 2



CIRM's systems-based funding model divides the funding opportunities into three stages that span candidate discovery through phase 3 clinical trials. Therapeutic development projects may enter at any stage and are expected to progress from one stage of funding to the next.

IQVIA Cell and Gene Therapy Center comprehensively supports both preclinical and clinical development of cell and gene therapies by leveraging the expertise and resources of IQVIA, Charles River Laboratories, Wuxi Apptec and City of Hope. It serves the needs of CIRM-funded and non-CIRM funded clients in areas such as project management, pre-clinical research, assay development and manufacturing and process development support.

To foster a collaborative approach toward achievement of CIRM-funded project milestones, CIRM utilizes a unique advisory panel support structure for both its TRAN and CLIN programs. The advisory panels leverage both internal CIRM expertise as well as external domain-specific expertise to help CIRM portfolio projects overcome bottlenecks and execute project tasks. The advisory panels have provided specific guidance and solutions to help project teams overcome manufacturing delays, design clinical trials with patient input, enhance trial enrollment, and apply for expedited regulatory designations.

This systems-based funding approach, which deployed $863M through 2019, has dramatically shifted CIRM's portfolio toward therapeutic assets. It added 98 discovery stage projects, 36 pre-IND stage projects, 21 IND-stage projects and, most notably, 46 clinical trial projects. One of the first programs to utilize the CLIN funding mechanism was a lentiviral gene therapy trial for adenosine deaminase severe combined immunodeficiency (ADA-SCID) at University of California, Los Angeles. This enabled the launch of Orchard Therapeutics, which went on to raise several rounds of venture financing before issuing a $225.5M IPO in 2018. Similarly, Poseida Therapeutics received an $18M CLIN award to fund the first-in-human phase 1 clinical of its next generation P-BCMA-101 CAR-Tscm cell therapy for multiple myeloma. P-BCMA-101 incorporated several innovations including a non-viral genetic engineering method, a fully human CAR construct and a high percentage of stem central memory T cells. The company leveraged its progress in the CIRM-funded clinical trial to secure three rounds of venture financing totaling $282.5M, including a $75M Novartis investment, and then issued a $204.8M IPO in July 2020.

CIRM's funding mechanisms have also enabled academic researchers and their institutions to continue de-risking therapeutic candidates after securing a licensing partner early in development. For example, Mustang Bio launched after licensing City of Hope's CAR-T cell technology in 2015 based on candidates discovered as part of a CIRM Early Translational Award. City of Hope continues to drive development of the CAR-T candidates by leveraging CIRM CLIN awards for clinical trials in glioma and brain-metastatic breast cancer. Similarly, AVROBIO licensed UC San Diego researcher Dr. Stephanie Cherqui's genetically engineered HSC therapy for the rare disease cystinosis at the preclinical stage. Dr. Cherqui and her team at UCSD progressed the candidate through IND-enabling studies and are currently studying it in a phase 1/2 clinical trial with CIRM CLIN awards.

The systems-based funding model has enabled CIRM to continually adapt its programs to the agency's funding situation as well as to emerging biomedical research needs and opportunities. In early 2019, as CIRM started deploying the last of its research funds, it took the opportunity to extend the impact of its research funds and address the unmet medical need in sickle cell disease. CIRM partnered with the National Heart, Lung and Blood Institute (NHLBI) on its initiative to cure sickle cell disease in 5-10 years. CIRM committed $30M to cost-share gene and cell therapy IND-enabling and clinical trials projects with NHLBI. The partnership also enabled NHLBI to adopt CIRM's accelerated, milestone-driven funding model. As of this writing, the program is actively soliciting and funding gene and cell therapy projects.

In 2020, CIRM had suspended soliciting new applications for all its funding opportunities save the sickle cell program. As the COVID-19 pandemic took hold in Spring

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2020, CIRM again was presented with a challenge to address the urgent need. It launched a rapid funding opportunity for COVID-19 therapy development that promised to evaluate and fund applications within 30 days. Between April-July 2020, the program funded 3 clinical trials and 17 drug discovery projects. Finally, as it recovered funds from closed awards through the first 6 months of 2020 CIRM rapidly re-opened its DISC and CLIN programs to fund additional therapeutic development projects, which are being reviewed for funding at the time of this writing.

On a broader level, CIRM has played a proactive role in engaging both the public and federal agencies to advocate for safe and effective stem cell-based therapies. It launched a "Stem Cell Champions" campaign to engage the patient community and to advocate for efficient yet safe regulatory approaches for stem cell-based treatments at the FDA. CIRM was also an early and strong advocate for the 21st Century Cures Act, which introduced the Regenerative Medicine Advanced Therapies (RMAT) designation for cell, gene and regenerative medicine therapies. RMAT designation has enabled early and often engagement from the FDA to efficiently guide clinical development of these innovative therapies. To date, 7 CIRM-funded clinical stage therapeutic candidates have received RMAT designation.

While the current operational model prioritizes support of therapeutic development programs, CIRM recognizes the importance of education and workforce training in supporting the future growth of the California regenerative medicine economy. For the past 11 years, it has funded stem cell research training for over 1400 undergraduate and masters students, many of them first-generation, at 16 California universities and colleges. The training programs incorporate coursework, laboratory internships as well as patient engagement to prepare students for careers in stem cell research and development. In addition, over the past 8 years, CIRM has funded stem cell research internships for almost 500 high school students at 10 leading California research institutions. The internships provide high school students with meaningful exposure to stem cell coursework, hands-on research, and engagement with patients.

CHAMPION THE PORTFOLIO

To further enhance industry partnership opportunities for its portfolio projects, CIRM launched the Industry Alliance Program (IAP) in 2018 [11]. The IAP leverages CIRM's resources to proactively engage the biopharma industry about its portfolio, and to facilitate one-on-one interactions between industry partners and its portfolio projects. The IAP leverages CIRM resources to facilitate and assist both CIRM grantees and industry partners at all stages of a prospective partnership interaction. For industry partners, IAP will initially provide curated access to CIRM's project portfolio based on specific criteria. Then, it will facilitate introductory meetings with CIRM grantees. As the interaction progresses, the IAP accelerates the partnering process by coordinating with academic technology licensing offices, helping CIRM grantees prepare data rooms, advising all parties on CIRM regulations and advising CIRM grantees on deal terms.

The CIRM Business Development team routinely engages a broad range of biopharma industry stakeholders including family offices, angel networks, venture capital firms, small and large companies and incubators/accelerators. To date, the IAP has also formally enrolled 8 partners with demonstrated commitment to cell and gene therapy development: Bluerock Therapeutics, Vivo Capital, Panacea Venture, Novo Nordisk, Vera Therapeutics, Frequency Therapeutics, ElevateBio and Bayer. The enrolled IAP partners represent companies both small and large, multi-national venture firms and innovative accelerators.

Over the past 18 months, the IAP program has enabled over 50 one-on-one partnership interactions across CIRM's portfolio from discovery stage pluripotent stem cell therapies to clinical stage engineered HSC therapies. CIRM's broader vision for the Industry

Alliance Program includes applying the IAP partners' resources into CIRM's funding model and to facilitate partnering opportunities between IAP members that will broadly benefit the California regenerative medicine economy.

Forward Looking Conclusion:

The cell and gene therapy industry in the state of California is showing little signs of significant slowdown even in the current economic environment. Looking forward, as the industry grows and matures, manufacturing challenges will continue to pose significant risks both for individual projects and the industry as a whole. Truly collaborative approaches are needed to solve the dual bottlenecks of manufacturing expertise and capacity. In particular, cross-functional partnerships that deeply integrate the operational experience of contract manufacturers with the technical expertise and innovative capacity of academic institutions and cell and gene therapy companies may be required at all stages of manufacturing process development. These public-private partnerships should also be utilized to educate and train a robust manufacturing workforce capable of immediate contribution at both the technical and leadership levels.

Similar coordination of funders, investors and strategic partners may also be beneficial. There are several sources of capital for cell and gene therapy researchers and developers. These include the prominent sources such as federal agencies, venture capital, public capital markets and biopharma but also emerging sources such as state funding agencies, disease foundations, angel investor networks and university systems. While any individual cell and gene therapy developer will thread several of these capital sources along its long march to the market, there exists relatively little coordination between the funding sources themselves. This presents an opportunity for a coordinated approach that leverages both the capital and domain expertise of all stakeholders to drive a portfolio of cell and gene therapy technologies from discovery to commercialization. Along the way, the coordinated effort could probably even realize impactful solutions to systemic challenges such as manufacturing, regulatory, pricing, and real-world patient access.

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