Report on CIRM Grants Working Group Program Meeting

September 26, 2019

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On September 26, 2019, CIRM held a public meeting with members of its Grants Working Group (GWG) to solicit feedback and recommendations on what CIRM should be thinking about to prepare for a possible life beyond 2020. The meeting brought together 28 current and former scientific members of the GWG, 6 patient advocate members of the GWG and a handful of public attendees along with the board chair and CIRM team (see Appendix A for roster of participants). This document memorializes the events and outcomes of that meeting.

The meeting took place just shy of 15 years since CIRM's creation in 2004 by California Proposition 71. CIRM was given a responsibility to manage $3B that would help stem cell research flourish in California and ultimately advance that research into the clinic for the benefit of patients. With nearly all of those funds committed, CIRM has issued over 1000 awards to advance the field including 60 clinical trials that have supported enrollment of over 2000 patients.

Although CIRM will continue to support existing grants and programs for some time, funds available to support new awards will very soon come to an end. In light of this, there is an effort independent of CIRM to renew funding for the institute through a California ballot initiative. An initiative has been proposed for the November 2020 election that would request $5.5 billion to continue and expand the efforts of CIRM. If the initiative fails, CIRM will begin a wind-down process and eventually close its doors. However, if the initiative succeeds, CIRM will have a re-infusion of funds to continue existing programs and begin new ones. Although it is unknown whether such an initiative will fail or succeed, preparing and planning for either of these possible outcomes is prudent.

The overarching question for CIRM to address is then: what should the institute be thinking about now to prepare for a possible life beyond 2020? More specifically, the following questions may be considered:

- How can CIRM deliver the greatest impact in the future?
- What opportunities might CIRM seize to accelerate the field?
- What challenges must be addressed?
- What types of CIRM programs should be sustained or expanded?
- What is missing, or needs more support?

CIRM intends to solicit feedback from various stakeholder groups to address these important questions, which may ultimately inform a future strategic plan. One of these groups is the GWG, which has had a central role in helping CIRM select the most scientifically meritorious stem cell projects to support and has been a gatekeeper for quality and mission alignment. In the course of 14 years, the GWG has conducted 117 peer-review meetings with over 3000 applications reviewed. That's a pace of over 200 per year on average.

The membership of the GWG includes scientists from outside of California that collectively hold expertise across a host of disciplines such as fundamental biology, translational research, medicine, product manufacturing, drug development, regulatory affairs, and clinical trials. The

group also includes patient advocate members who serve on CIRM's Governing Board and contribute a patient perspective and strong familiarity with CIRM's mission and goals. The collective experience of this group lends great value the advice they give to CIRM and a key reason to solicit their feedback on the central questions mentioned above.

To facilitate meaningful feedback, it was important to provide all participants with a brief history of CIRM's programs and accomplishments. All participants of this meeting were provided with contextual background information on CIRM programs organized along the agency's five major investment pillars: Discovery, Translation, Clinical, Infrastructure and Education (see Appendix C). In addition, CIRM provided participants a list of questions intended to stimulate reflection and ideas (see Appendix B). The materials were provided several weeks ahead of the meeting date to allow participants to review and bring well-considered ideas when they convened. In addition, each GWG member was assigned to a specific pillar to which they could focus ideas. Members were instructed to think creatively both within their assigned pillar and more broadly of CIRM as a whole. An effort was made to balance each group with members that have the most familiarity with a pillar (e.g., a customary reviewer for the clinical program in the Clinical pillar) and members who can offer a different perspective from their experience in another program.

The meeting itself was organized into two main sessions, one in the morning and another in the afternoon. During the morning session, participants were divided into five breakout groups based on the funding pillars. The discussion was facilitated by a GWG leader assigned to each group and assisted by a CIRM team member. The goal was to have small group discussion to develop and propose three or more recommendations to CIRM broadly related to the central questions. The afternoon session brought everyone together to hear a presentation of the recommendations made by each of the groups and to solicit additional feedback from other participants. The goal was to bring different perspectives into the consideration of these recommendations and fine-tune, adjust or make additional points.

This report presents the recommendations made by the GWG and the relevant discussion by each breakout group that led to the 27 total recommendations to CIRM. Each section presents a brief review of the program scope within that pillar followed by a discussion of each recommendation.

DISCOVERY GROUP

Background

CIRM's Discovery pillar covers programs that include both therapeutic candidate research for product development as well as fundamental or exploratory research. Within these programs, CIRM has funded SEED and innovation programs to support development of new ideas but also projects that dive deep into basic biological mechanisms. In the last few years, CIRM has focused mostly on projects that are aligned with therapeutic candidate discovery and much less on mechanistic studies.

Among the five major pillars, Discovery has had the largest contribution of CIRM funding with $904 million expended as of August 2019 and over $1 billion in awards approved by CIRM's governing board.

CIRM gathered members of the GWG to get their feedback on the utility of these programs and particularly what CIRM might do in the future to enhance or further develop this funding pillar. CIRM provided key questions shown in Appendix B to solicit feedback and inspire discussion. The Discovery Group focused their discussion mostly on the following 5 questions:

1. Research aimed at gaining fundamental knowledge related to human disease pathology and biological mechanisms is important, but given its mission, how basic is too basic for CIRM? For example, should CIRM fund research on: Drosophila, yeast, invertebrates or mammals? Should CIRM maintain a focus on human research?
2. How should CIRM balance funding of basic research versus therapeutic candidate discovery work?
3. What are basic research and candidate discovery funding gaps that CIRM can uniquely address in regenerative medicine?
4. How can CIRM better support innovation and creative ideas at the basic research and discovery stage? How do we overcome risk-aversion from applicants and reviewers?
5. Are there benefits to funding investigators based on their track record as opposed to the merits of a specific project?

The summary below presents highlights of the discussion that contributed to each of the recommendations put forward by the group.

Discussion and Recommendations

Recommendation: *Continue to prioritize work 1) that cannot be funded or is underfunded by others, 2) that is aligned with CIRM's mission, and 3) that maintains a human focus.*

One of the most important contributions CIRM has made, in the opinion of the members, is funding research that the federal government or others cannot fund. Use of fetal tissue and human embryonic stem cells has been key in advancing the field but has been met with policies that even today continue to limit or stymie their use. It is important to support a stable research enterprise that is free of shifting policies and political biases as CIRM has done in California. Studies using human embryos or fetal tissue as well as development of in-utero gene or cell therapies are examples of research that still encounter problems and may not be supported by others.

Members discussed the importance of supporting basic research to advance knowledge of biological mechanisms and promote innovation. It was noted that model systems are very useful for general knowledge-building but also limited in their ability to reveal human-relevant information. In many cases, model systems fail to adequately mimic the human condition and are not predictive of outcomes in humans. Given CIRM's mission, the group agreed that a focus on research that is relevant to human biology is critically important if it is to inform therapy development. On balance, too many limitations are also not desirable. Discovery research requires a degree of freedom and flexibility to nurture innovation. Therefore, a proposed use of model systems might simply require a convincing rationale for how it informs on human biological mechanisms. The greatest flexibility should exist at these early stages of research and could be narrowed at the translational stage when projects embark on a true therapy development path.

Recommendation: *High-risk, high reward projects should be encouraged at the discovery stage.*

The group discussed the challenge of encouraging innovation and creativity in the projects CIRM funds. Many reviewers tend to be conservative in the selection of projects, often with an emphasis on the likelihood of successful outcomes. However, the group felt there is an important place for high-risk, high reward projects in basic biology as this represents another area that is under-funded by others and where CIRM can fill a need. It should be more of a "Wild West" in basic biology (as opposed to later research stages), one member said. Allowing investigators the freedom to explore allows for innovative ideas to emerge.

Recommendation: *Look into innovative ways to improve peer-review such as rapid revision as allowed with CLIN applications, composition of panel, and alignment with goals of specific call.*

Supporting innovative ideas that may not yet garner a lot of attention is important, but achieving this is difficult when applicants are conservative in proposing ideas and reviewers are conservative in their evaluations. To help overcome these tendencies, the group suggested exploring alternatives to conventional peer review systems, which tend to be conservative by nature and may not be appropriate for a competition that seeks innovation. There are methods used by other industries that could inform improved ways of conducting a review. Suggestions were made to add a lay-person review group to measure impact or use smaller review groups to overcome the need for a large consensus. It was also suggested that disagreements with at least one negative opinion by a reviewer might demonstrate that a proposal is "edgy". The group also noted that some proposals present an impactful idea but have fixable deficiencies that would benefit from an opportunity to make revisions. Shortening feedback time on applications to allow applicants to fine tune their proposals or implementing a revision system as is done with clinical applications could address this. Additional suggestions included using principles from venture capital to select projects, or allowing conditional funding of proposals.

Recommendation: *Encourage or convene expert groups to write white papers to periodically examine gaps in the field. Focus on bottlenecks, best practices, and standardization.*

The discussion group did not call out specific areas of investigation that they thought should be a focus for CIRM. Rather, they encouraged CIRM to hold workshops and convene expert groups in broad areas of interest to help identify the most relevant needs and bottlenecks on a periodic basis. Funding should be targeted where it is needed as informed by known gaps in the field. Identifying key problems and bottlenecks in clinical and translation research can set the stage for relevancy of basic/discovery research. Expert groups could also identify opportunities where CIRM funding might have the most impact, such as therapeutic approaches that are closest to the clinic. Connecting basic scientists with clinicians was also raised as an important approach to bring awareness and knowledge of clinical needs to investigators.

The group asserted that there should be a balance of basic biology aimed at fundamental knowledge and therapeutic candidate discovery. Pushing in only one direction is not desirable. The group also felt that maintaining a broad portfolio of projects in varied disease areas will maintain balance and have the most impact on society.

Members reflected on what some of the wide-ranging needs in the field might be that CIRM could explore further. It was suggested that a better understanding of gene regulation, developing relevant animal models or disease models, single-cell analyses, and maturation of tissues made from pluripotent cells are important areas. The development of tools and technologies for cell monitoring and methods for cell delivery were also highlighted.

Recommendation: *Expand scope beyond stem cells broadly into regenerative medicine including approaches such as gene therapy.*

The group felt that CIRM should allow for advancement of a broader set of technologies beyond stem cells, but still within regenerative medicine. Stem cells are a great tool but additional regenerative approaches such as gene therapy are also worthy of pursuit.

Recommendation: *Encourage creation of centers, team approaches, and collaborations to enable discovery research with standardization.*

Team efforts, particularly interdisciplinary collaborations, that leverage diversity in knowledge and expertise were encouraged to more effectively tackle scientific problems and advance promising ideas into therapeutic development. Team efforts could take the form of collaborations among a few investigators or perhaps more formalized structures within specialized centers. Collaborations that bring together biologists with physicists, engineers, or other disciplines may open up new avenues to discovery and innovation. How CIRM structures an RFA may encourage collaborations. For example, a solicitation for projects on cell tracking would naturally pull in physicists. Additionally, having centers of expertise that can produce reagents or provide services in a consistent and standardized way, could provide the field a valuable resource, particularly for investigators that have limited capabilities within their labs. It was suggested that CIRM consider ways to facilitate such efforts.

The group briefly discussed reproducibility of scientific results at the discovery level. It was felt that forcing labs to have work reproduced by others places an unnecessary burden on investigators and is not likely to improve outcomes. Investigators are generally not interested in replicating experiments conducted in other labs unless they are specifically interested in advancing the work themselves. Many labs develop such specialized systems that their work may be difficult to reproduce elsewhere. It was felt, however, that reproducibility should be encouraged where it matters most, such as functional validation of a candidate in standardized models.

Aligned with this idea, the group recommended that CIRM encourage the development of standards in the field, where it may be helpful to advance research. For example, developing key criteria that define pluripotency in iPSC lines, criteria for research-grade or GMP-compatible reagents, and use of FAIR[1] practices for publication of research results to allow reproducibility. The goal is to facilitate use of new knowledge and allow investigators to adopt new methods quickly and advance research findings. Additionally, standardization can support improved data sharing and analysis across multiple labs. Similarly, outlining best practices for investigators such as what makes a good bank or a good grant would help improve proposals.

[1] Research conducted using FAIR practices means the data meet standards of findability, accessibility, interoperability, and reusability as first described by Wilkinson M.D., et al. (15 March 2016) *Scientific Data* 3: 160018. doi: 10.1038/sdata.2016.18

Recommendation: *Support some individual investigators to grow field and complement project-based research.*

The group briefly discussed the idea of funding research based on an investigator's track record versus on the merits of a specific projects. Members felt that there is room for supporting individual investigators based on track record in basic biology, but perhaps only within specific programs. The group discussed potential pitfalls of funding research on this basis but felt it could complement project-based funding by attracting investigators to the field and providing a different mechanism for scientific exploration.

Recommendation: *Support big data approaches and mechanisms of cell therapy informed by gaps that exist at the translational and clinical stages.*

Given CIRM's mission, it is important to support research that tackles key gaps that hinder or limit the translation and clinical implementation of candidate therapies. Support of research aimed at the understanding of basic biological mechanisms is key to this goal as it strengthens clinical rationale and the likelihood of clinical success. The group emphasized the need for CIRM to support research into mechanisms as a core element of the CIRM Discovery pillar. This recommendation stems from the same discussion that highlighted the need to maintain the relevancy of the research to human biology and pathology. An understanding of the mechanisms that underlie human disease or the therapeutic action of a candidate are an important part of advancing therapies to the clinic.

In addition, the group advocated for data sharing and facilitating use of big data to support discovery research. In alignment with the group's recommendation for standardization and team approaches, the collection and dissemination of data in ways that allow analyses by multiple groups can help the field more effectively identify and overcome bottlenecks and pursue the most promising ideas.

Discovery Group Recommendations:

1. Continue to prioritize work 1) that cannot be funded or is underfunded by others, 2) that is aligned with CIRM's mission, and 3) that maintains a human focus.
2. High-risk, high reward projects should be encouraged at the discovery stage.
3. Look into innovative ways to improve peer-review such as rapid revision as allowed with CLIN applications, composition of panel, and alignment with goals of specific call.
4. Encourage creation of centers, team approaches, and collaborations to enable discovery research with standardization.
5. Support some individual investigators to grow field and complement project-based research.
6. Support big data approaches and mechanisms of cell therapy informed by gaps that exist at the translational and clinical stages.
7. Expand scope beyond stem cells broadly into regenerative medicine including approaches such as gene therapy.
8. Encourage or convene expert groups to write white papers to periodically examine gaps in the field. Focus on bottlenecks, best practices, and standardization.

TRANSLATIONAL GROUP

Background

CIRM has funded translational activities since 2010 through early CIRM Disease Team awards where these were supported as part of a broader objective. The current CIRM Translational program, implemented in 2015, focuses more specifically on early development stage activities for stem/progenitor-based therapeutics, diagnostics, devices, and tools. While the specific activities funded for each type of product vary, the majority of Translational awards to date have supported the development of therapeutics. The Translational program supports activities for products that already have initial proof of concept and need further development to prepare for regulatory submissions or broad use. The expected outcome of therapeutic translational awards is to conduct a pre-IND meeting with the FDA, or equivalent.

The group spent a significant portion of time discussing the overarching value of CIRM and the best directions in which CIRM can continue to contribute to regenerative medicine. The group also brainstormed about specific ways to strengthen the Translational program. Using the CIRM provided questions as an anchor for the discussion, the key questions of focus for this group included:

1. Which therapeutic modalities would fit best with CIRM's focus on regenerative medicine? Why?
2. Should CIRM focus only on curative or restorative therapies? For example, should CIRM fund research aimed at palliative remedies that may not target the underlying disease but improve quality of life? What are your thoughts on funding preventive approaches utilizing regenerative medicine? Why or why not?
3. While the TRAN program supports therapeutic, device, diagnostic and tool development, CIRM received very few applications in the latter three categories. Should we continue to support device, diagnostic, and tool development? If so, what can we do to encourage more applications? How do we better support translational stage activities for these areas?
4. How might we best support projects that seem to fall in between funding opportunities (e.g., not quite ready for our Translational program but somewhat beyond candidate discovery)?

Discussion and Recommendations

Recommendation: *CIRM needs to focus on the regenerative aspect, not just stem cells.*

Therapeutic modalities and regenerative medicine
The group strongly agreed that CIRM should be agnostic to therapeutic modalities, as long as they met the definition of regenerative medicine: It is difficult to predict what will work, and the best path forward is to fund all regenerative medicine modalities, not just stem cells. Application review should focus on whether the underlying science is solid and whether the therapeutic could have impact, and not focus on whether the therapeutic is a small molecule, cell-based, or gene therapy. GWG members agreed there is momentum in the cell therapy field, and although there are remaining issues to resolve (e.g., delivery, immunity, mass transfer) a comprehensive approach is more valuable than earmarking any single bottleneck for funding.

Funding of preventative approaches
CIRM should not fund preventative approaches and should maintain a focus on funding regenerative medicine. There was some discussion on the importance of CIRM specifically funding regenerative treatments, not just 'disease modifying'. CIRM could add value in the regenerative space which is not actively being pursued by pharma/industry, which focuses on symptom modifying and disease modifying products. Epidemiological studies and other population-based tools have benefit but would potentially be prohibitively expensive to fund and finding a pathway to a therapeutic treatment may be difficult to implement.

Translational stage funding
The group members agreed that CIRM should focus on funding projects that will not be funded elsewhere. With a $5.5 billion initiative, CIRM would need to be very focused on regeneration, and not broaden the scope.

Ideas for CIRM included:

- Decreased emphasis on basic research, which can be funded through NIH
- Continue funding across the entire development pathway, which is unique to CIRM
- Focus on funding translatable research/applied approaches
- Fund first-in-human and non-human primate proof-of-concept studies which are always hard to get funding for, and which generate data that are needed for VC funding
- Drug repurposing screening and tools such as disease-in-a-dish should be funded

Recommendation: *Maintain institutional knowledge through data sharing.*

Data dissemination and sharing
There was significant discussion around the importance of data dissemination, particularly to learn from failures, and how CIRM could potentially facilitate this process. Many examples of previous and current efforts in data sharing were raised, as well as the idea of building an

'institutional memory' that could outlive CIRM. The underlying motivation is to create opportunities to find utility in the data, even if a project fails. There was general agreement that this is not new ground, but many challenges exist in implementation, particularly for earlier stage projects that may have significant variability in data collection, methodology, cell culture conditions, and cell line characterization.

Possible ideas on how to share/structure project data/information:

- Create a data repository – all CIRM awardees are required to put data in a shared repository
- Implement tiered levels for release of data (e.g., after grant closes, after publication)
- Create a statistical arm of CIRM to help awardees evaluate/analyze data
- Include sharing of manufacturing best practices

Recommendation: *Translational applications and review should be forward-looking and focus on desired clinical outcomes.*

Incentivizing entry into the translational space

The group discussed various ways to encourage academic researchers to move beyond the discovery stage given the very specific goals and tight timeline of the Translational Program awards. Different iterations of the Translational Program were proposed. Several members thought that the current thirty-month timeline of the awards seemed tight for cell therapies and suggested exploring other timelines. The possibility of offering more frequent program submission deadlines was discussed, similar to the monthly application cycle of the Clinical Program. In the end, the group thought that three reviews per year for the program was likely to be sufficient, and, for applications that were not recommended, allowed applicants adequate time to revise and resubmit.

Supporting translational stage applicants

The group discussed the importance of maintaining applicant entry into the CIRM 'pipeline' at any point in the development pathway. Members thought prior CIRM-funded discovery stage awardees may have greater success in acquiring translational stage awards perhaps due to a desire by reviewers to advance previously supported projects. A greater effort to encourage 'new' applicants should be made. The group emphasized the importance of reaching out to potential applicants who may not be thinking past the proof-of-concept stage and encouraging them to 'get on the bandwagon.' Two suggestions were (1) offer planning grants as a way to help applicants form the right team with the needed expertise, (2) leverage/coordinate usage of Alpha Clinics and IQVIA to support translational activities.

Increasing the quality of applications to improve scientific review and award outcomes

In addition to increasing interest in translational development, the group also discussed practical ways to structure the application process to provide an orienting framework which the applicants can utilize during the development process. The group members emphasized that applicants need to define the desired clinical outcomes early, at the translational stage. The

application should (1) increase focus on the target product profile (TPP) and (2) include a clear description of the expected clinical trial outcome. Applicants need to get input from clinical experts early and utilize the desired clinical outcome to drive the project, with the understanding that goals will change over time, and (3) increase clarity on current and planned process development/manufacturing activities.

Translational Group Recommendations:

1. CIRM needs to focus on the regenerative aspect, not just stem cells. Not only stem cell driven, but regenerative medicine driven, anything with impact.
2. Maintain institutional knowledge through data sharing.
    a. Mistakes can be powerful; embracing variability as part of the true clinical experience – need access to that data.
    b. Manufacturing issues that are repeated in different centers.
3. Translational applications and review should be forward-looking and focus on desired clinical outcomes. Proposals must consider what is going to be the intended disease indication and what type of patients will be targeted.
4. Support planning grants for applications not quite ready for TRAN: those that need to engage clinical, regulatory and manufacturing expertise.
5. Important that CIRM fills in the holes, gaps to get to pre-IND and IND meetings, things others do not fund.

CLINICAL GROUP

Background

The Clinical Program at CIRM was designed to fund clinical trials and IND-enabling preclinical research projects. The GWG members in the Clinical breakout group were provided background information and data on CIRM's clinical funding programs. Highlights of these data are summarized below and available in Appendix C.

Prior to 2015, CIRM issued several RFAs focused on therapeutic development, which funded projects that spanned multiple stages of development of a single therapeutic candidate. IND-enabling and clinical trial activities represented the final objectives of these longitudinal projects. In contrast, the Clinical Program established in 2015 funds projects that are each focused on a single goal, which may be IND-enabling preclinical activities or single clinical trials for a single therapeutic candidate. An overview of CIRM funds deployed on clinical stage projects as of August 2019 is shown below:

Disease Team Awards ($406M)
Strategic Partnership Awards ($32M)
Clinical Program ($492M)

As of September 2019, CIRM has funded a total of 56[2] clinical trials, 39 trials (funded via 41 grant awards) that have been supported under the new Clinical Program established in 2015. The clinical trials projects span all major disease areas with cancer representing 32% of the portfolio. The trials range from phase 1-3 with a majority being phase 1 trials. The projects include all therapeutic modalities eligible for CIRM funding with adult stem cell-based projects representing a majority. Gene-modified cell therapies represent over a third of the clinical trial portfolio. Nine CIRM-funded clinical projects have expedited designations from the FDA including 6 projects with FDA Regenerative Medicine Advanced Therapy (RMAT) designation.

CIRM has also funded 20 IND-enabling preclinical projects since 2015, five that have successfully progressed to achieve clinical trial funding from CIRM. Twenty clinical trial projects have received previous funding from CIRM and, thus, represent pipeline projects.

GWG members were provided with general questions regarding overall funding scope and prioritization as well as questions specifically focused on CIRM's clinical funding programs.

[2] On October 31, 2019 the Application Review Subcommittee of the ICOC approved funding for four additional clinical trials and one additional IND-enabling study bringing the total trials funded to 60 and preclinical projects to 21.

Discussion and Recommendations

Recommendation: *CIRM should remain agnostic toward disease modalities.*

The group first addressed the general topics of scope and prioritization. CIRM had posed several questions asking whether CIRM should limit or focus its funding to maximize the impact of its funding opportunities (Appendix B). The members broadly agreed that CIRM should not limit its scope any more than it already is and that it should retain flexibility. Many GWG members noted that regenerative medicine is hard to define and strict interpretations could lead to projects straining to meet eligibility or could limit CIRM's ability to fund otherwise meritorious projects. They agreed that CIRM should not limit funding to specific therapeutic modalities, which could run the risk of missed funding opportunities for novel emerging approaches. They agreed that preventative care and palliative treatments that alter the course of a disease could be appropriate for CIRM funding if other eligibility criteria are met.

There was general interest among the group in CIRM targeting specific areas of focus (see also Moonshot idea below). Group suggestions included various disease areas, microbiome, bioprinting, modulating immune response to cell therapies, and manufacturing as potential focus areas. Some members also believed that CIRM should continue to fund what others, such as the NIH, do not. These discussions on the general questions led to the first formal recommendation from the group that CIRM should fund all modalities that meet the general eligibility criteria.

Recommendation: *CIRM should factor in planning for payment of and access to novel therapies from an early stage.*

The topic of unmet medical needs brought the group to consider whether a novel therapy that is only affordable and accessible to a select few is considered as effectively addressing an unmet medical need. The group thought that planning for payment and access models for novel CIRM-funded therapies could begin at the pre-clinical stage via CIRM-funded access to external expertise. They noted that such analyses would require involvement of all major stakeholders including, but not limited to, disease area experts, healthcare providers, payors, and patient advocacy groups.

Group members also agreed that CIRM could form an internal team that interfaces with major stakeholders such as insurance companies, the Centers for Medicare and Medicaid Services (CMS), Institute for Clinical and Economic Review (ICER), and others to broadly address access to novel regenerative medicine therapies. Members noted that, in fact, payors in other countries such as the UK are routinely involved as stakeholders in the clinical development stages of novel therapies. This early involvement could have several benefits including offsetting patient care costs in trials and facilitating planning for pricing and access. Just as importantly, the collaborative approach would serve to educate both the investigators and payors on how healthcare systems can effectively deliver novel therapeutic modalities.

The group also cited examples of clinical development and commercialization strategies that could better inform pricing and access such as efficacy-to-effectiveness trials proposed by Tufts Medical Center researchers, which link establishing initial efficacy with determining real-world effectiveness. CIRM could require that clinical trial projects include exploratory endpoints designed to assess health-related quality of life outcomes.

Recommendation: *Establish centers of excellence to support CIRM and non-CIRM therapeutic development programs.*

The group considered how CIRM could further add value to its funded projects and set them up for long-term success at each stage of funding. Group members noted that in many instances the investigator teams, especially academic teams, may not have the requisite product development and regulatory expertise to efficiently drive their projects to the clinic. In addition, the investigator teams may not have access to in-house resources and facilities with specialized expertise to meet their project needs. Finally, they noted from their own experiences that services such as vector manufacturing are in such high demand that long lead-times and unfavorable contract terms can limit access or severely penalize investigator teams.

The group recommended that CIRM ensure all funded projects have access to external consulting services for regulatory planning, product development and clinical trial design, contract product manufacturing and process development, core labs and other CRO services. At the clinical stage, such consulting services could be incorporated into clinical advisory panels (as discussed below) leading to more efficient trial designs, expedited regulatory designations and timely regulatory approvals. Group members suggested that CIRM could help support such access by establishing centers of excellence or identifying preferred service providers. This would also have the added benefit of securing fair and consistent pricing across all of CIRM-funded projects. They acknowledged that CIRM has developed relevant expertise in implementing Alpha Clinics that could be applied in establishing these additional centers of excellence.

Recommendation: *Enhance the function of CIRM Clinical Advisory Panels.*

When considering additional value-adds that CIRM could provide its grantees, the group focused on enhancing the function of advisory panels. CIRM routinely convenes clinical advisory panels (CAPs) composed of external advisors, patient advocates and CIRM team members for every IND and clinical stage project funded through its Clinical Program. The advisory panels work collaboratively with the investigator team to assess projects, solve technical challenges and plan for future regulatory and product development steps. The CIRM team informed the group that the long-term plan for CAPs involves incorporating regulatory and pricing/reimbursement advisory services for all projects. The GWG members noted that CIRM is unique in providing advisory panel services to all of its clinical program grantees. They commended the collaborative approach and its impact on achieving project goals. They thought that the scope of the CAPs should be enhanced and broadened to focus on subsequent stages of product development and commercialization. Suggestions included contracting with

appropriate consultancies to provide gap analyses of clinical, regulatory and commercial development plans. Group members indicated that such analyses are not within reach for early stage therapeutic development projects especially those in academic settings. Thus, these services would be a significant value-add that could put the program on the most efficient development pathway early on.

Recommendation: *Establish moonshot-like RFAs targeting specific disease areas.*

A consistent theme during the session was the need for multidisciplinary approaches to both execution of the CIRM-funded project as well as the overall development of new therapies. For example, group members noted that academic investigators who were responsible for discovery of a new candidate therapeutic may not have all the necessary expertise and resources for downstream development activities such as GMP manufacturing, trial design and trial execution. In addition, many regenerative medicine therapies have multiple components such as cells, viral vectors, or scaffolds, all of which require different expertise and resources.

Several group members also pointed out the value of consortia-based therapeutic development and highlighted their own experiences. For example, members mentioned the GForce initiative, which is a loose international consortium of investigators, each developing their own stem cell-based therapies for Parkinson's Disease. While the consortium members are, in a sense, competitors they find value in sharing expertise on specific aspects of their projects such as vector manufacturing, clinical trial design, animal models, and so on. More traditional examples of consortia include the NCATS rare disease clinical research networks, which help facilitate multi-center trials by coordinating IRB approvals, recruitment, and patient education for specific rare diseases. Group members suggested that the consortium approach could allow CIRM-funded projects to tap leading expertise outside the state. However, some members raised the concern that the geographical restrictions of CIRM funding may limit the inclusion of national and international experts and institutions in CIRM-funded consortia.

Another consistent theme was striking a balance between prioritizing funding to make a significant impact on rare diseases or prioritizing funding to make an impact on significant diseases with high prevalence. Group members noted examples of the former within CIRM's portfolio of therapies for rare diseases. These have significant impact on the individual diseases, which may not affect a large proportion of California patients, but may lead to platform approaches that could be translated to other diseases. An example cited by the group was that better understanding and treatment of a very rare disease, Fanconi anemia, could have profound impact on the development of novel therapeutics for common solid tumors, like breast cancer. On the other hand, the group noted that there are relatively common diseases, such as neurodegenerative disorders that have not seen much progress. In these prevalent diseases, a relatively smaller advance, such as slowing down disease progression, could substantially impact a broad patient population and the healthcare system as a whole.

These lines of discussion coalesced into a group recommendation for a moonshot-like idea focused on a particular disease area. The group thought that CIRM, with the help of special emphasis panels, could identify the disease area where there have been promising new discoveries and announce RFAs encouraging high impact, multi-disciplinary approaches. Such an RFA would be complementary to the discrete project-based funding model currently employed by CIRM. They stressed the concept of a multi-disciplinary approach that incorporated not just different levels of technical expertise but also clinical, product development, regulatory and patient advocacy expertise. Funded projects would span academic and industry institutions and disciplines but would tackle specific bottlenecks to therapeutic development in the target disease area. Group members highlighted several potential target disease areas such as rare pediatric diseases, age-related macular degeneration, stroke, neurodegeneration, heart failure, metabolic disorders and diabetes. Several members recommended selecting disease areas that are prevalent in California. They also discussed examples of bottlenecks that could be addressed by the projects including gene delivery technologies and imaging technologies.

Other topics of discussion

The group also addressed several of the other clinical program discussion questions. They did not think that CIRM should limit its funding on a particular stage of clinical development but to continue funding all stages from IND-enabling to phase 3 clinical trials. Several members did note that CIRM funding has greater potential for impact on earlier stage clinical trials (i.e. phases 1-2), thus CIRM may consider prioritizing funding for phase 1 and phase 2 clinical trials. They had several suggestions for improving industry partnering prospects for CIRM-funded projects. Firstly, they recommended that academic PIs be provided entrepreneurial training. They recommended that either CIRM or an external advisor could provide a report outlining the market potential and potential partnering strategies for CIRM-funded projects. Finally, they recommended incorporating an industry steering committee similar to other funding organizations such as the Michael J. Fox Foundation. Such a committee could guide the development and partnering of the most promising CIRM-funded projects.

Feedback from GWG on Clinical Group recommendations

During the presentation of group recommendations to the broader GWG, comments and suggestions were made by audience members to further add to the recommendations. There was a strong recommendation for incorporating pharmacoeconomic analyses within CIRM award management to plan for broad, affordable access for therapies, especially those that impact prevalent diseases. Regarding the moonshot RFAs, there was a recommendation that CIRM carefully analyze the strengths and weaknesses of ongoing cancer moonshot efforts to inform its own approaches. There was significant discussion on the potential scope and structure of the moonshot approach, which led to the group members to clarify that the moonshot would need to be very deliberate with respect to the nature of the collaborative effort, the expected outcomes, and impact on other disease areas.

There was also discussion of whether CIRM should focus on funding clinical development of therapies that may not have strong commercial potential but may be both broadly affordable and clinically impactful. Finally, there was a discussion about future funding support for CIRM's active clinical trial projects portfolio and a recommendation that CIRM consider selecting the most promising clinical trial projects for further funding support. Without presuming to know how a new initiative would be structured, it was noted by CIRM staff and board members that current portfolio projects would likely have an opportunity to submit applications for further funding support under future CIRM funding programs.

Clinical Group Recommendations:

1. Fund all therapeutic modalities that meet CIRM's general eligibility criteria (i.e. remain agnostic to modalities).
2. Establish centers of excellence for core services that will benefit both CIRM and non-CIRM funded development programs (i.e. GMP manufacturing, lab services, consulting services).
3. Enhance the function of advisory panels by requiring expert consultant review in key areas to more effectively drive product development.
4. Support planning and development of payment and access models for CIRM-funded therapies.
5. Establish moonshot RFAs targeting specific disease areas of relevance to California citizens.

EDUCATION GROUP

Background

Since its inception, CIRM has funded a number of programs geared towards creating a skilled work force that can discover and translate stem cell therapies to patients with unmet needs. One major program, the "Research Training Grant Program" (2005-2017), provided research support for graduate and postdoctoral/clinical fellows at major research universities, institutes and medical schools around the state. The alumni from this program, deemed "CIRM Scholars", have gone on to become faculty members and leaders in the stem cell/regenerative medicine community both inside and outside of California. A second major program, the "Bridges Grants" (2009-present), target community colleges and state universities, providing undergraduate and masters level education to a diverse population of students. These programs include specialized coursework, patient engagement and outreach activities, followed by stem cell research internships in host laboratories at major universities, institutes and biotechnology companies. Bridges alumni emerge from their studies well prepared for careers in regenerative medicine and typically find immediate employment as research technicians or choose to continue their education in graduate or medical school. A third major training program, the Creativity/SPARK Awards (2012-2020), provides summer research internships for high school students in stem cell laboratories at major universities and research centers. Finally, in addition to training individuals, CIRM has supported education through Conference Grants, which sponsor the development and conduct of scientific conferences in California on topics with relevance to CIRM's mission.

Topics

Prior to discussion, GWG members were provided information on the history and outcomes of CIRM training programs, as well as a set of questions to ponder regarding scope and priorities of future training initiatives. One key question was whether CIRM should implement a new training program for graduate and postdoctoral level individuals, and if so, whether the skills to be developed through this program should be similar to what was targeted previously, or if new programs should be developed that align more closely to the current needs of the regenerative medicine community. Group members were also asked to consider whether faculty level training should be considered and if so, what type of training would be most beneficial for helping investigators transition their research to the development pathway. In considering the development of new types of training programs, group members were asked to identify any workforce expertise gaps that CIRM could uniquely address to accelerate development of regenerative medicine therapies, and who might be recruited to be trained in those skills. They were also asked to consider additional ways that CIRM could foster diversity and encourage participation from under-represented populations to bring needed perspective to the discovery, translation and implementation of stem cell therapies. Finally, group members were

encouraged to think outside the box of traditional training grant models and consider other ways to structure training programs to develop workforce expertise in regenerative medicine therapies, such as through individual apprenticeships or "trade school" type approach.

Discussion and Recommendations

Before discussion of individual questions began, several group members expressed some key ideas that they believed should serve as overarching themes. These included an emphasis on "team science"; a desire to support areas of workforce development that are underfunded by the NIH or other agencies, such as physician-scientist or medical scientist training programs; a desire to better educate the public about stem cell research and therapy development, through outreach or possibly formal curriculum development, targeting high school students, their teachers, and patient advocates.

Recommendation: *SPARK and Bridges programs should continue. Bridges programs should be expanded to reach more areas of state, particularly community and city colleges. CIRM should consider a flexible funding structure to accommodate changes in tuition and cost of living adjustments for students.*

The Bridges program appears well-regarded by all group members. GWG members noted that the caliber of Bridges alumni is unparalleled and has captured notice by educators and hiring managers outside of the state. They also noted that there are very few comparable programs around the country, such as University of Minnesota Master's program, and there was agreement that more such programs are needed. Because all agreed that the Bridges program should continue, discussion centered on potential ways to improve the program or expand its reach.

- The idea of expanding the program to include more community (or city) colleges was strongly supported; community colleges represent a potentially untapped talent pool, of diverse students in terms age, gender, ethnicity, and economic opportunity.

- Given the high cost of living in CA and extended length of Bridges grants (5 years), the group discussed the possibility of budget flexibility to cover tuition hikes, and higher stipends to a) help students cover their living expenses during the internship period, where they must reside near their host institution; and b) incentivize individuals to enroll in Bridges programs who otherwise might decide to enter job market at a lower position with less potential for career growth.

- Group members endorsed the addition of elements to Bridges programs that could allow non- Bridges students or others to indirectly benefit from the Bridges programs; such as the General Education Courses that were developed as part of the first round of

Bridges funding. Other suggestions were to incorporate more formal community outreach, including interactions with public school students and teachers.

- Some discussion centered on the types of research projects that should be the focus of Bridges internships. Currently, Bridges students must use human stem cells in their projects. Some group members agreed that work with human cells is most important and relevant to careers in the biotech industry and ultimately, for translational studies; others argued that scientific research on other mammalian stem cells or model organisms would be perfectly appropriate for developing the skills that are necessary to become an independent investigator, particularly one that would progress to a PhD or other professional program. Ultimately, group members suggested that the research scope should be aligned with CIRM's mission but also flexible enough to encompass strengths of the individual program, and take into consideration the desired career trajectory of the trainee; for example, if a trainee is interested in data science, he/she could be just as well served learning to analyze data from murine stem cells as human stem cells, as the expertise gained could be broadly applied to other systems.

The Creativity/SPARK programs were also highly regarded by members who endorsed continuation of the program. A suggestion was made to expand the programs, if feasible.

Recommendation*: Develop a "physician pipeline" training program that targets pre-med, medical students and clinical fellows to prepare them for careers as MD/PhD stem cell physician scientists, or as physicians practicing regenerative medicine. Education should emphasize diversity and inclusion.*

Discussion of the Research Training Grant Program began with an explanation for why this program was discontinued by CIRM after 8 years of operation. In essence, these training grants had provided stipends to support graduate students, postdoctoral fellow and clinical fellows that had already been enrolled and/or recruited to laboratories at the various CA research institutions. Because those institutions continue to recruit and enroll graduate students and fellows without issue, it was not clear that the added CIRM support was increasing the work force any more than what was already being achieved. Moreover, CIRM always had and continues to support graduate students and fellows as personnel on CIRM funded research grants, which achieves the same purpose but offers training that is more closely aligned to CIRM's mission as it evolves. Given these facts, group members discussed whether it is worth re-initiating the Research Training Grant Program as it existed previously, or whether it should be adapted or even replaced with other programs that better address the current needs of the regenerative medicine community.

- Group members generally agreed that the Research Training Grant Program, as originally conceived and offered, is no longer the optimal method for creating a stem cell-specialized workforce of faculty level investigators. After briefly discussing an alternative approach, which involved awarding individual fellowships for trainees that

could be "bolted on" to existing CIRM grants, the group ultimately determined this would be a "rich get richer" strategy, and instead, opted to consider new types of training programs for this level of trainee.

- The group recognized a need to recruit individuals from under-represented backgrounds to leadership positions in regenerative medicine – not for social purposes, which is outside CIRM's mission, but for scientific reasons. Their perspective can bring fresh and critical new insights into the types of diseases that are investigated, how treatments can be delivered, and how patients can be recruited.

- Towards reconfiguring a training program to align with current needs of the regenerative medicine community, group members raised the issue of federal funding cutbacks for physician-scientist training programs and a current dearth of well-trained physicians with stem cell expertise, or "stem cell physicians". Suggestions were made to develop a special training program targeted at doctors in training, i.e. "physician pipeline" including pre-med, medical students and clinical fellows. These programs would offer training in stem cell research and development and other skill sets relevant to patient needs, such as accessibility, diversity and inclusion – something more than the usual "doctor shadowing" that is presently offered in many medical school preparatory programs.

Recommendation: *Develop a training program for MD/PhD or postdoctoral level students to produce "Stem Cell Ethicists", i.e. career professionals with dual expertise in bioethics and stem cell research who are needed to address current and future challenges of the regenerative medicine field. This could be implemented by offering more extensive ethics training to PhD/MD level stem cell investigators, or alternatively, a specialized stem cell ethics program could be developed and administered either as a stand-alone training program, or as a joint training program between philosophy and science departments.*

In discussing work force needs for future discovery and implementation of stem cell therapies, the group discussed a growing need for professionals with expertise in both stem cell science and ethics. The term "ethics" was parsed further, to differentiate the new and needed expertise from the typical "research ethics" that is taught to scientists. Group members determined that specialized training is needed to confront emerging questions in the regenerative medicine field, such as weighing the consequences and benefits of a transformative new technology; considering issues around accessibility and affordability of new treatments; and communicating the legitimate, ethical way of translating stem cells to the clinic as opposed to what is offered at the unregulated "stem cell tourism" clinics that are victimizing vulnerable patients. Very few individuals have this expertise currently, and many scientists, including GWG members, would welcome the advice of such ethicists towards communicating their research to the public. The group next discussed what components of training would be essential to developing expertise in a so-called "stem cell/regenerative medicine ethics". All agreed that such professionals should be well-versed in research oversight, Institutional Review Boards, ethics of human

subject research and informed consent, regulatory affairs, policy, and access/reimbursement issues for new therapies. Some suggested the training should be a mixture of science and philosophy, noting that a few philosophy departments around the state offer a specialized training program for MDs. One argued that a new Stem Cell/Bioethics training program might be modeled after one of these already-existing programs, or build off of them.

Recommendation: *Develop programs to educate the general public at high school level, including sponsoring ~three-day retreat/training course for high school teachers; develop an analogous course for training patient advocates.*

Another area of need identified by some group members was better training for public high school students in the sciences, and particularly in the area of stem cell science/biomedical research. One referenced Senate Bill 471, (Romero, Steinberg and Torlakson), the California Stem Cell and Biotechnology Education and Workforce Development Act of 2009, which led to development of a free "stem cell curriculum" that is available for high school teachers and others to utilize in their classrooms. While other members appreciated the idea of developing additional curricula that could be shared, some argued that these types of programs are really "preaching to the choir" and do not necessarily reach the types of students and teachers that would benefit from this knowledge. Instead, they suggested that expanded outreach activities might be a better way to educate members of the public about stem cell research and its potential. One suggestion was to develop a stem cell boot camp for high school teachers, delivered in the form of a three-day, all-expense paid retreat/training course on stem cells, with which they could return to their schools and incorporate into their own curriculum. Another member suggested a similar outreach program for training patient advocates would be useful.

Recommendation: *Develop a "trade school" model to teach post-bachelor level (and perhaps other level) individuals technical, high-demand skills such as process engineering, manufacturing, analytics, quality systems, GMP.*

After discussing traditional education and training programs, the group turned their attention to key skill sets that are desperately needed to accelerate the translation of therapeutic discoveries from bench to bedside. All agreed that a critical gap exists for knowledge and expertise in the manufacture of cell therapies and advanced biologics, which includes process development, analytics, quality systems, Good Manufacturing Practices, and regulatory affairs. These skills are not typically taught in university settings and require highly specialized equipment and facilities. Moreover, much of the existing manufacturing expertise has been developed and fostered in pharmaceutical/biotech industry, which primarily focuses on the manufacture of traditional drugs (small molecules and antibodies). Although a few academic and medical centers that run clinical trials have GMP facilities, the general lack of experts in cell therapy manufacturing represents a major bottleneck in the translation of regenerative medicine. To train new experts, group members discussed the notion of a "stem cell trade school" program where individuals could train as apprentices with experts, i.e. analogous to the

journeyman/master craftsmen structure of trade guilds. To further this goal, members also recommended the development of new manufacturing infrastructure to support both manufacturing and training, possibly by leveraging the existing network of Clinical Science Training Institutes (CTSI).

Recommendation: *Develop a training course for academic/faculty level investigators to provide skills and expertise needed for translational research, such as product development, IRBs, clinical trial recruitment, regulatory affairs. Courses could possibly be linked with CTSI around the state.*

Another underdeveloped skill set identified by the group pertains to the growing number of academic investigators who are innovating novel stem cell therapies and seek to translate them but have only superficial knowledge of the drug development process and regulatory path. They recommended that CIRM develop a special training program for such investigators.

Recommendation*: Develop a "Young Investigators" training program that supports a postdoctoral fellow for one to two years and then in his/her third year, supports transition to a career position in CA.*

As the breakout session drew to a close, several group members wanted to quickly revisit the discussion on whether to re-initiate the traditional Research Training Grant Program, given their prevailing sense that the NIH is pulling back on training programs in general. While most agreed that the original implementation of the training program would not be ideal, there was strong support for developing a "Young Investigators" program, which could support training of postdoctoral/clinical fellows that are transitioning into careers in regenerative medicine. A suggested model would be to provide two years of training followed by a year of support while transitioning to a research position in California.

Recommendation: *All training programs should include patient engagement activities.*

Group members noted that that patient engagement and exposure is an important element towards maintaining focus on CIRM mission, from the most basic scientist at the bench to the doctors delivering the therapeutic. A general recommendation emerged that all CIRM funded training programs should require patient engagement activities as a core component.

Education Group Recommendations:

1. All training programs should include patient engagement activities.

2. SPARK/Bridges programs should continue; Bridges programs should be expanded to reach more areas of state, particularly community and city colleges; programs should consider a flexible funding structure to accommodate changes in tuition and cost of living adjustments for students.

3. Consider developing for pre/post PhD and MD level training:

    a. A "physician pipeline" training program that targets pre-med, medical students and clinical fellows to prepare them for careers as MD/PhD stem cell physician scientists, or as physicians practicing regenerative medicine. Education should emphasize diversity and inclusion.

    b. A training program to produce "Stem Cell Ethicists", i.e. career professionals with dual expertise in bioethics and stem cell research who are needed to address current and future challenges of the regenerative medicine field. This could be implemented by offering more extensive ethics training to PhD/MD level stem cell investigators, or alternatively, a specialized stem cell ethics program could be developed and administered either as a stand-alone training program, or as a joint training program between philosophy and science departments.

    c. A "Young Investigator" type program that supports a post doc for one to two years and then in their third year, supports transition to a career position in CA.

4. Consider programs to educate the general public at high school level, including sponsoring ~3 day retreat/training course for high school teachers; similar course for patient advocate training

5. Consider developing a "trade school" model to teach post-bachelor level (and perhaps other level) individuals technical, high-demand skills such as process engineering, manufacturing, analytics, quality systems, GMP.

6. Consider developing a training course for academic/faculty level investigators to provide skills and expertise needed for translational research, such as product development, IRBs, clinical trial recruitment, regulatory affairs. Courses could possibly be linked with CTSI around the state.

INFRASTRUCTURE GROUP

Background

Infrastructure programs at CIRM were designed to fund the construction of new research buildings and laboratories, and establish research and clinical development resources. In this category, CIRM has contributed nearly $500 million as of August 2019 to a variety of programs as outlined below.

Buildings and labs

- Physical research buildings ($271M)
- Shared core laboratories ($69M)

Research resources

- iPSC repository ($32M)
- Genomics initiative ($40M)

Therapy and clinical development

- Alpha Stem Cell Clinics ($40M)
- Accelerating Center ($15M)
- Translating Center ($15M)

The creation of shared core laboratories and research buildings occurred early in CIRM's lifetime and were intended to facilitate the conduct of human embryonic stem cell research that was otherwise limited under federal grant support. These programs also intended to grow the field by making equipment and facilities available more broadly. CIRM also sought to create resources that would facilitate and augment research such as the iPSC repository and genomics initiative. As the field matured and projects became ready to enter the therapeutic development phases, CIRM put in place programs that would increase the likelihood of success by providing guidance and assistance with key development activities such as toxicology studies, regulatory advice, patient enrollment and coordination of clinical trials.

Ahead of the meeting, GWG members were provided with background material for CIRM's infrastructure programs along with questions covering priorities and scope for the discussion. Questions included which services would be most impactful for CIRM to support in the future to accelerate the development of regenerative medicine therapies, how that infrastructure should be designed to benefit multiple groups, and best practices for the management of those programs. The group elaborated on these themes for most of the discussion.

Discussion and Recommendations

Framing considerations:
The group moderator provided an introduction at the onset of the session to encourage the group to freely address a variety of topics including capital expenditures, intellectual capital or business, education, or clinical and manufacturing. Some members encouraged the group to think about the value proposition for infrastructure projects and identify gaps in resources, but to not propose infrastructure projects simply because other agencies are funding it. There was a desire to capture value for California in any infrastructure spending, and consider the question of whether public-private partnerships offer the most pragmatic model to accomplish this.

Recommendation: *Build manufacturing infrastructure as a centralized private company.*

Commercial/late- stage manufacturing scale-up
Manufacturing of cells was discussed for the majority of the session as a key area that would benefit from improved infrastructure. One gap in particular is the large-scale manufacturing of cell products that is required for phase 3 clinical trials and commercialization. These products would include those derived from embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells, and cells derived from adult progenitors. Group members stated that cell therapy developers often delay manufacturing scale-up due to the difficulty and especially the expense of establishing a scalable process. Product development can proceed through early phase clinical trials without addressing scale-up issues, and companies hedge financial risk by delaying scale-up development until clinical data are in hand. This can result in a delay of clinical development activities after phase 2 trials since phase 3 trials must be carried out using the manufacturing methods that would be used to make the final commercial product. Existing academic good manufacturing product (GMP) sites are generally at capacity, both for cell and vector manufacturing, and are generally not available or suited for detailed scale-up studies. Group members felt that academic centers are not suited to take on development of methods for large scale commercial manufacturing. Group members also asserted that there are likely to be several broadly applicable technological improvements that could be useful in the commercial manufacturing and delivery of extensively expanded cell products of all types. These could include, for example, improvements in methods and hardware for culturing, harvesting, cryopreservation, thawing, and shipping. CIRM could greatly accelerate commercialization of cell products by creating infrastructure where staff would focus on development of these improvements. Solving some of these general cell expansion issues could also, in the long run, take development costs out of the system by reducing duplicative efforts for multiple cell products. In principle, these cost saving could be reflected in cost savings to patients.

Early stage manufacturing scale-up
A second gap in manufacturing that was discussed is in cost-efficient manufacturing of products for early stage clinical trials sponsored by commercial entities. Several group members noted that academic manufacturing centers generally have limited capacity for projects by outside groups. Existing commercial manufacturing entities also have limited capacity and often are too expensive for small companies or academic groups. This is a major bottleneck in the development of cell products. The group felt that CIRM should carefully review the capacity for affordable manufacturing of cell products for early stage clinical trials and consider establishing independent infrastructure to increase this capacity as necessary.

To address both of these gaps, members recommended that CIRM establish a manufacturing center where early stage contract manufacturing for companies could be carried out and where staff could focus on solving common problems in late stage and commercial process development. Time did not allow for discussion of details, but several ideas were floated. The center might get started by initially providing a few specialized services and later expand as the center becomes established and develops a reputation. All group members believed the center should develop intellectual property and expertise in generic methods and approaches (as opposed to production capacity or specific products) for cGMP-grade commercial products. Focus areas should include common needs like sterility, freezing and banking. The center should not focus on potency assays because they are too specialized with each product. Embryonic stem cells are still the gold standard for developing processes and CIRM could fill the gap in developing manufacturing standards because it places no restrictions on their use. In general, there should be an emphasis on phase transition where there are complex technology transfer needs from the clinical development sponsor.

Structure/Governance:
There was general agreement among the members that CIRM should not provide additional funding to existing academic manufacturing centers. Instead, a CIRM-supported manufacturing center should be a private, centralized enterprise that builds up expertise. CIRM could generate incentives to use a manufacturing center and accumulate knowledge in a centralized facility by offering "coupons" with its grants to use a manufacturing center. However, the center should not just be a resource for CIRM awardees, capacity should be available to the field.

Costs should be an important consideration. Group members encouraged CIRM to think about cost-of-goods and engage with reagent providers to bring down supply costs with a center. Viral vectors were also mentioned as an expensive bottleneck for developing cell and gene therapies. Strategies to bring down these costs will be a key driver of value for any manufacturing center. Bringing down costs and increasing development speed would be a strong incentive to bring academic investigators to use a CIRM-supported center. Again, cost savings can ultimately be reflected in the cost of commercial products for patients.

To keep a private manufacturing center focused on these goals, group members argued that the organizational structure should be set up with the capacity for CIRM to be directive with

programs and management. California state agencies are not allowed to hold equity or intellectual property, so alternative mechanisms such as holding governing board seats were discussed. The need to generate a return on investment for CIRM support of a private enterprise was emphasized. Intellectual property provides one source of return (see below). The value to California could be in the form of money returned the state, reduced cost-of-goods, or reduced cost of therapeutic product.

Recommendation: *Set up an intellectual property generation consortium.*

The high costs of GMP manufacturing, including cost-of-goods and methods, was cited by several participants as a bottleneck for developing cell therapies. Examples of technologies that could help accelerate cell therapy development include:

- Cell banking: freezing, containers / systems
- Assay development (potency assays / detection methods); machine–based-standardized-automated testing methods desired
- Real-time testing methods to address transplantation at risk
- Human embryonic stem cell (hESC) scale-up
- Creation of biomass

Development of any of these technologies is associated with new intellectual property that drives up GMP cell production costs. To address this issue, the group suggested that CIRM could sponsor a consortium to develop IP and expertise related to generic methods and approaches for GMP-grade manufacturing. The consortium could be created through a CIRM-private partnership model with multiple members. Existing manufacturing facilities could be leveraged if possible. Process development scale-up technologies (e.g. supporting transition from phase 2 to phase 3) may be a high need.

Group members recommended that the consortium should be a public-private partnership with CIRM. Partners could "buy into" the consortium with matching support from CIRM. It would be pitched as a pre-competitive space where there is benefit to all members with shared IP and shared processes. The incentive to join would be access to licensed IP at reduced costs and faster access to technology. CIRM funding would act as the lever to lift the generation of IP under the consortium. Group members predicted that access to manufacturing methods and know-how will be key IP protections in the future under current US Patent and Trademark Office rules.

CIRM would not own the IP generated by consortium, but should control the consortium. CIRM would need to establish staff or capacity with expertise in long-term management of IP to manage this effectively. It could build capacity internally or contracted externally to manage IP and realize value for California. The Leducq Foundation and NIIMBL were cited as examples for this type of model.

Recommendation: *Support targeted workforce development and training.*

There is a paucity of professional talent in cell therapy manufacturing. Engineers are often needed for cell manufacturing, but most engineers do not have cell culture experience or understand regulatory issues. The session participants voiced a need for more trained technical and clinical professionals with regulatory and technology transfer expertise.

Group members suggested that CIRM should support workforce development in regulatory affairs, GMP manufacturing, and clinical fellowships in cell therapy. CIRM could coordinate with state licensure organizations to establish standards for training. Training has been effective within the community college system. Apprenticeships in GMP manufacturing facilities would also be a value route for training in this field.

Additional Infrastructure Considerations

Background on the Alpha Stem Cell Clinics was given during the session. Session participants agreed that it would be valuable to support education for clinical practice and standards for administering cell therapies.

Bioinformatics was also discussed. Data is largely unstandardized and difficult to compare. Establishment of a Center for Bioinformatics was mentioned as a way to centralize data. How a bioinformatics center could be set up to add value remained an open question.

Infrastructure Group Recommendations:

1. Build manufacturing infrastructure as a centralized private company. Provide affordable early stage manufacturing of cellular products. Address gaps in manufacturing, process, assay development for early and late state processing. Run via private enterprise in partnership with CIRM.
2. Set up an intellectual property consortium. This could be integrated into manufacturing infrastructure. A key driver would be lowering cost of goods via creation of new IP. Members could "buy in" into consortium to get access to IP. Bring in academics and industry, but control by CIRM.
3. Support targeted workforce development in regulatory affairs, GMP manufacturing, clinical fellowships related to cell therapies. Training could be through apprenticeships.

Although not formal recommendations, the group also advised collecting information on:

Bioinformatics hubs (e.g., genomics, clinical data)

Alpha Clinics – structure and utilization

APPENDIX A

GRANTS WORKING GROUP MEETING PARTICIPANTS

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APPENDIX B

SEPTEMBER GWG MEETING DISCUSSION QUESTIONS

The goal of this meeting is to gather feedback, suggestions and recommendations for how CIRM might deliver the greatest impact in regenerative medicine should it have the opportunity to do so in the future. Because the GWG has helped us identify the most scientifically meritorious projects to fund over the last 14 years, your perspective is important to us.

We are providing you the questions below as a starting point to fuel your thoughts about program scope, priorities, and approaches, but hope that you'll have additional questions to contribute to the discussion as well. Our intent is to engage in a high-level discussion that is forward-looking and aimed at providing recommendations for CIRM to consider as well as questions or topics that CIRM should explore further. These will add to information we expect to gather from various stakeholders in the next year and may ultimately help us inform a strategic planning process, if CIRM establishes new funding.

The questions are organized under each of our five funding pillars (Discovery, Translation, Clinical, Infrastructure, Education) and under general questions where the questions are wide-ranging. Please use these questions as a starting point for your group discussion, but feel free to think broadly across the different programs as you will have the opportunity to contribute your thoughts to all.

General Questions

CIRM Funding Scope

The expected scope of the new initiative maintains CIRM's focus on regenerative medicine. CIRM defines regenerative medicine broadly to include stem cell research, gene therapy, tissue engineering, and any technology that aims to replace, regenerate, or repair the function of aged, diseased, damaged, or defective cells, tissues, and/or organs.

1. Which therapeutic modalities would fit best with CIRM's focus on regenerative medicine? Why?
2. Should CIRM focus only on curative or restorative therapies? For example, should CIRM fund research aimed at palliative remedies that may not target the underlying disease but improve quality of life? What are your thoughts on funding preventive approaches utilizing regenerative medicine? Why or why not?
3. Should CIRM consider allocating funding to address unmet medical needs in specific disease areas?
4. Would consortia-based projects help advance the field of regenerative medicine? If so, how should CIRM encourage and fund consortia-based projects to have the most impact? (Examples of potential consortia-based projects include development of

therapies in a specific high-priority disease indication or development of a technology platform.)

5. Is it important or relevant to evaluate whether or not a project could be funded by others (NIH, VC, etc)? What information would be necessary to properly evaluate this?

CIRM Funding Prioritization:

CIRM has evolved in the various types of programs it has offered and funded over the years and are generally categorized under 5 pillars.

- Basic research and Candidate Discovery
- Translational
- Clinical
- Infrastructure
- Education/Workforce training

1. Are there scientific opportunities you believe should be a **top** priority for future CIRM funding? Why?
2. CIRM funding opportunities are largely based on supporting the progressive stages of therapeutic product development from discovery to clinical trials. Are we missing anything using this model (i.e. funding of technology platforms, tools, devices, etc.)? Are there additional and complementary ways to structure funding opportunities?
3. Are there additional pillars CIRM should consider? Are there potential areas of funding that are not addressed by any of the above? (Ex. Healthcare access to underserved populations, business models, ethics, etc.)
4. Should the level of industry engagement/investment have any impact on CIRM funding priorities (consider development stage, disease area, technology, modality, etc.)?

Discovery Questions

The Discovery questions cover programs that include both therapeutic candidate research for product development as well as fundamental or exploratory research. Within these programs, CIRM has funded SEED and innovation programs to support development of new ideas but also projects that dive deep into basic biological mechanisms. In the last few years, CIRM has focused mostly on the Discovery Program, which supports candidate discovery and much less on mechanistic studies.

Program Scope:

6. We expect that if future funding is realized, basic research will be an important target, ie. research aimed at gaining fundamental knowledge related to human disease pathology and biological mechanisms. How basic is too basic for CIRM? For example, should CIRM fund research on: Drosophila? Yeast? Invertebrates? Mammals? Should CIRM maintain a focus on human research?

Priority Setting:

7. CIRM's goal is to accelerate transformative regenerative medicine therapies to the clinic. CIRM has funded two types of discovery research in its lifetime: (1) basic research and (2) therapeutic candidate discovery. How should CIRM balance funding of the two?
8. What are **basic research** funding gaps that CIRM can uniquely address in regenerative medicine? What are key areas that we need to know more about? Ex. Derivation of hepatocytes, reverse translation?
9. How can CIRM better support innovation and creative ideas at basic research and discovery stage? How do we overcome risk-aversion from applicants and reviewers?
10. What are **candidate discovery** funding gaps that CIRM can uniquely address to accelerate development of regenerative medicine therapies?
    a. Are there therapeutic modalities of particular promise that CIRM should fund at the discovery stage (stem cell, gene therapy, small molecule, biologics, devices, other)?
    b. Are there specific disease areas that present a unique funding opportunity at the discovery stage?
    c. Are there specific tool/technology candidates that should be funded at the discovery stage, such as those to develop model systems, new imaging technologies, etc.?
11. Are there benefits to funding investigators based on their track record as opposed to the merits of a specific project?

Translational Questions

What we define today under our Translational program was funded previously in our Preclinical Development awards and the first iteration of the Disease Team awards. The recent Translational Program attempted to create a path that addressed the specific requirements for development of varied products including devices, diagnostics, tools, and therapeutics.

Program Scope:

1. While the TRAN program supports therapeutic, device, diagnostic and tool development, CIRM received very few applications in the latter three categories. Should we continue to support device, diagnostic, and tool development? If so, what can we do to encourage more applications? How do we better support translational stage activities for these areas?
2. How might we best support projects that seem to fall in between funding opportunities (e.g., not quite ready for our Translational program but somewhat beyond candidate discovery)?
3. How do we incentivize progression of projects along the development pipeline?

Priority Setting:

4. What are **translational stage** funding gaps that CIRM can uniquely address to accelerate development of regenerative medicine therapies?

a. Are there key translational activities that are generally difficult to find funding for?
b. Are there therapeutic modalities of particular promise that CIRM should fund at the translational stage (stem cell, gene therapy, small molecule, biologics, devices, other)?
c. Are there specific disease areas that present a unique funding opportunity at the translational stage?

Clinical Questions

The current Clinical Program prioritizes stem cell therapies over other modalities, prioritizes clinical projects in rare and pediatric diseases, and, while supporting all stages of clinical research, tapers down funding for later stages. Previously, CIRM funded clinical trials under the Disease Team Awards, Targeted Clinical Development Awards, and Strategic Partnership Awards.

Program Scope:

1. How can CIRM's Clinical program be more adaptable and flexible to remain at the forefront of rapidly evolving science, regulatory pathways and pricing/reimbursement schemes in regenerative medicine?

Priority Setting:

2. What are clinical development funding gaps that CIRM can uniquely address to accelerate development of regenerative medicine therapies?
    a. How might CIRM best accelerate the development and approval of gene and cell-based therapies?
    b. Are there therapeutic modalities of particular promise that CIRM should fund at the clinical stage (stem cell, gene therapy, small molecule, biologics, devices, other)?
3. Should CIRM focus its funding on particular stages of clinical development? If so, why and what should be the desired outcome of CIRM-funded clinical projects (i.e. phase 1 safety, initial efficacy, de-risk for industry partnership, etc.)?
4. How can CIRM play a more impactful role in industry partnering of programs?
5. How can CIRM encourage grantees to anticipate healthcare economics issues and initiate commercialization plans and to continually develop them over the course of the CIRM-funded project?

Infrastructure Questions

CIRM has funded infrastructure to support physical buildings, core services for therapeutic development and research, and considered funding public private partnerships. Some programs, such as the funding of physical buildings in the form of research institutes, were a way to address the inability of researchers to use federal funding for embryonic stem cell research at

that time and are unlikely to be funded further. Other infrastructure programs such as the Alpha Clinics fund institutions that provide core services for stem cell therapy clinical trials, career development for clinicians performing clinical trials, and a community and network of sites that are currently the most actively utilized infrastructure program.

Program Scope:

1. Is there a need for funding physical buildings in the future? Why or why not?
2. What types of service are most impactful to support? Core services for therapy development or basic research tools or both?
3. Should CIRM fund infrastructure programs that are already available outside California?

Priority Setting:

4. What are **infrastructure** funding gaps that CIRM can uniquely address to accelerate development of regenerative medicine therapies?
    a. Are there infrastructure resources that are high areas of need for specific groups (academic researchers/clinicians, small commercial developers)? How can they be/should they be designed to benefit multiple groups?
    b. Academic translational stage projects often need support in designing and implementing robust development plans. How can CIRM facilitate the process of integrating the appropriate experts needed to create and execute these projects?
    c. Is there infrastructure that CIRM has not supported previously that should now be considered?
5. What are best practices for infrastructure program management, and how involved/prescriptive should CIRM be? (ex. Pricing of services, IP ownership)
6. How can we best establish and maintain infrastructure programs that are readily accessible to all public and private institutions?

Education Questions

CIRM expects to continue its high school (SPARK) and college (BRIDGES) research internship programs if funding is available, which are designed to spark early interest in and access to stem cell research and stem cell-based medicine. In 2014, CIRM opted not to renew its traditional training grants supporting PhD students, postdoctoral and clinical fellows.

Program Scope:

1. Should CIRM reconsider funding post-graduate level training grants? And if so, what might that look like?
2. Should faculty level training be offered? If so, what types of training would benefit this group? What kind of training/expertise or work force development programs could benefit motivated academic investigators in transitioning their research into the development pathway?

Priority Setting:

3. What are workforce expertise gaps that CIRM can uniquely address to accelerate development of regenerative medicine therapies? Considering the personnel and workforce that may be necessary to develop and deliver the next generation of cell and gene therapies, who should we be looking to train? (ex. manufacturing/process development, regulatory, project management, trial operations, healthcare delivery)
    a. What types of skills are anticipated as work force needs?
    b. What are areas of greatest need for training?
4. A secondary goal of CIRM training programs is to produce a workforce that reflects the diversity of the state of California. Offering education programs at state universities and city/community colleges extends opportunities to students that might otherwise have not been made aware of opportunities for such training. Are there other ways CIRM programs can foster diversity and encourage participation from under-represented groups?

Our current BRIDGES programs require matriculation at a "home" institution/university for coursework, followed by research internships conducted at "host" laboratories, which may be located at universities, medical schools or biotechnology companies. These programs culminate in BS/MS degrees or certificates of expertise from the home institution.

5. Are there other ways to structure training programs to develop workforce expertise in regenerative medicine therapies, such as through individual apprenticeships, or via different types of "host" programs? If so, how could these be implemented?

APPENDIX C

BACKGROUND DATA AND INFORMATION

CIRM provided GWG members a set of slides that present an overview of funding programs within each investment pillar and data on funding allocations and award statistics as background information for their discussion. The full set of slides is presented in the following pages.

Note that the data represents information as of August 2019 when it was assembled for the GWG members.

SOMETHING BETTER THAN HOPE

Right now.

GWG Meeting
September 26, 2019

CIRM
CALIFORNIA'S STEM CELL AGENCY

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

1

2004
CIRM created by Patient Advocates and California Stakeholders-Proposition 71

$3B
Committed to CIRM Mission

1000
Cutting Edge Research & Transformative Programs funded

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

>2000 Patients *
Patients enrolled in CIRM-funded clinical trials

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CIRM
CALIFORNIA'S STEM CELL AGENCY

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2

* This slide was corrected to report the number of patients enrolled in CIRM-funded clinical trials and remove an incorrect reference to patients enrolled in Alpha Stem Cell Clinics.

GWG Contribution to CIRM: 2005-2019

117 GWG REVIEWS

200+ AVERAGE APPS SUBMITTED PER YEAR

3000+ APPS REVIEWED

750+ TIER 1 SCORES

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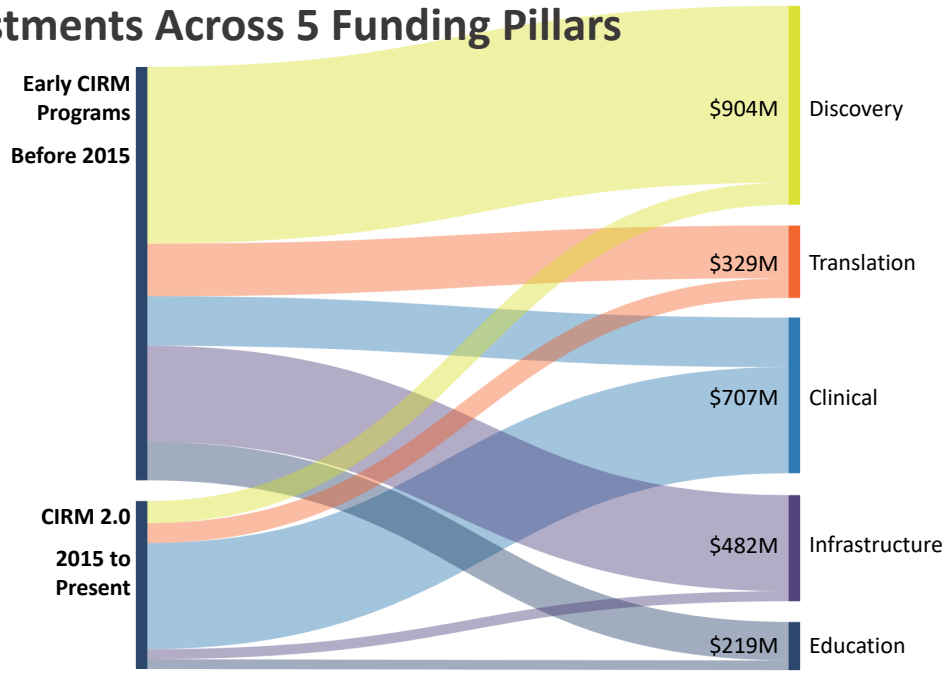
3

CIRM Investments Across 5 Funding Pillars

$2.6B
1000+
Awards



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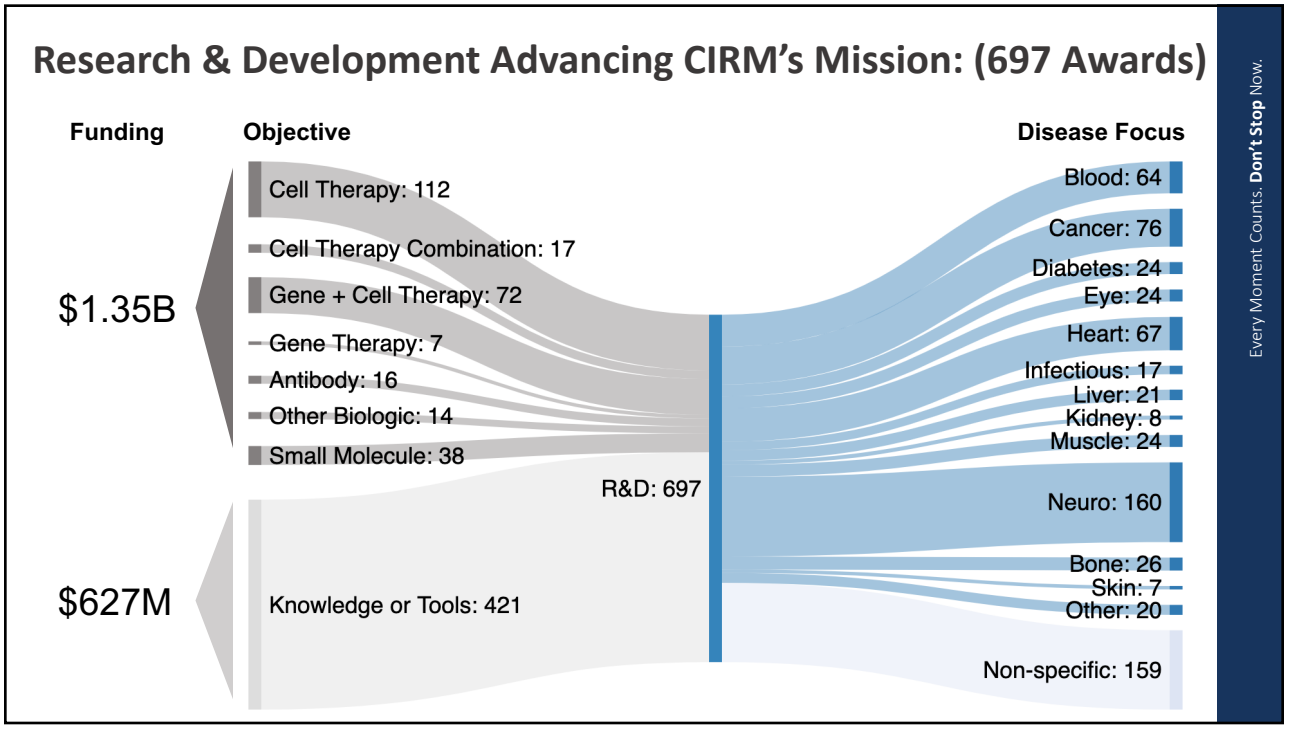
4

Funding amounts shown are based on the total amount awarded as of August 2019, not the total amount approved by the ICOC.



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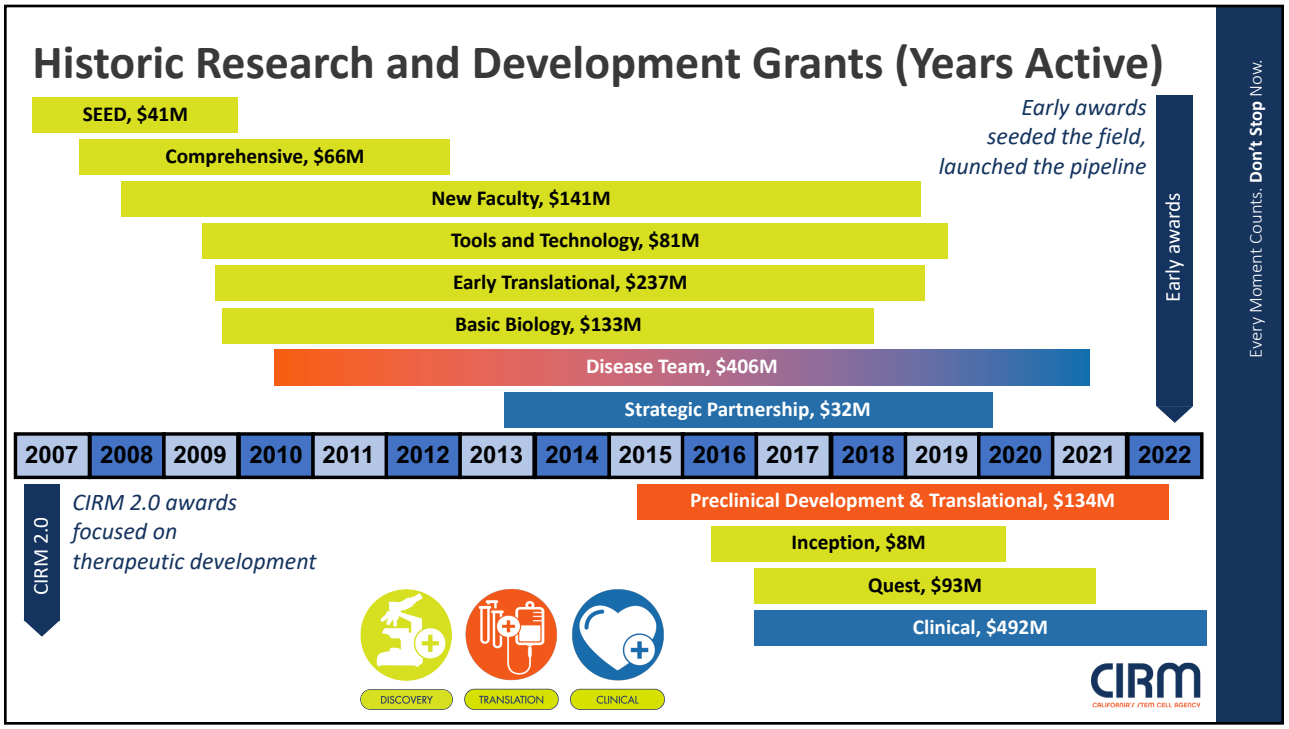
Funding amounts shown are based on the total amount awarded as of August 2019, not the total amount approved by the ICOC.

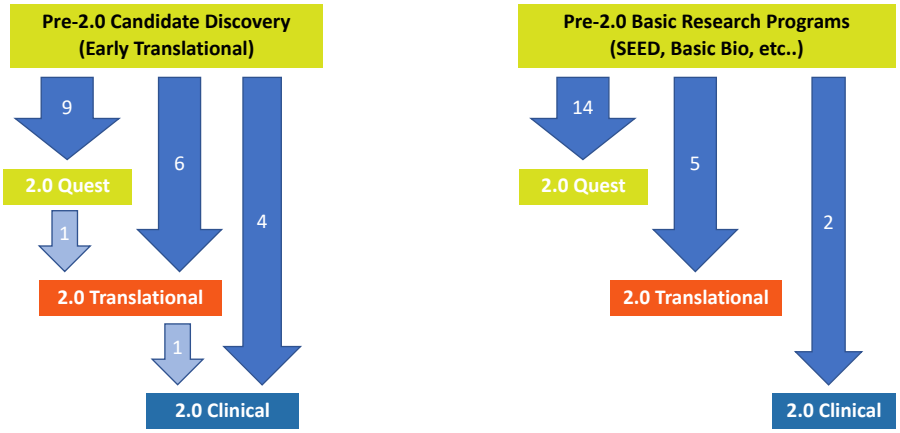


6

Funding amounts shown are based on the total amount awarded as of August 2019, not the total amount approved by the ICOC. The programs shown do not represent a comprehensive list of CIRM funding opportunities.

Early Stage Pre-2.0 Projects Feeding CIRM 2.0 Pipeline

Basic research and candidate discovery pre-CIRM 2.0 projects have entered and advanced within the CIRM 2.0 development pipeline.



Figures exclude progression of projects that entered the pipeline under CIRM 2.0 (see next slide).

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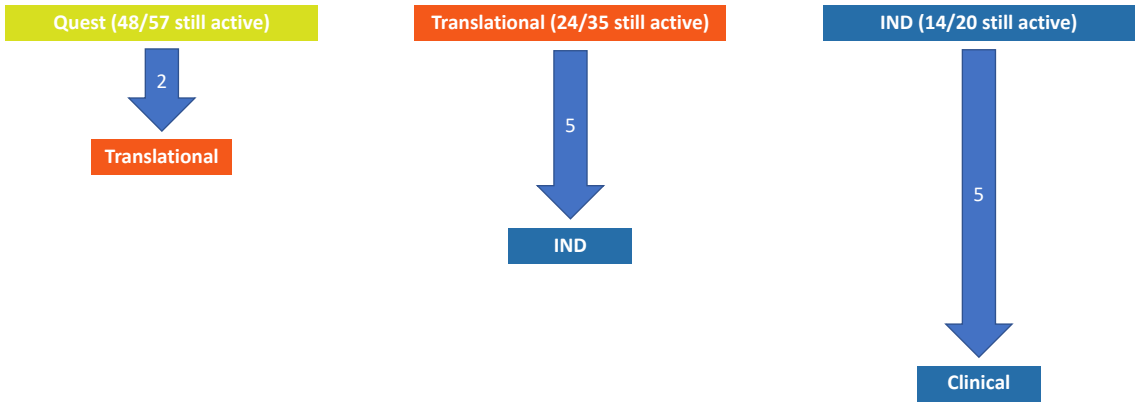
CIRM 2.0 Pipeline Progression

While most awards are still active, some of the completed CIRM 2.0 projects have successfully progressed within the CIRM 2.0 pipeline.



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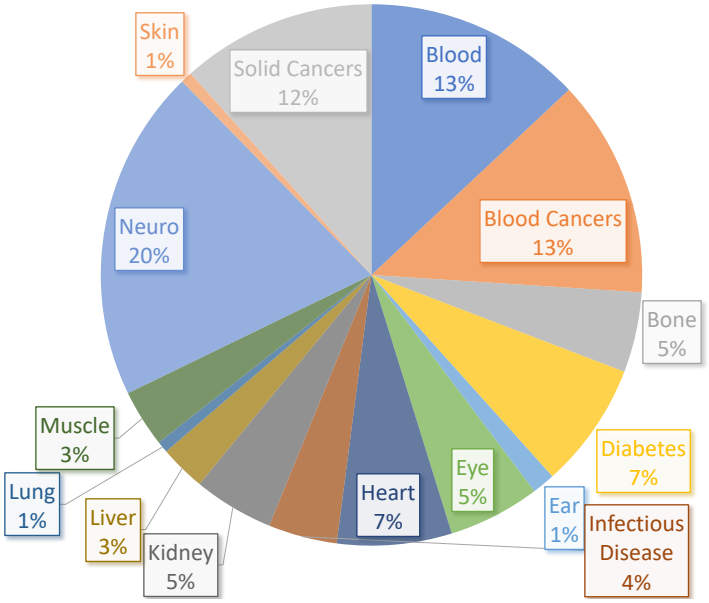
CIRM 2.0 Disease Areas (n=153)

Discrete yet seamless CIRM 2.0 funding opportunities continue to have broad disease representation.

Strong presence in neuro, cancer and blood disorders.



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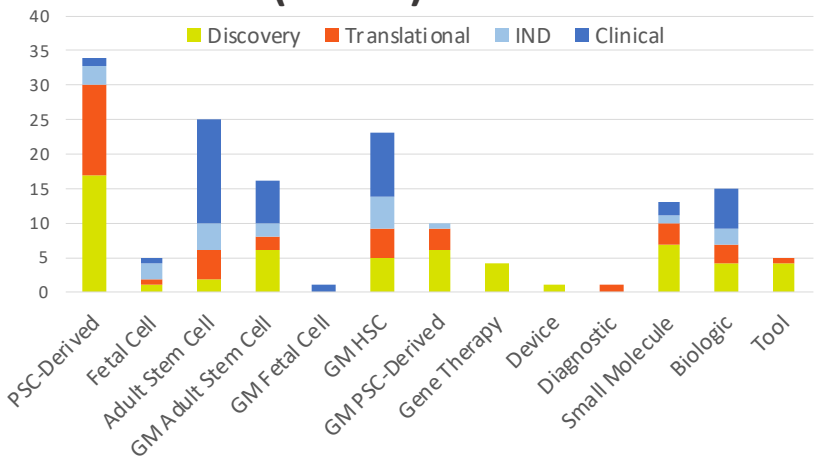
CIRM 2.0 Candidates (n=153)



CIRM 2.0 funding programs cover all therapeutic modalities and technologies eligible for CIRM funding.

- Majority of clinical projects are adult stem cell and gene-modified adult stem cell therapies.
- PSC-derived and gene-modified PSC-derived therapies are more prevalent in preclinical programs.

GM: gene-modified

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10

This slide was changed from the copy provided to GWG to correct the clinical candidate numbers across the shown categories .

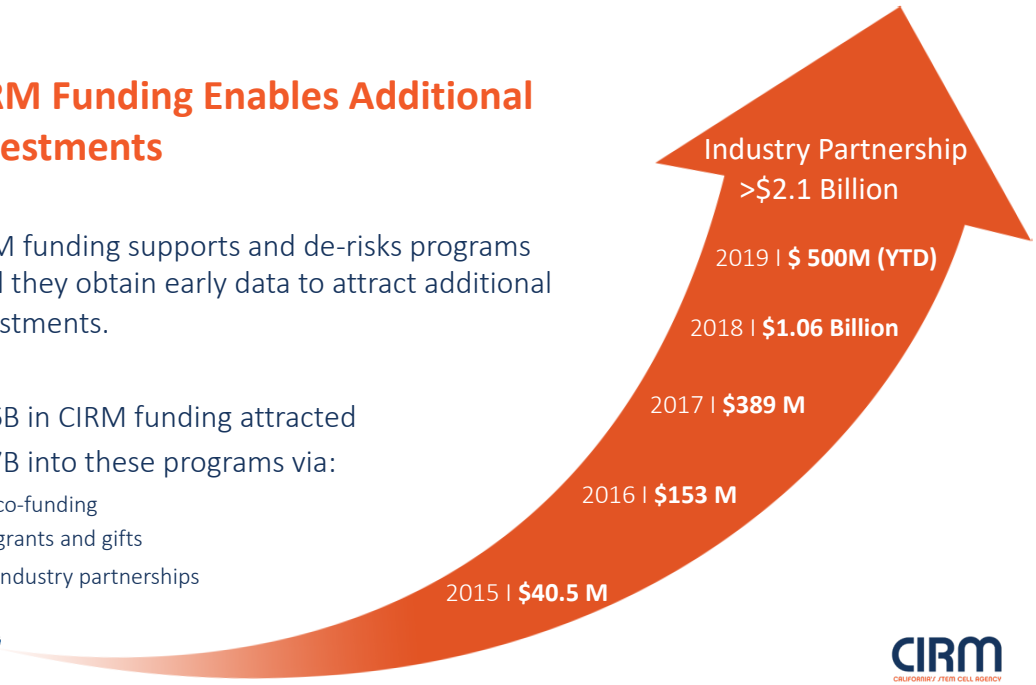
CIRM Funding Enables Additional Investments

CIRM funding supports and de-risks programs until they obtain early data to attract additional investments.

$2.6B in CIRM funding attracted

$3.7B into these programs via:

- co-funding
- grants and gifts
- industry partnerships



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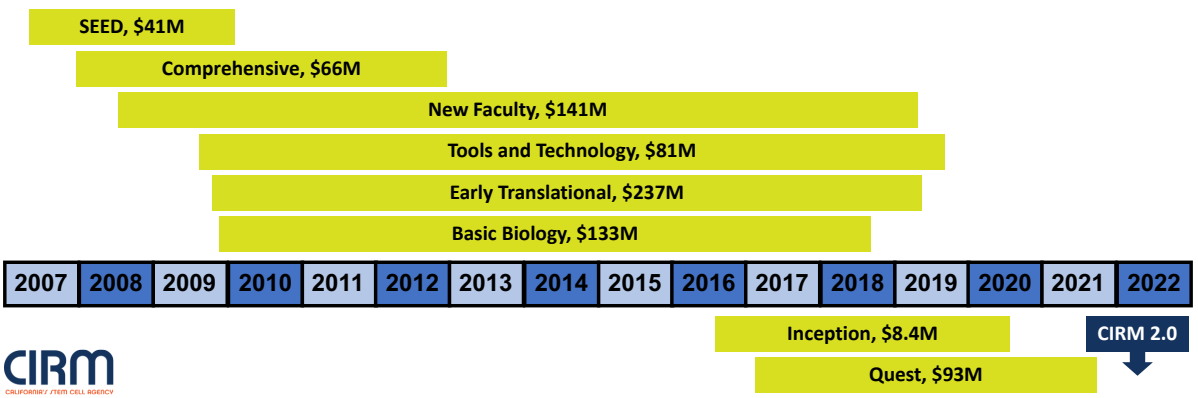
11

Basic Research & Discovery Overview

DISCOVERY

- **SEED, Comprehensive:** attract new and support established investigators in hESC research
- **Basic Biology:** human stem cell biology, differentiation, mechanisms, disease
- **Early Translational:** therapeutic candidate discovery
- **Tools and Technology:** tools to overcome roadblocks in translation of stem cell research
- **New Faculty:** support promising scientists in the critical early stages of their careers
- **Inception:** seed funding for new ideas in human stem cell research
- **Quest:** therapeutic and tool/technology candidate discovery



CIRM CALIFORNIA'S STEM CELL AGENCY

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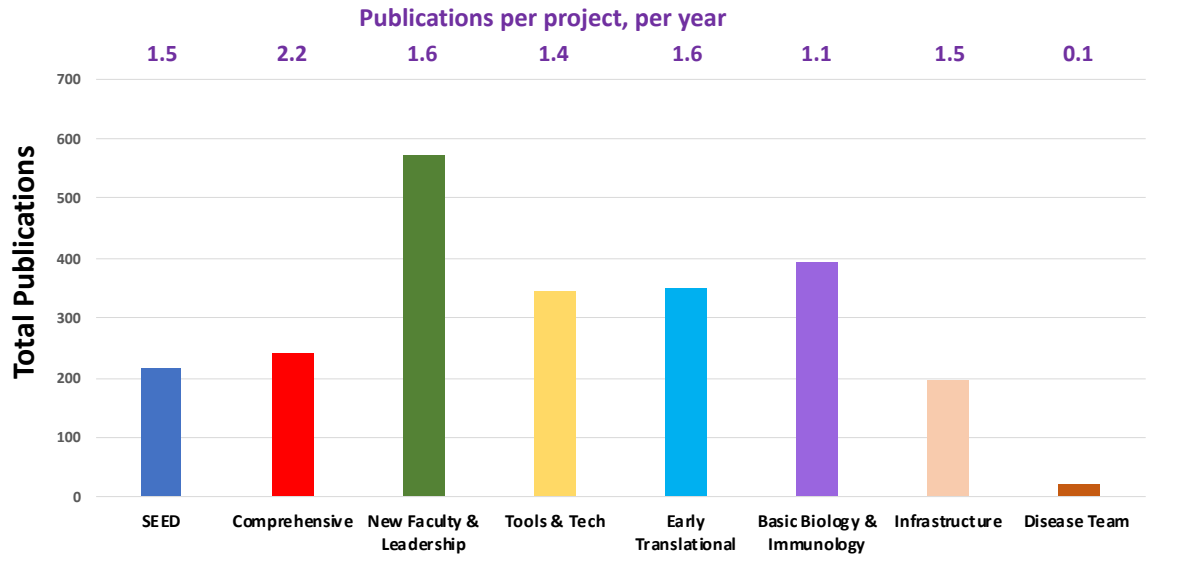
Impact of Early Programs: Publications (2006-present)



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13

Quest Candidate Discovery Program (2015 to Present)

57 awards

$93M
total funding

18 candidates received prior CIRM funding

DISCOVERY

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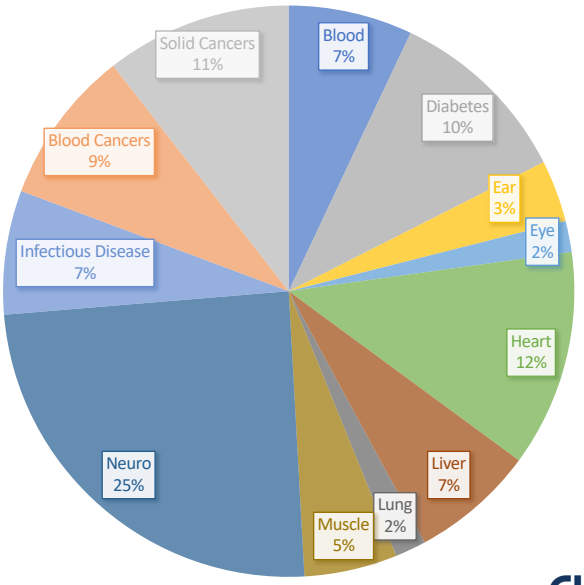
14

Funding amounts shown are based on the total amount awarded as of August 2019, not the total amount approved by the ICOC.

Quest Projects (n=57): Disease Indications

Quest Candidate Discovery Stage Projects have the broadest and most balanced disease area coverage compared to later stage CIRM funding opportunities.

Particularly, neurological disorders and heart disease constitute a higher proportion of this program's portfolio compared to later stage programs.



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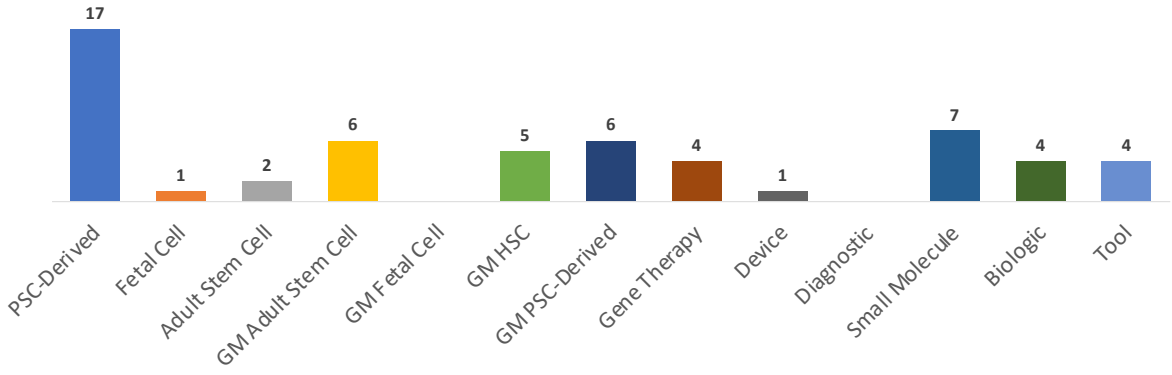
15

Quest Projects (n=57): Candidates



PSC-derived cell therapy candidates represent 41% of Quest projects.

Gene-modified cell therapies and gene therapies represent 37% of Quest projects.

GM: gene-modified

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16

Candidate Discovery Award Outcomes

- 48 out of 57 awards are still active
- 9 awards closed or terminated
- 3 candidates have progressed to translational stage (+1 pending)

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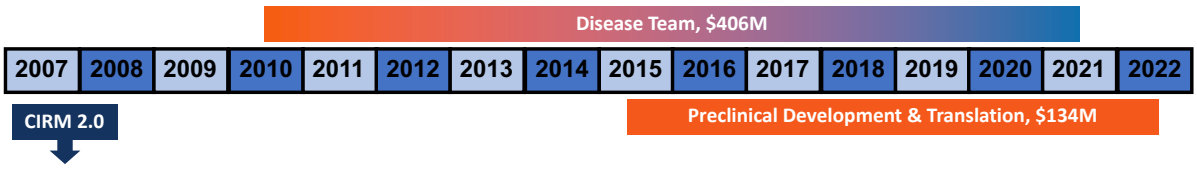
17

Translational Overview

- **Disease Team:** some awards supported translational stage activities as part of a broader objective
- **Preclinical Development:** translational development culminating in pre-IND/IDE meeting
- **Translation:** translational development culminating in pre-IND/IDE meeting



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Funding amounts shown are based on the total amount awarded as of August 2019, not the total amount approved by the ICOC.

Current Translational Program (2015 to Present)

35 awards

$134M
total funding

12 awards completed

5 progressed to CLIN1

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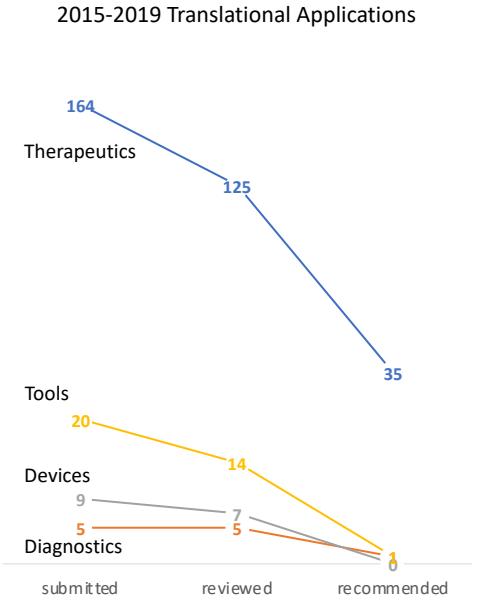
19

Funding amounts shown are based on the total amount awarded as of August 2019, not the total amount approved by the ICOC.

Current Translational Program

- Encompasses funding for translational stage activities for
  - Preclinical Development (PC1)
  - Therapeutics (TRAN1)
  - Diagnostics (TRAN2)
  - Medical devices (TRAN3)
  - Tools (TRAN4)
- Project costs, time limits, activities, and eligibility requirements were dependent on the product type



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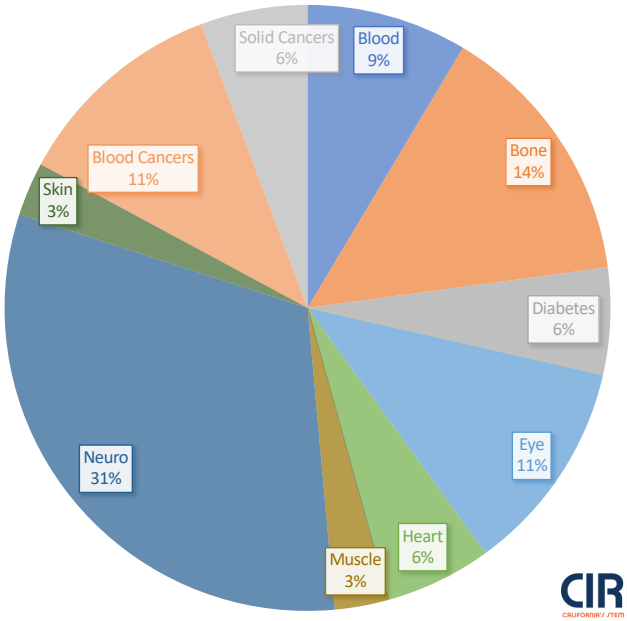
20

Translational Projects (n=35): Disease Indications

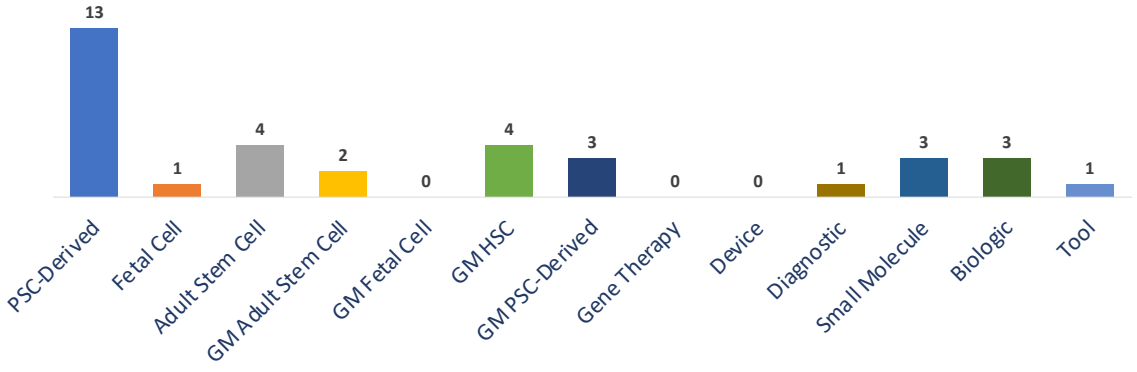
Over 30% of Translational projects are focused on neurological disorders.

- 75% of the neuro projects are developing PSC-derived therapies.



21

Translational Projects (n=35): Modalities



75% of Translational awards are developing cell therapies.

35% of translational awards are developing PSC-derived cell therapies.

GM: gene-modified

22

Translational Award Outcomes

- 24 out of 35 awards are still active
- 8 pre-IND meetings completed or scheduled
- 2 out of 3 terminated awards were due to process development failures
- 5 received follow on CLIN1 Awards to support IND enabling studies
- Pipeline Projects (received prior CIRM funding)
  - 19 projects progressed from early CIRM programs
  - 2 projects progressed from Quest Awards (candidate discovery)

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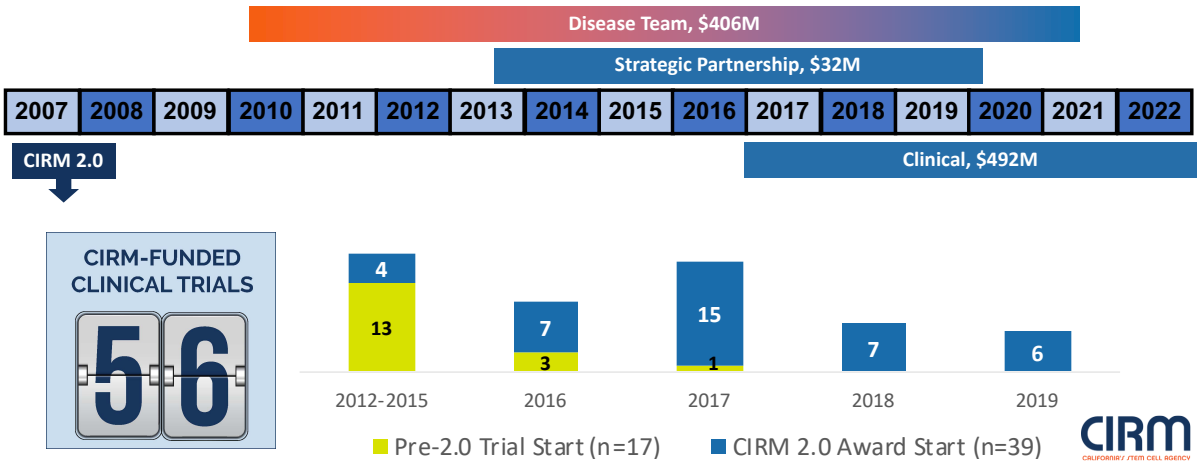
23

Clinical Overview

- **Disease Team & Strategic Partnership:** A single award spanned multiple development stages from Discovery to Clinical
- **Clinical:** Three types of awards each span a single development stage
  - CLIN1: IND-enabling, CLIN2: Clinical Trials, CLIN3: Registrational Trials

CLINICAL



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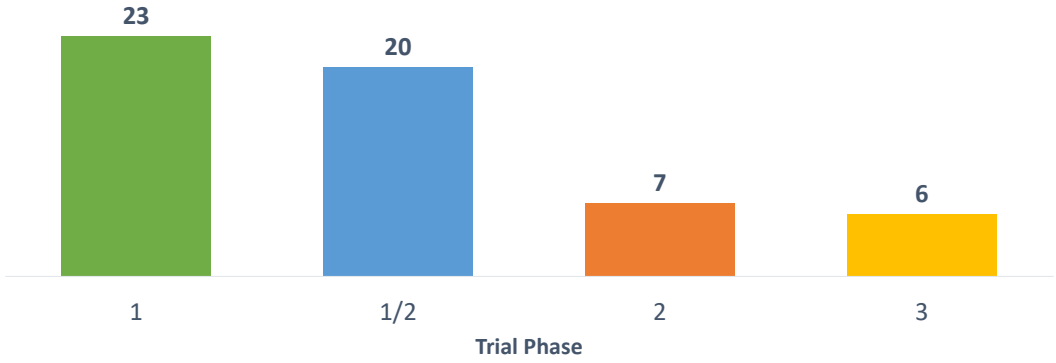
All Clinical Trials (n=56): Phases



Active Phase 3 Trials

1. Humacyte (AV Dialysis Graft)
2. Medeor (Kidney Transplant Tolerance)
3. Brainstorm (ALS)

Projected BLA Filings
(As publicly reported by Sponsor)

1. Orchard OTL-101: 2020
2. Poseida BCMA-101: Q4 2020

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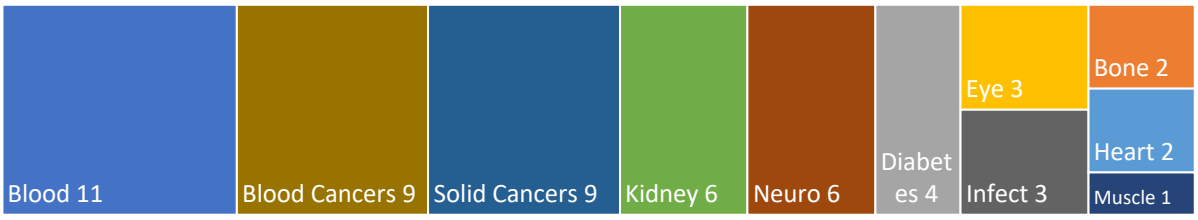
25

All Clinical Trials (n=56): Disease Areas



CIRM's clinical trials portfolio broadly represents disease areas with significant unmet medical needs.

Blood disorders and cancer are the most prevalent disease areas in CIRM's clinical trials portfolio.

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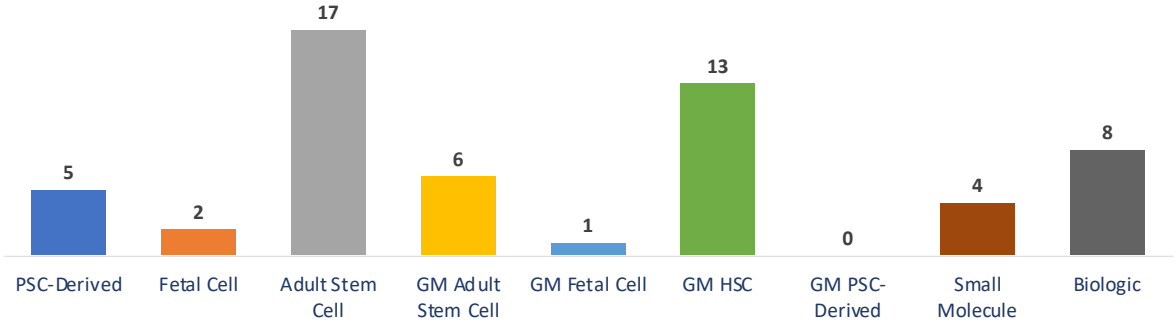
26

All Clinical Trials (n=56): Therapeutic Modalities



CIRM's clinical trials portfolio is weighted toward adult stem/progenitor cell-based therapies.

Gene-modified cell therapies represent over a third of this portfolio.

Seven trials are studying gene-modified HSC therapies for blood disorders.

GM: gene-modified

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27

All Clinical Trials: FDA Designations

Grantee	Disease Area	Therapeutic Modality	FDA Designation
Humacyte	Kidney	Biologic	RMAT, Fast Track
jCyte	Eye	Fetal-Derived Cell	RMAT, Orphan Drug
Lineage Cell (Asterias)	Neuro	PSC-Derived Cell	RMAT
Capricor	Neuro	Adult Stem Cell	RMAT
Orchard	Blood	GM HSC	Breakthrough
Brainstorm	Neuro	Adult Stem Cell	Fast Track
Poseida	Cancer	GM Adult Stem Cell	RMAT, Orphan Drug
Medeor	Kidney	Adult Stem Cell	Orphan Drug
St. Jude	Blood	GM HSC	RMAT

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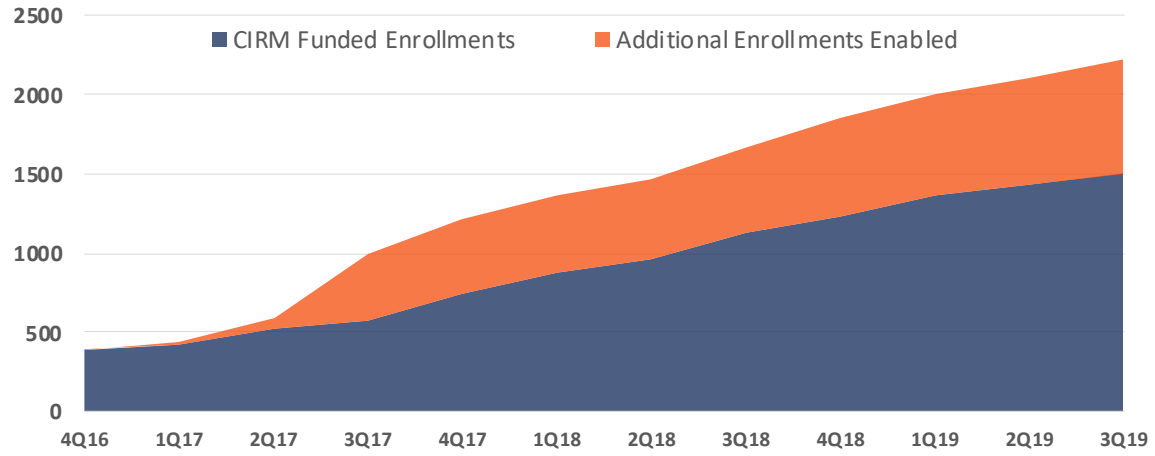
28

All Clinical Trials (n=56): Enrollment



CIRM Funded Enrollments: All enrollments by California awardees and enrollments in California by Non-California awardees.
Additional Enrollments Enabled: All enrollments outside of California by Non-California awardees.

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Current Clinical Program Overview (2015 to Present)

61 awards*

$492M
total funding

5 IND awards progressed to clinical trials

CLINICAL

*CLIN1 and CLIN2

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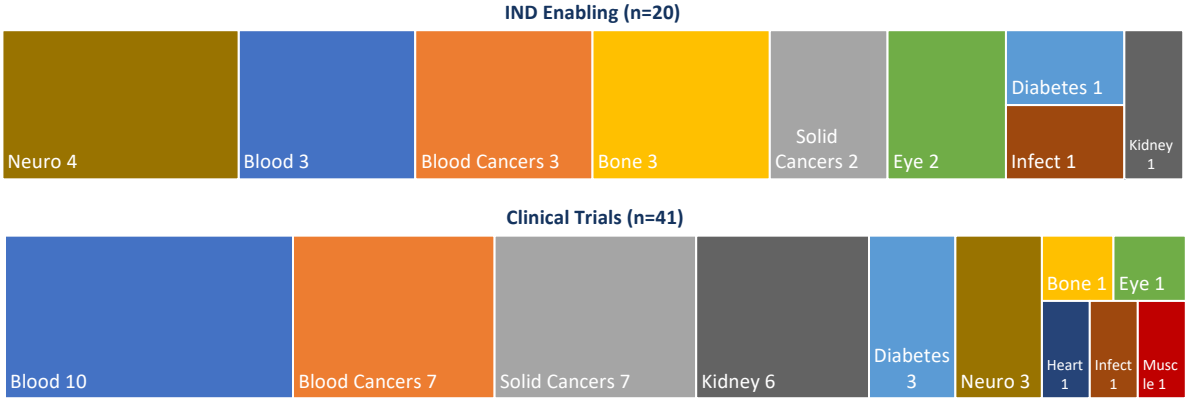
30

Funding amounts shown are based on the total amount awarded as of August 2019, not the total amount approved by the ICOC.

CIRM 2.0 Clinical Awards: Disease Areas



Broad disease area representation in both clinical funding programs.

Blood Disorders:
- 15% of IND Projects
- 25% of Clinical Trial Projects

Cancer:
- 20% of IND Projects
- 34% of Clinical Trial Projects

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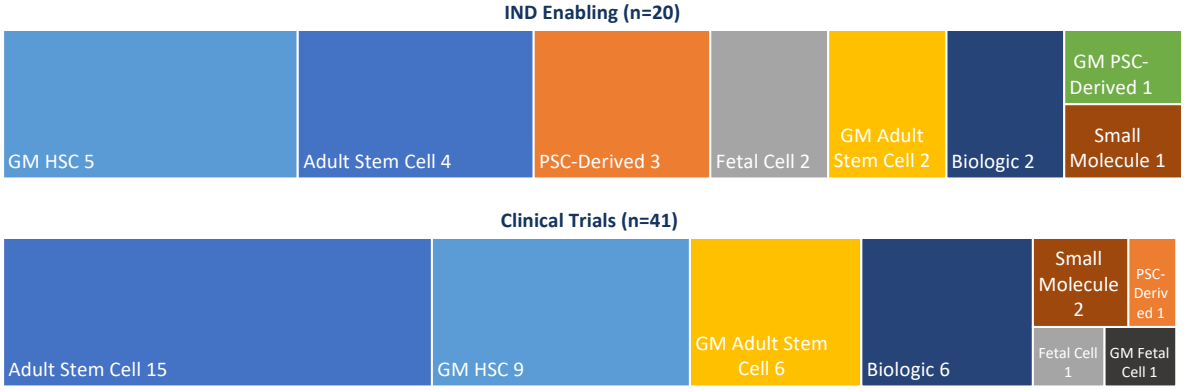
31

CIRM 2.0 Clinical Awards: Therapeutics Modalities



Adult Stem Cells:
- 20% of IND Projects
- 36% of Clinical Trial Projects

Gene-modified cell therapies:
- 40% of IND Projects
- 40% of Clinical Trial Projects

Biologics & Small Molecules:
- 40% of IND Projects
- 20% of Clinical Trial Projects

GM: gene-modified

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32

CIRM 2.0 Clinical Award Outcomes

- IND Enabling Awards (n=20)
  - 7 successfully filed IND
  - 5 progressed to CLIN2
- Clinical Trial Awards (n=41)
  - 2 Trials Completed
  - 2 Trials Terminated

- Pipeline Projects (received prior CIRM funding)
  - 6 IND awards
  - 20 Clinical Trial awards

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

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Infrastructure Overview

7 initiatives

$482M
total funding

48 awards

INFRASTRUCTURE

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Funding amounts shown are based on the total amount awarded as of August 2019, not the total amount approved by the ICOC.

Infrastructure Overview

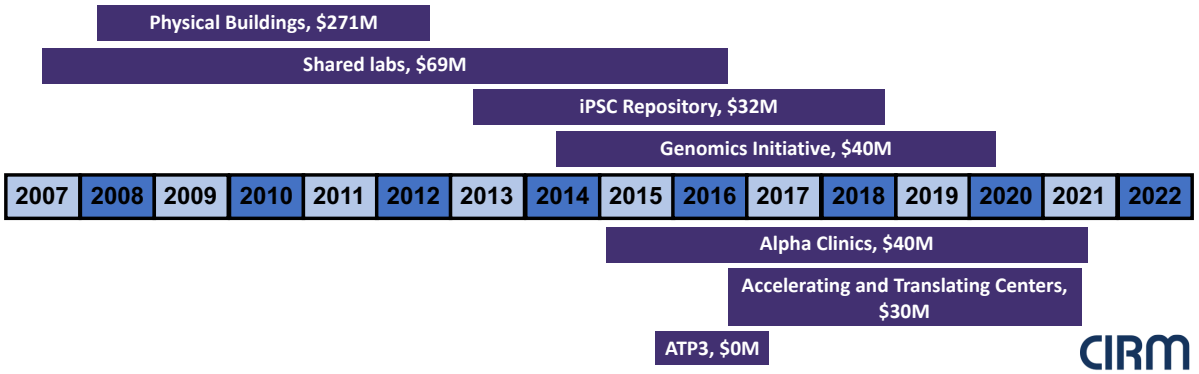
Buildings and Labs
- Physical Buildings
- Shared Labs

Therapy Development
- Alpha Clinics
- Accelerating Center
- Translating Center

Research
- iPSC Repository
- Genomics Initiative

Business
- ATP3

INFRASTRUCTURE



CIRM CALIFORNIA'S STEM CELL AGENCY

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Physical Infrastructure

12 institutions funded throughout California

Historical rationale to enable hESC research
- 12 research facilities – institutional use
- 1 GMP facility (UCD) – several outside institutional clients

Total direct CIRM funding: $271M
Private/Institutional funding: $543M

Buck Institute
Sanford Burnham Institute
Stanford
USC
UC Berkeley
UC Davis
UC Irvine
UC Los Angeles
UC Merced
UC San Francisco
UC Santa Cruz
UC Santa Barbara

Stanford Lokey Building

UC Davis GMP facility

CIRM CALIFORNIA'S STEM CELL AGENCY

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Shared Labs

Creation of dedicated laboratory spaces for the culture and maintenance of hESCs

Historical rationale to enable hESC research independent of federal restrictions

Total CIRM funding: $69M

- 17 core facilities
  - Buck Institute
  - Children's Hospital LA
  - Gladstone Institute
  - Salk Institute
  - Sanford-Burnham Institute
  - Scripps Research Institute
  - Stanford University
  - USC
  - UC Berkeley
  - UC Davis
  - UC Irvine
  - UC Los Angeles
  - UC Riverside
  - UC San Diego
  - UC San Francisco
  - UC Santa Cruz
  - UC Santa Barbara
- 90+ hESC cell lines derived
- 173 publications
- hESC training courses established

UC Santa Cruz Institute for the Biology of Stem Cells

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Research Infrastructure – iPSC Repository

9 awards totaling $32M

- Centralized iPSC bank
  - Lines owned by CIRM
  - Lines banked and distributed by FujiFilm Cellular Dynamics
- 2400 unique lines created with uniform production method
- Standardized consent language
- IP agreement to use lines commercially
- Clinical and demographic information, but no access to longitudinal studies from donors
- ~1000 lines sold

fujifilmcdi.com/the-cirm-ipsc-bank/

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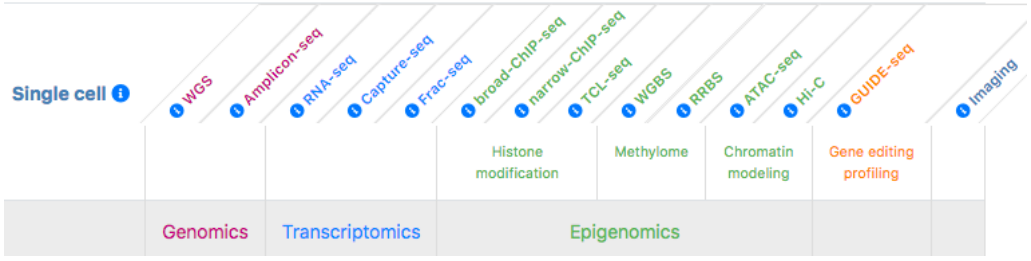
Research Infrastructure – Genomics Initiative

3 awards totaling $40M

- Consortium for academic projects with major genomics components – over 20 laboratories
- 2 central sequencing centers (Stanford and Salk)
- 1 data hub (UCSC)
- Diverse projects with uniform data processing and organization for analysis
- Shift to single cell sequencing
- Most funds used for data collection

The Stem Cell Hub
Center for Excellence in Stem Cell Genomics
CIRM

cirm.ucsc.edu



CIRM

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Development Infrastructure – Alpha Clinics

$40M to fund 5 sites

- City of Hope
- UCLA/UCI
- UCSD
- UCSF
- UC Davis

CIRM ALPHA CLINICS
Delivering Patient Treatments

Medical clinics specializing in delivering cell therapies to patients

- Trial sites for 97 sponsored programs (CIRM and non-CIRM)
- 493 patients enrolled
- Shared protocols
- IRB Reliance agreement
- MD fellowships (UCD, UCSF)

CIRM

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Trials supported by Alpha Clinics (n=97)

CIRM ALPHA CLINICS
Delivering Patient Treatments

Number of Trials by Technology Type		%
Engineered Immune Cells	40	44.9%
Hematopoietic (HSC) Derivative	20	22.5%
Embryonic (hESC) Derivative	6	6.7%
Mesenchymal (MSC) Derivative	6	6.7%
Small Molecule or Biologic	3	3.4%
Non-Cellular Gene Therapy	2	2.2%
Other (e.g. observational studies)	20	22.5%

- 65% industry sponsored
- 35% academic sponsored

Number of Trials by Cell Type	
1. Autologous	58
2. Allogeneic	28
3. Not Applicable	11

https://www.cirm.ca.gov/patients/alpha-clinics-network/alpha-clinics-trials

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Development Infrastructure

Cell And Gene Therapy Center | IQVIA™

An integrated information and technology-enabled global healthcare service provider for cell and gene therapies

Accelerating Center - $15M award
- Cell therapy focused CRO
- Services offered:
  - clinical operations
  - regulatory support
  - pharmacoeconomics
  - commercial services

Translating Center - $15M award
- IQVIA CGTC with partners City of Hope, Charles River Labs, and WuXi AppTec
- Services offered:
  - project management
  - regulatory strategy
  - GMP manufacturing
  - preclinical animal studies

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Business Infrastructure – ATP3

Accelerating Therapies Public Private Partnership

- Award would allocate $75M with an equal match from the applicant to create a stem cell focused enterprise to commercialize CIRM funded products
- A single applicant organization provides a business plan to in-license and advance to commercial development CIRM-funded technologies from the current IP holders at universities, non-profit research institutions, and for-profit companies. The Company would be expected to be sustainable and exhibit growth beyond the five-year award period.
- RFA did not proceed to review

CIRM

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Education & Training Overview

54 Programs

$219M
total funding

2700+ alumni

EDUCATION

CIRM

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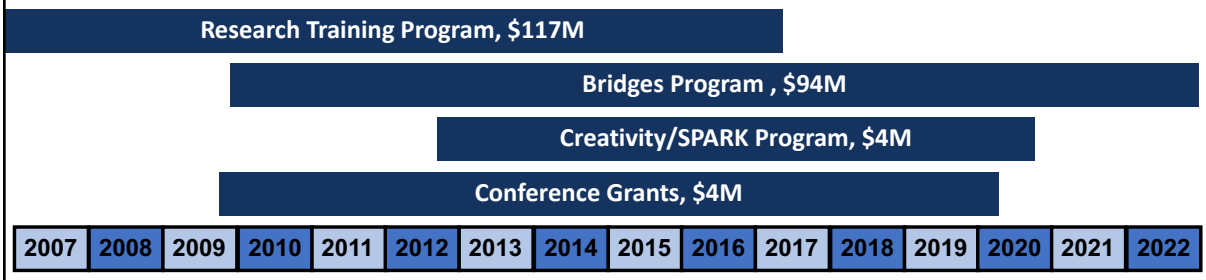
Education and Training Programs Overview

- **Creativity/SPARK:** high school summer internships in stem cell laboratories
- **Bridges Program:** undergraduate, Masters level training and certificates of expertise
- **Research Training Program:** predoctoral, postdoctoral and clinical fellowships
- **Conference Grants:** sponsorship of scientific conferences with relevance to CIRM's mission

EDUCATION



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Training Programs Impact 2005-2019

HIGH SCHOOL	UNDERGRAD/MASTERS	PRE/POSTDOCTORAL, CLINICAL
9 programs 454* trained	16 programs 1427* trained	18 programs 940 trained

*Alumni and Presently Completing

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Creativity/SPARK Program Overview (2012-2020)

- Creativity/SPARK grants fund summer stem cell internships for high school students at world class university and research institutions in California
- Interns learn about stem cells and regenerative medicine, conduct research, and present their work at the annual SPARK conference
- 9 programs implemented (7 active) across California
- 484 students trained* to date

*Alumni and Presently Completing

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Bridges Program Overview (2009-2020)

- Bridges targets undergraduate and Masters students at California universities and colleges that do not have major stem cell research programs of their own
- After completing coursework, students conduct research at "host" laboratories at major research universities, medical schools and/or biotechnology companies
- Students receive training in cell therapy development and participate in patient engagement and outreach activities that engage California's diverse communities
- 16 programs implemented (14 active) across California
- 1419 students trained to date (alumni and completing); 50% 50% are employed in research labs; 30% are pursuing PhDs, MDs or other professional degrees

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Research Training Program and Outcomes (2006-2015)

- Research Training Grants supported the training and development of "CIRM Scholars" at the predoctoral, postdoctoral, and clinical fellow levels, as future leaders of effective stem cell research programs
- 18 programs implemented across California
- Programs were tailored to align scope (level of training) and capitalize on scientific strengths of each institution
- 940 alumni; 1100 scientific publications reported to CIRM
- Research Training Grants were not formally renewed in 2016, as CIRM's direct funding of predoctoral, postdoctoral and clinical fellows through CIRM-sponsored research grants served the same needs and allowed better alignment with CIRM's mission as it evolved

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