Cell Stem Cell
Forum

Translating Science into the Clinic: The Role of Funding Agencies

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https://doi.org/10.1016/j.stem.2020.03.010

CIRM has created a unique funding process and structure aimed to make a meaningful impact on translating science into the clinic. By sharing some of the lessons learned by CIRM, we hope to provide insights into concrete improvements that have made a difference in our efforts.

Maturation in the field of stem cell and applied genomics research has led to a surge in efforts to translate the science to therapies for patients with a myriad of incurable and debilitating medical conditions. Discoveries that could result in a meaningful impact on the overall health of patients often seem too far away from a practical clinical application. Moreover, the modest investment from public and private sources in biomedical research only increases the difficulty of advancing research toward clinical outcomes. Nevertheless, patients, health care providers, and the public are determined to see new treatments become available sooner.

The creation of the California Institute for Regenerative Medicine (CIRM) in 2004, the New York Stem Cell Foundation (NYSCF) in 2005, and the Cancer Prevention and Research Institute of Texas (CPRIT) in 2009 are a manifestation of this ambition to accelerate therapy development. Recently, the NIH launched the Cures Acceleration Network (in 2010) and the Cure Sickle Cell Initiative (in 2018), also in response to this need. With patient needs at the forefront, these and other organizations have taken on the challenge to advance translational and clinical stage research projects in the hopes of having a meaningful impact in the near future. Achieving this goal, however, is not so simple.

Research funders have generally operated under a tenet that by introducing money into the scientific arena, it will stimulate more research, which in turn means progress can happen more quickly. Although financial support is essential for research, it is not by itself sufficient to accelerate our progress to the clinic. The therapy development path is filled with obstacles, particularly in emerging fields like cell therapy, where the regulatory landscape is shifting and technical challenges abound. Success requires a careful orchestration of efforts, a high degree of situational awareness, and an availability of resources. Therefore, funding would ideally be strategically structured to align with these needs.

CIRM has created a unique funding process and structure that aims to address this challenge. We will describe our efforts to track measurable indicators of acceleration for improved application success, resource deployment, and strategic partnerships. By sharing some of the lessons learned by CIRM, we hope to provide insights into concrete improvements that have made a difference in our effort to accelerate stem cell science to the clinic.

Creating a Structure that Supports Acceleration

During the build phase of CIRM, the stem cell field was still nascent and CIRM focused on creating laboratory infrastructure and funding basic research. As programs began to mature and potential therapeutic development candidates were arising from the basic research, we were faced with a new challenge of helping our researchers address the difficulty of "translating" the science toward clinical development. We needed to better define outcomes that would enable researchers to reliably produce a therapeutic candidate and carry out the necessary work to support the regulatory requirements of bringing the program to clinical testing. Without clear milestones, CIRM grantees were not enabled or even incentivized to advance projects in any specific direction. CIRM was fulfilling its basic commitment to fund research, but it was unclear whether the needle on acceleration to the clinic was moving.

With a mission to accelerate the research, CIRM conducted an overhaul of its funding process in 2015 to refine a complex grant application process, to create a more predictable and recurring schedule for funding opportunities, and to identify areas of need among projects where shared infrastructure or resources could be deployed.

Maximizing efficiency and removing obstacles were essential to improving our internal operations. For instance, our grants management expended considerable effort processing over 300 minor expenditure requests annually from grantees and approving nearly all of them (98.9%), most often for expenses that had already been made. A simple change in policy allowing grantees more discretion in reasonable expenditures (while still maintaining accountability) suddenly freed a considerable portion of staff time as well as grantee time in filing the requests. Streamlining by aligning process with mission led to improvements across the organization and the most significant ones are those that truly moved the needle on acceleration.

Because therapy development is a core component of the CIRM mission, funding opportunities were restructured to align with key regulatory and product development requirements. For instance, projects qualified for a translational award only if there was existing data to support that there was a definitive "development candidate;" for a preclinical Investigational New Drug (IND)-enabling award, only if the project team already had a pre-IND meeting with the FDA; and for a clinical award, only if the team had an

active IND with the FDA. Applications were expected to incorporate and account for the requirements of the given type of award, describing their scientific, manufacturing, development, and clinical trial design, as appropriate for that stage. CIRM established operational milestones for each award based on the approved proposal that were designed to guide the project to a successful completion. Thereafter, the expected outcome of one award became the entry criterion for the next along the pipeline to avoid gaps. Therefore, projects funded by CIRM became focused on achieving a clear measurable objective and activities that detracted from that goal were not supported.

We addressed interruptions in funding by offering predictable and frequent application submission cycles and standing program announcements for basic, translational and clinical programs. This obviated the need to "force fit" projects into artificial timelines and allowed projects to come in when they were ready, setting them up for a better chance of success.

With these comprehensive changes, the number of applications we reviewed increased four-fold, but the cost of processing an application was reduced by 57% and, importantly, the time from submission to approval was reduced from an average of 6.5 months down to about 3.5 months across all programs with turnaround in as little as 80 days for our clinical program. The enhanced efficiency has enabled CIRM to grow its portfolio of clinical trial projects from 16 to 60 (in over 35 disease indications) in 4 years. By adopting a milestone-based award structure, where award payments were linked to accomplishment of tangible milestones, we were better able to help investigators stay on track, identify key bottlenecks, and disperse funding in the most efficient and responsible way. Upfront milestone setting set clear expectations and this has allowed many programs to successfully complete their projects. We have noted a 110% increase in programs progressing from one stage to the next after implementing the new model.

In addition to streamlining existing processes, CIRM adopted new approaches that would increase the effectiveness of our efforts. One of these was to develop an outreach program to identify investigators and projects with the potential to enhance our portfolio of funded projects. By encouraging investigators with good ideas to apply and providing guidance on developing competitive proposals, the percentage of applications recommended for funding by peer review increased from an average of 43% to about 57% over 2 years in our clinical program. So not only did changes to our process increase our application pool, it also impacted the quality of proposal submissions.

Another critical component of our structure that helps accelerate progress is the inclusion of patient advocates and patient voices in the process and governance to help keep the focus on what's important. With a mission to accelerate therapies to the clinic, funders and scientists need input on what ultimately matters to patients if indeed one hopes to have a meaningful impact. Investing effort and money on imagined solutions that will have little value to patients is a delay on work that really matters. Seeking a cure may not always be possible, but making a significant improvement in disease manifestation or quality of life could make a big difference to patients. There is no substitute to hearing directly from patients to understand unmet need and to assess the balance of risk versus benefit. Consistent with this perspective, organizations like the Department of Defense Congressionally Directed Medical Research Program, the National Cancer Institute, CPRIT, and CIRM have incorporated patient voices within their peer-review process (Ciccarella et al., 2018). Even beyond peer review, patient voices can help guide funded projects and facilitate and strengthen patient participation in clinical trials. As much as science drives the process of rigorous medical research, patients ultimately determine its relevance.

A Partnership that Maximizes Success

The path from basic science to the clinic is filled with obstacles that money alone cannot overcome. In many cases, projects encounter knowledge or resource gaps that must also be filled. Therefore, if funding agencies intend to fulfill their mission of acceleration, it is imperative that they facilitate guidance and assistance where needed to bolster project success and increase the likelihood of a return on investment. Such strategic guidance means that funders would necessarily need to have greater involvement in the advancement of the projects they fund.

Having a funder actively engaged in the progress of a project might expectedly generate unease for those used to a hands-off approach. However, we have found that in the vast majority of cases grantees feel they have benefited from such partnerships with CIRM and appreciate the additional resources brought to their team. This partnership does not imply that the funder is assuming ownership or control of the project. Rather, the aim is to make the project team stronger and more capable without getting in the way.

CIRM accomplishes this by appointing each of its funded clinical projects (and many of its translational projects) an advisory panel composed of external scientific advisors with expertise that complements that of the project team, patient advocate advisors, and CIRM officers. The charge of the advisory panel is to provide guidance and bring together all available resources that will maximize the likelihood of achieving the project objective on an expedited timeline. Appointed experts may offer advice on regulatory, manufacturing, or other key areas that may help advance the project. This type of partnership between funder and grantee fosters trust that allows researchers to share both the negative and positive outcomes and to anticipate problems and resolve issues as they arise. Done effectively, an ongoing system of communication maintains autonomy for the research team but also provides support (e.g., an expanded network of advisors or resources) and improves the chances of meeting milestones and the appropriate use of funds.

Over a span of 4 years, CIRM has assembled 78 different Clinical Advisory Panels (CAPs) to serve its IND-enabling and clinical trial projects and held over 250 meetings with project teams. In an attempt to measure the effectiveness of these groups, we have recorded the number of "impacts" or instances where CAP feedback helped the research team by optimizing project execution such as improving trial design or enhancing enrollment, or resolving a specific challenge

such as a manufacturing issue. As of this writing, CIRM has recorded 238 impacts across its clinical projects. More recently, Translational Advisory Panels (TAPs) were also implemented for earlier-stage projects on an as-needed basis given the initial success of CAPs. Thus far, 64 impacts have been recorded for just 7 projects under the program. The needs addressed will vary by project but also by stage of development. Early-stage projects often demonstrate challenges in process development for cGMP manufacturing or a need for regulatory advice. Later-stage projects are more likely to encounter clinical trial design or patient enrollment issues.

An important aspect of the partnership is that the relationships built are not just with the funder itself but also with the network of experts and resources created or fostered by the funder. Funders have a unique ability to forge productive relationships with other agencies as well as support the creation of new infrastructure. Therefore, a successful partnership could mean access to infrastructure designed to provide specialized guidance and perform key therapy development activities that would otherwise be too expensive or impractical for a research team to take on themselves. The experience and collective knowledge of dedicated centers makes them efficient and important resources for accelerating development. For new therapeutic modalities, such as cell therapy, building this specific infrastructure is key to getting treatments to patients. Funding organizations can support the creation of such infrastructure as NIH has done broadly with National Center for Advancing Translational Sciences (NCATS) and the Clinical and Translational Science Awards Program. In California, the Alpha Stem Cell Clinic Network and the Cell and Gene Therapy Center were specifically created to fill the need in regenerative medicine (Jamieson et al., 2018). By supporting these types of infrastructure programs, funders are protecting their broader investments in research. Even when a funding organization cannot create their own, extending their network through collaborations with independent service providers is still helpful. In the United Kingdom and Canada, the UK Cell and Gene Therapy Catapult and Centre for Commercialization of Regenerative Medicine (CCRM), respectively, provide specialized technical, business, regulatory, and manufacturing services and expertise. The emergence of independent not-for-profit organizations such as these enhances the network that funders can bring to the table. In June 2019, the NHLBI of the NIH and CIRM entered into a partnership to co-fund cell and gene therapy programs for the Cure Sickle Cell Initiative; this partnership leverages the CIRM funding infrastructure and process to accelerate the pace of research and increase the probability of success.

CIRM's ultimate goal is to have therapies become available to patients, which is generally made possible through commercialization of a therapeutic product by a pharmaceutical or biotechnology company. To complement our network of resources, CIRM has established an Industry Alliance Program that teams the agency with leaders in industry and venture capital and there has been considerable increase in industry partnership over the past 4 years (totaling over $3.3 billion). CIRM facilitates partnerships between promising CIRM-funded projects and companies capable of bringing an approved therapy to market. As CIRM-funded projects mature, interest from investors has begun to grow and we have now witnessed some exciting partnerships emerge. A CIRM-funded project to develop a gene-modified cell therapy for ADA-SCID by Dr. Don Kohn at UCLA was partnered and licensed to Orchard Therapeutics, which is now leading the charge to make the therapy broadly available to patients. Similarly, a project to develop an antibody therapy for cancer received CIRM funding during its early stages of development at Stanford University that enabled the creation of the spin-out company, Forty Seven, to advance the therapy into late-stage clinical trials. The company has been recently acquired by Gilead for $4.9 billion. The underlying principle that CIRM has adopted is to provide support that not only allows project teams to achieve the goals of a specific grant, but to also position the team for success through all subsequent stages of therapy development. Through funding and programmatic support CIRM de-risks strong science in the early stages and positions these programs to attract the needed investment and support in the late stages from strategic commercialization investors and partners.

Conclusion

For CIRM, it is clear that a change in thinking has led to changes in operations, which in turn have resulted in measurable improvements aimed at accelerating progress toward the clinic. To be effective, funders that seek to advance research into the clinic must understand the bottlenecks and obstacles that impede progress, including their own practices, so that the funding process is structured to overcome them and expectations are focused on achieving meaningful goals. Funders must avoid making research proposals wait and become stale from a lengthy application and review process, infrequent solicitations, or unsuitable funding opportunities. Although challenging for many reasons, funders should strive to create continuous, comprehensive, and relevant funding opportunities whenever possible. Funders should also forge improved partnerships with grantees and other potential funders to enhance their support and maximize the return on their investments. Through a holistic and concerted effort, acceleration of strong science to the clinic is possible while maintaining scientific rigor. By setting up the appropriate process and structure, stakeholders can work collaboratively to reduce barriers to translating promising science to therapies for patients with unmet medical needs.

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