CALIFORNIA'S STEM CELL AGENCY

Funding Opportunity Concept Plan

INFR5: California Cell and Gene Therapy Manufacturing Network

BACKGROUND

The mission of the California Institute for Regenerative Medicine (CIRM) is to accelerate world class science to deliver transformative regenerative medicine treatments in an equitable manner to a diverse California and world. The manufacturing of cell and gene therapies is a complex, ever-evolving science. Currently, the capacity for and expertise in the many technologies needed for process development and manufacture of cell and gene therapies is limited. These capacity and expertise limitations can pose bottlenecks at both early and late stages of cell and gene therapy development.

The expertise and capacity for early process development and early clinical manufacturing of cell and gene therapy candidates is concentrated at academic research institutions with small-scale good manufacturing practice (GMP) manufacturing facilities. The academic GMP manufacturing facilities have varying capabilities and limited capacities, personnel, and resources to meet the growing demand for cell and gene therapy manufacturing. While industry presence with large-scale manufacturing capacity is growing, there is limited partnership and collaboration between the academic and industry stakeholders to support process development and GMP manufacturing throughout the lifecycle of development and commercialization for cell and gene therapies. In addition, there is an immediate and growing need to build a diverse and highly skilled workforce to support the cell and gene therapy manufacturing demand in the state.

CIRM therefore provides this unique biphasic funding opportunity to non-profit academic GMP manufacturing facilities to enhance operations, and to establish productive partnerships with industry and non-profit stakeholders to further advance California as the world-class hub of cell and gene therapy manufacturing.

OBJECTIVE

The overall objective of the funding opportunity is to establish a statewide manufacturing network comprising academic process development and GMP manufacturing facilities as well as industry manufacturing partners that will:

(1) Accelerate and de-risk pathways to commercialization for cell and gene therapies

(2) Advance industry standards and incorporate quality-by-design in cell and gene therapy manufacturing

(3) Build a diverse, highly skilled manufacturing workforce in California.

Examples of how the California Cell and Gene Therapy Manufacturing Network may function to meet the goals of this funding opportunity include (but are not limited to):

- Offering world-class expertise and capacity across a range of cell and gene therapy manufacturing and analytical technology platforms
- Implementing innovative manufacturing models that support the delivery of cell and gene therapies for rare and ultra-rare diseases
- Operationalizing academic-industry partnerships that accelerate and de-risk late-stage and commercial manufacturing of cell and gene therapies
- Establishing standards and requirements for quality and accreditation of cell and gene therapy manufacturing facilities
- Enabling inclusive workforce entry and advancement opportunities in technical and leadership career pathways

To effectively achieve the program objective, CIRM will issue two phases of awards governed by two separate requests for applications (RFAs). The first phase of awards will fund California academic GMP facilities to make initial progress toward the three network goals (described above) at their individual facilities. The second phase of awards will operationalize the California Cell and Gene Therapy Manufacturing Network by funding collaborative partnership-driven proposals that effectively scale phase 1 outcomes across the network. CIRM will coordinate a steering committee composed of awardees, industry partners and external representatives that will bridge the two award phases by driving collaboration, knowledge-sharing and standard-setting between the participating network facilities and collaborators.

AWARD INFORMATION

How is the Program Structured?

The first phase of the program will fund individual California non-profit GMP manufacturing facilities to address cell and gene therapy manufacturing bottlenecks at their individual facilities, which could include external partnerships where appropriate. The awardees will be expected to implement quality-driven enhancements that de-risk manufacturing of cell and gene therapy projects, to propose and make operational progress on specialization areas of value to the network, and to develop inclusive workforce development programs for technical and leadership career pathways. Successful outcomes of phase 1 awards may include, but are not limited to, quality-driven improvements on cell and gene therapy manufacturing project execution compared to historical performance, demonstration of competency in specialization areas with execution of pilot project(s), and enrollment of first trainee cohorts for technical and leadership training programs.

The second phase of the program will solicit collaborative proposals toward operationalization of a California Cell and Gene Therapy Manufacturing Network that collectively addresses the three goals of this funding opportunity. The proposals must include partnerships within or between California academic facilities and industry cell and gene therapy manufacturing stakeholders. Phase 2 awardees will be expected to further develop, scale, or make broadly available any individual facility enhancements, functional area specializations and/or workforce development programs from the first phase of awards. In addition, phase 2 awardees will be expected to participate in collaborative steering of projects across network sites to rapidly mitigate capacity and expertise gaps. Successful outcomes of the second phase awards may include but are not limited to: success rate of partnership-driven progression of projects to late-stage and commercial manufacturing phases; utilization rate of specializations by collaborating facilities; evidence of adoption of network-wide quality standards, protocols and best practices; and sustained enrollment in training programs and success rate of trainee job placement.

To facilitate achievement of the California Manufacturing Network Goals, CIRM will coordinate a Steering Committee to help drive the formation and function of the network. The Steering Committee will be composed of the Program Directors of the awardee institutions, leaders from California industry stakeholders, external key opinion leaders and CIRM staff. Examples of Steering Committee functions could include supporting consistent implementation of industry quality standards, protocols and best practices, developing potential criteria for facility accreditation, facilitating collaborative opportunities between network members for phase 2 proposals, establishing processes and systems for sharing protocols, resources

and operational data, and mitigating capacity and expertise gaps across the network.

What activities will CIRM fund?

CIRM funds will support the following activities under this opportunity

- Implementation of quality-driven enhancements that de-risk and accelerate early and late-stage process development and GMP manufacturing of cell and gene therapies. Potential enhancements could include but are not limited to:
    - Application of industry quality standards and quality-by-design principles
    - Implementation of services to support sponsors with process development, technology transfer, quality-by-design, etc.
    - Development of electronic records systems and technology transfer package templates
    - Collaborating with manufacturing partners to transition projects for late-stage manufacturing
    - Analytical and manufacturing technology development

- Specialization in one or more functional areas that overcome bottlenecks in the development and delivery of cell and gene therapies. Specialization areas could include but are not limited to:
    - Current and emerging cell and gene therapy technology platforms
    - Innovative manufacturing models for cell and gene therapies for rare and ultra-rare (N-of-1) diseases
    - Application of quality-by-design in deep product characterization, identification of critical quality attributes and critical process parameters, and process control strategies.
    - Correlation of product characteristics to clinical outcomes
    - Novel manufacturing technology platforms
    - Systems for sharing manufacturing protocols, data, and analytics

- Mitigation of project delays and long lead-times resulting from capacity or expertise gaps. Mitigation strategies could include but are not limited to:
    - Implementation of project prioritization processes.
    - Facilitating technology transfer between GMP manufacturing facilities.
    - Triaging projects across the network of California GMP manufacturing facilities based on expertise and capacity.

- Workforce development programs for technical and leadership positions, preferably in partnership with CIRM EDUC-funded programs, California cell

and gene therapy industry stakeholders, and California academic institutions. Workforce development activities include but are not limited to:

- Development of paid training and/or certification programs for technical positions
- Recruitment, technical training and leadership mentoring programs for facility leadership positions
- Partnering within network of California GMP manufacturing facilities for cross-functional training, job placement and other coordinated activities.

CIRM funds cannot be used to support the following activities under this opportunity:

- Costs associated with process development or manufacturing activities for individual projects.
- Construction or renovation of physical facilities.
- Activities already budgeted or paid for under a prior, existing or future CIRM award.
- Equipment costs exceeding 5% of the direct project costs.

What is the award amount and duration?

The CIRM Governing Board has allocated $20 million for funding of phase 1 awards, and $60 million for funding of phase 2 awards.

The awards in the first phase will provide up to $2.0 million in total funding over a maximum two-year period. The awards in the second phase will provide up to $5.0 million in total funding over a maximum five-year period. CIRM will not fund indirect costs for awards issued under this funding opportunity.

How will funds be awarded?

Awards will be made in the form of a grant. CIRM will disburse funds pursuant to a Notice of Award (NOA) and based on operational milestones. Costs resulting from a delay or failure to meet an operational milestone will be the sole responsibility of the recipient. Successful applicants will have thoughtfully accounted for foreseeable project risks and developed contingency plans that do not require additional funding from CIRM. Continued funding is contingent upon timely progress, and, when applicable, the ongoing ability of the applicant to fund its operations and to satisfy its co-funding commitment.

ELIGIBILITY

What types of projects are eligible for funding?

(1) Must be ready to initiate work on the funded project within 90 days of approval

Given the urgency of CIRM's mission, all approved awardees must initiate work on the funded project within 90 days of approval and authorization for funding by the Application Review Subcommittee of CIRM's governing board, the Independent Citizens' Oversight Committee ("ICOC").

(2) Must have a California operating location

Only non-profit California organizations are eligible to apply. At the time of the application deadline, the applicant organization must be located in California and must have the appropriate process development and GMP manufacturing facilities in California. If these requirements are not met, CIRM may terminate all further action on the application.

(3) Must have demonstrated ability to perform process development and/or GMP manufacturing for cell or gene therapy development projects

The applicant organization must demonstrate a track record of performing GMP manufacturing activities, having supplied at least one cell or gene therapy clinical trial. Applicants will be required to identify process development or GMP manufacturing projects that are either active or would be initiated in the first year of the award periods that they will execute on to demonstrate achievement of applicable award objectives.

(4) Application must be accurate and complete

All required components of the application must be completed and may not contain false or inaccurate information.

(5) Applicant must be in "good standing"

Applicants must certify that they are in good standing, as follows:

a. The applicant's Chief Executive Officer, Chief Financial Officer, and Principal Investigator must not have been convicted of, or currently under investigation for, crimes involving fraud/misappropriation;

b. The applicant must have accounting systems in place that are capable of tracking CIRM funds; and

c. The Program Director or key personnel named in the application must not be currently under investigation for research misconduct by the applicant institution or a funding agency and must not be currently debarred by HHS Office of Research Integrity.

(6) Must include a project manager

The project team must include a project manager with experience in GMP manufacturing facility operations and be able to devote at least 50% effort to the project.

(7) Must demonstrate co-funding support

CIRM will require all applicants to co-fund at least 20% of the total "Allowable Project Costs". Allowable Project Costs are those costs permitted under CIRM policies and regulations and include direct and facilities costs. Indirect costs are not supported by this funding opportunity. The sum of CIRM funds requested plus the co-funding contribution by the applicant make up the total Allowable Project Cost. The co-funding may come from any funding source arranged by the applicant. Documentation demonstrating the commitment of funds to cover the proposed co-funding amount must be provided at the time of application submission.

Who can apply?

Only California Organizations are eligible to apply for this opportunity.

California Organizations may use CIRM funds for eligible project costs incurred both in California and outside California. To qualify as a California organization, the organization must have >50% of its employees located in, and paid in, the state of California, and must direct and control the award activities from the California location.

Who can serve as the Program Director (PD)?

To be eligible, the PD must satisfy the following requirements:

- Must be the Director of the GMP manufacturing facility of the applicant organization or must hold an equivalent position.
- Must be an employee of the applicant organization or be accountable for the conduct of the proposed project to the applicant organization through a formal contract

- Must propose a level of effort on the project consistent with achieving the project's aims and not less than 30% on average over the project period (note: "project" includes both the CIRM-funded, applicant co-funded components and steering committee participation). Any effort for which salary from CIRM is claimed must be expended in California
- Must be authorized by the applicant organization to conduct the proposed activities and assume the responsibilities of the PD
- Must be authorized by the applicant organization, and be able to commit the level of effort required, to participate in the California Manufacturing Network Steering Committee
- Must not currently have another application pending review or approval under this funding opportunity
- Must not currently have another application that is substantially similar or has overlapping activities pending review or approval under any CIRM opportunity.

ADDITIONAL REQUIREMENTS

Addressing the Needs of Underserved Communities in CIRM-Funded Projects

All applicants to the Funding Opportunities in this program will be required to provide a statement describing:

1. How their proposed project activities will improve access to cell and gene therapies by underserved and disproportionately affected populations.
2. How the project team will bring diverse and inclusive perspectives and experience to the implementation of proposed activities.
3. How well the research team demonstrates a successful track record for promoting and valuing diversity, equity and inclusion (DEI).
4. How any proposed workforce development programs will increase workforce participation by underserved and disproportionately affected populations in California.

Knowledge Sharing Plan

The CIRM 2022-2027 strategic plan prioritizes knowledge sharing and collaborative approaches to the discovery, development and commercialization of regenerative medicine therapies. Applicants should describe how they will contribute to knowledge sharing in the California Cell and Gene Therapy Manufacturing Network. Applicants are encouraged to allocate funds in their proposed budget for personnel and/or activities related to managing and sharing knowledge.

Applicants should develop plans intended to capture and disseminate within the network any operational data, protocols, processes, expertise, guidance or other information vital to achieving the three goals of the California Cell and Gene Therapy Manufacturing network. The sharing plan may also include the ability to support CIRM TRAN and CLIN awardees that may utilize the Manufacturing Network in meeting their own CIRM data sharing requirements.

Organizational Business Plan

In the application proposal, applicants will be required to describe their plans for maintaining sustainability beyond the immediate project period of any proposed operational enhancements, quality-based improvements, specialization areas and training programs that will be developed, implemented and/or scaled up as part of these funding opportunities.

SCHEDULE AND DEADLINES

Applications Due	January 2023
Grants Working Group (GWG) Review	Approximately 90 days post submission
ICOC Review and Approval	Approximately 120 days post submission
Award Start	Must start within 90 days of award approval (i.e., approximately 210 days post submission)