



Funding Opportunity Concept Plan

INFR6: Shared Resources Laboratories for Stem Cell-Based Modeling

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.

Stem cell-based modeling of human biology and disease is a promising approach to advance our knowledge of human disease mechanisms and to identify new therapeutic targets, biomarkers, and drug candidates. To generate such in vitro models, human pluripotent (hPSC) or adult stem cells, either derived from patients with specific diseases or engineered to represent those diseases, are differentiated into cell types that are relevant to the biological or disease-related questions under investigation. Such models can range in complexity from single layers of differentiated cell types to multidimensional systems such as organoids and bioengineered tissues/organs on chips.

There is abundant interest and expertise in the California research community to capitalize on the promise of stem cell-based modeling. Many laboratories are interested in acquiring this expertise as a core competency, while others seek to address specific research questions through collaboration. However, not all research laboratories that need these models have local access to relevant infrastructure and training, nor do all have the opportunity to collaborate with a stem cell-based modeling laboratory. Laboratories well-versed in stem cell-based modeling that share their expertise and/or provide models collaboratively can't meet demand, as it is time consuming and costly to divert resources to educating and supporting other researchers.

In addition, to accelerate the impact of stem cell-based modeling researchers in the field must overcome important challenges including limited reproducibility

across projects employing similar stem cell-based models, and the need to better understand these models' predictive value for elucidating human biology and disease.

CIRM intends to increase and diversify contributions to the field and help overcome some of the hurdles described above by funding dedicated Shared Resources Laboratories (SRLs) for Stem Cell-Based Modeling across the state of California. Funded SRLs will become part of a collaborative network offering infrastructure, expertise, access to stem cell-based models, training and standardization of resources and protocols, with the goals of accelerating discoveries in regenerative medicine, growing and diversifying the cohort of stem cell researchers in the state, and promoting reproducibility of stem cell-based modeling experiments within and across laboratories. CIRM expects SRLs to become self-sustaining by the end of the award period.

The concept for SRLs is grounded in CIRM's experience with 17 Shared Laboratories funded from 2007 to 2016 under Proposition 71 (Prop 71 SLs). These laboratories provided California researchers with dedicated research space, specialized instrumentation, cell lines, and cell culture materials free from federal restrictions on human embryonic stem cell (hESC) research that existed at the time. With CIRM funding, Prop 71 SLs also provided training in stem cell culture and related technologies, making the emerging field of human pluripotent stem cell research more accessible to California researchers. Under Prop 14, CIRM now intends to re-establish and expand this unique opportunity for California scientists, providing access to cutting edge stem cell-based modeling as a shared resource, and further advancing California as a leader in this space.

The SRL for Stem Cell-Based Modeling Awards Program represents one of several technology competency hubs programs envisioned in CIRM's 2022-2027 strategic plan. Together with a future Data Infrastructure, SRLs will broadly connect and empower California's regenerative medicine research ecosystem toward advancing world class science and therapeutic innovation.

OBJECTIVE

The overall objective of this funding opportunity is to accelerate regenerative medicine research by creating a network of SRLs that will:

- 1) Broaden access to stem cell-based models across CA
- 2) Advance standards and reproducibility of stem cell-based models
- 3) Increase access to educational opportunities in stem cell-based techniques
- 4) Develop sustainable stem cell core infrastructure

Examples of how a network of SRLs for Stem Cell-Based Modeling may function to meet the goals of this funding opportunity include (but are not limited to):

Providing researchers, locally at grantee institution and regionally at nearby institutions, access to:

- Cell culture facilities to conduct stem cell-based modeling experiments
- High-cost and highly specialized technologies, needed for stem cell-based modeling

Providing researchers, locally and across California, access to:

- Well characterized, unmodified and modified hPSC collections, locally and by shipment
- Partially or fully differentiated stem cell-based models, locally and by shipment,
- Training in the creation and use of stem cell-based models, offered locally in cores through hands-on training, and via regular workshops / classes, video tutorials, etc., for broad participation

Providing educators, regionally and/or across California, access to:

- Formal techniques courses in stem cell culturing and stem cell-based modeling for student education
- Other student experiences with stem cell-based modeling, e.g., workforce development in partnership with CIRM EDUC-funded programs

Implementing sustainability plans

- Fee for service, recharge
- Alternative funding sources

To effectively achieve the program objective, CIRM will coordinate a Steering Committee composed of SRL Program Directors and external stakeholders, to drive knowledge-sharing and standard-setting among funded SRLs and external partners, accelerating stem cell-based modeling research across California.

AWARD INFORMATION

How is the Program Structured?

The program intends to fund two different types of SRL:

- 1) Establishing (E)-SRLs to provide local access to stem cell-based models, training, specialized equipment, and educational opportunities in geographic areas/locations where access to models is limited; and
- 2) Enhancing / Expanding (E/E)-SRLs to enable leading experts in stem cell-based modeling to share their models and expertise locally and broadly across California.

Since the two SRL types differ in focus and scope, applications will be solicited through two separate requests for applications (RFAs).

RFA INFR6.1 (E-SRL) targets California non-profit research institutions that currently do not conduct, or conduct very limited, stem cell-based modeling research at their institution and can demonstrate that establishment of that expertise would enable (1) researchers at the grantee and neighboring institutions to pursue impactful scientific questions they cannot currently address, due to the absence of relevant stem cell-based modeling expertise in their vicinity, and (2) stem cell / regenerative medicine-focused educational programs for diverse and/or underserved student populations.

Awardees will be funded to renovate and equip a stem cell-based modeling core facility, establish necessary expertise – if necessary in partnership with expert investigator(s) from other non-profit and/or for-profit organizations, and offer use of the SRL to researchers at the grantee and nearby institutions. Successful outcomes include, but are not limited to, renovation, equipping, and staffing of the SRL, implementation of stem cell-based modeling expertise, utilization of core facility (with a focus on labs that have limited access to stem cell-based modeling expertise), establishment of and sustained enrollment in training and educational programs, success of projects utilizing core, implementation of sustainability plan, and contributions to SRL Network functions (see below).

RFA INFR6.2 (E/E-SRL) targets California non-profit research institutions that conduct cutting edge stem cell-based modeling research and can demonstrate local, regional, and statewide interest in the expertise to be offered.

Awardees will be funded to equip an existing space as a core facility that offers stem cell-based modeling expertise to researchers not only from the grantee institution, but also broadly across California and beyond. Broad sharing of expertise should be an emphasis for E/E-SRLs. In addition to local expertise at the grantee institution, additional stem cell-based models may be established and offered at the core, in partnership with investigators from other non-profit or for-profit organizations. Successful outcomes include, but are not limited to, equipping and staffing of the SRL, implementation of stem cell-based modeling expertise, utilization of core facility, including by labs that have limited access to stem cell-based modeling expertise, establishment of and sustained enrollment in training and educational programs, broad sharing of stem cell-based models across California, success of projects utilizing core and shared models, implementation of sustainability plan, and contributions to SRL Network functions (see below).

All SRL awardees will be members of the **CIRM SRL Network**. A CIRM-coordinated Steering Committee, composed of SRL Program Directors and external stakeholders in the stem cell-based modeling field, will drive network functions and will be responsible for its outcomes. These may include, but are not limited to, establishment of processes and systems for sharing models, best practices, knowledge, and other resources; standardization of cell lines, reagents, and quality control/validation across the network, where deemed feasible for improving reproducibility; and development of collaborative approaches toward improving reproducibility of stem cell-based models.

Awardees are expected to provide and implement plans (1) for financial support of SRL facility operations through, e.g., user recharge and (2) for **sustainability of the SRL in the long term**. SRL awards will be realized in 3 phases.

E-SRL Awards are up to 5-years:

- Phase A – 18 months of renovating and equipping SRL core facility
- Phase B – 24 months of CIRM-supported operations
- Phase C – 18 months of tapered CIRM support (half of Phase B operational costs) during implementation of long-term sustainability plan

E/E-SRL Awards are up to 5-years:

- Phase A – 6 months for equipping SRL core facility
- Phase B – 30 months of CIRM-supported operations
- Phase C – 24 months of tapered CIRM support (half of Phase B operational costs) during implementation of long-term sustainability plan

During Prefunding Administrative Review of funded applications, CIRM will work with awardees to make adjustments to the timing of the phases, as needed.

Pursuant to Proposition 14, Shared Resource Laboratories are intended to be operational in the first five years following the effective date of the initiative (December 2020). Therefore, applications must propose plans that are achievable within the outlined phases above.

What activities will CIRM fund?

The SRLs must serve as shared resources regionally and across California. The core facility, i.e., equipment and trained personnel, must be available not only to stem cell and regenerative medicine researchers at the grantee institution but also to those from nearby institutions without such facilities.

CIRM funds will support the following activities:

Creation of core facility

- Renovation of laboratory space to create a core facility for stem cell-based modeling approaches (*E-SRLs only*)
- Acquisition of major equipment (e.g., incubators, hoods, freezers, liquid nitrogen containers, microscopes, cell sorters, sequencers), necessary for culturing and analyzing stem cell-based models (*no co-mingling with federal funding for purchase of capital equipment*)
- Establishment of stem cell-based modeling expertise in core facility, obtained internally within grantee institution and/or externally through collaboration with partnering institutions

Operations

- Supporting use of SRL by investigators from grantee and nearby institutions, including maintenance of the SRL
- Providing specialized services (e.g., gene delivery, gene editing, omics, bioinformatics), necessary for manipulating and analyzing stem cell-based models
- Broad sharing of reagents and partially or fully differentiated models across California (*optional for E-SRL*)
- Training of researchers in use of SRL, creation/use of models
- Educational activities
 - Formal courses on general hPSC culturing techniques and creation/use of stem cell-based models (*optional, additional funding provided*)
 - Other activities for students from diverse backgrounds, such as science fairs, remote projects, etc. that are designed to stimulate interest in stem cell and regenerative medicine research

SRL Network

- Participation in CIRM-organized SRL Network activities, including establishment of processes and systems for sharing know-how and resources, participation in efforts to improve reproducibility

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

- Research studies: use of SRLs for research projects will be funded through CIRM pillar programs and other funders

What is the award amount and duration?

The CIRM Governing Board has allocated \$50 million for funding of the SRL program: \$26M for Build & Equip facilities funds and \$24M for operations.

The awards for E-SRLs (RFA INFR6.1) will be up to \$5.4 million (with techniques course) or up to \$4.4 million (without techniques course), and the awards for E/E-SRLs (RFA INFR6.2) up to \$4.3 million (with techniques course) or up to \$3.0 million (without techniques course) each in total allowable costs over a maximum five-year period. The indirect cost rate will be set at 20% for non-profit applicant organizations, based on the sum of operating costs for personnel and supplies and O&M, but not for the costs of space development/renovation and equipment.

Pursuant to Proposition 14, CIRM shall prioritize applications for Shared Resource Laboratories that offer matching funds or verified in-kind support, consistent with the highest medical standards, as established by the CIRM governing board.

Funding received by a grantee from an institute award for construction shall be subject to prevailing wage laws

How will funds be awarded?

Awards will be made in the form of a grant. Funds will be disbursed pursuant to a CIRM Notice of Award. Except for the first payment issued upon initiation of an award, payments will be disbursed upon completion of specific operational milestones. Continued funding is contingent upon timely progress, as outlined in the operational milestones established under the Notice of Award, and, when applicable, the ongoing ability of the applicant to fund its operations and to satisfy its co-funding commitment, if applicable.

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.

Pursuant to Proposition 14, CIRM shall prioritize applications for Shared Research Laboratories that enhance the geographic distribution of resources across the state.

ELIGIBILITY

What types of projects are eligible for funding?

(1) Eligibility specific to this funding opportunity

Modeling expertise offered in the proposed CIRM-funded SRL is limited to in vitro models using human stem or progenitor cells¹ (collectively, “stem cells”).

(2) Must be ready to initiate work on the funded project within 150 (E-SRL) or 120 (E/E-SRL) days of approval

Given the urgency of CIRM’s mission, all approved awardees must initiate work on the funded project within 150 (E-SRL) or 120 (E/E-SRL) days of approval and authorization for funding by the Application Review Subcommittee of the Independent Citizens’ Oversight Committee.

(3) Must include a Lab Manager

The project team must include one or more Lab Managers with experience in managing a core cell culture lab, ideally related to stem cell research, and able to devote at least a combined total of 100 percent effort to the project.

(4) Co-funding is required for E/E-SRLs

E/E-SRLs are required to co-fund at least 20% of the total “Allowable Operational Project Costs”. Allowable Operational Project Costs are those costs permitted under CIRM policies and regulations and include direct and indirect costs, but not Build/Renovate and Equip costs. The sum of CIRM funds requested for operations, plus the co-funding contribution by the E/E-SRL applicant, make up the total Allowable Operational Project Costs. The co-funding may come from any funding source arranged by the applicant.

Documentation demonstrating the commitment of funds to cover the required co-funding amount (E/E-SRLs) must be provided at the time of application submission.

(5) Application must be accurate and complete

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

(6) Applicant must be in “good standing”

¹ Under Proposition 14, progenitor cells are “multipotent or precursor cells that are partially differentiated but retain the ability to divide and give rise to differentiated cells.” Progenitor cells may include directly reprogrammed cells if they meet the criteria in the above definition.

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

- a. The applicant's Chief Executive Officer, Chief Financial Officer, and Program Director 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.

Who can apply?

Only California Non-Profit Organizations are eligible to apply for this opportunity.

Non-Profit 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.

Only one application will be accepted per institution across the SRL program, i.e., an institution can only submit a single application to either RFA INFR6.1 or RFA INFR6.2, not both.

Who can serve as the Program Director (PD)?

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

- 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 commit at least 20 percent effort to working on the project. (note: "project" includes CIRM-funded and 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 SRL Network Steering Committee
- Must not currently have another application pending review or approval under this INFR6 funding opportunity.

ADDITIONAL REQUIREMENTS

Diversity, Equity and Inclusion (DEI)

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

- How the proposed activities will ensure that core users and recipients of stem cell-based models & expertise represent diverse goals, approaches, perspectives and backgrounds
- How any proposed educational activities will ensure participation by underserved populations
- How the SRL team and other contributors will bring diverse and inclusive perspectives and experience to the implementation of proposed activities
- How the SRL team and contributors demonstrate a successful track record for promoting and valuing diversity, equity and inclusion
- How the SRL will offer stem cell lines with ancestral and sex diversity that may increase the applicability of research outcomes to diverse populations

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 CIRM SRL Network and are encouraged to allocate funds in their proposed budget for personnel and/or activities related to managing and sharing knowledge. Once CIRM implements the data knowledge platform, successful SRL applicants will be required to work with their CIRM officer to align data and processes to make them available through CIRM's data infrastructure. Applicants should develop plans intended to establish processes and systems for sharing models, best practices, knowledge, and other resources; standardization of cell lines, reagents, and quality control/validation across the network, vital to accelerating regenerative medicine research in California and to improving reproducibility of stem cell-based models. Proposed knowledge sharing plans of funded SRLs will be coordinated through the Steering Committee.

Data Sharing and Management Plan

The sharing of data and knowledge produced from CIRM-funded projects is key to advancing the field of regenerative medicine and accelerating treatments to patients. CIRM requires applicants to develop and execute a Data Sharing and Management Plan (DSMP) that includes management and preservation of data and making applicable data available to the broader scientific community. CIRM

also requires applicants to allocate funds in their proposed budget for personnel and/or activities related to managing and sharing data produced from the funded project. CIRM requires sharing of data in accordance with [FAIR](#) (Findability, Accessibility, Interoperability, and Reusability) and [CARE](#) (Collective Benefit, Authority to Control, Responsibility, and Ethics) data principles, through established repositories including, but not limited to, specialized repositories, generalist repositories, cloud platforms and institutional repositories. The repository(ies) selected, and summary of the data shared must be reported to CIRM during and after the project period. To promote the generation of knowledge CIRM may publicly share where CIRM-funded data are deposited.

A DSMP for data generated during SRL operations, such as omics, FACS, imaging and other data generated for cell model quality control and validation, must be included in the application². The DSMP is subject to evaluation by the Grants Working Group. Reviewers will be asked to comment on the quality of the Data Sharing and Management Plan and advise CIRM on any improvements they recommend.

Organizational Business Plan

In the proposal, applicants will be required to describe their plans for supporting operational costs during the award period through, e.g., user re-charge, and for ensuring sustainability beyond the immediate project period of any proposed operational, researcher training, and educational programs that will be developed and implemented as part of these funding opportunities.

SCHEDULE AND DEADLINES

Applications Due	March/April 2023
Grants Working Group (GWG) Review	Approximately 60 days post submission
Facilities Working Group (FWG) Review (E-SRL only)	Approximately 90 days post submission
ICOC Review and Approval	Approximately 120 days post submission

² Data generated by research projects, funded by CIRM or other agencies and conducted at the cores, will comply with their individual data sharing and management requirements, and should not be included in the SRL DSMP.

Award Start	Must start within 150 (E-SRL) and 120 (E/E-SRL) days of award approval (i.e., approximately 240/210 days post submission)
--------------------	---