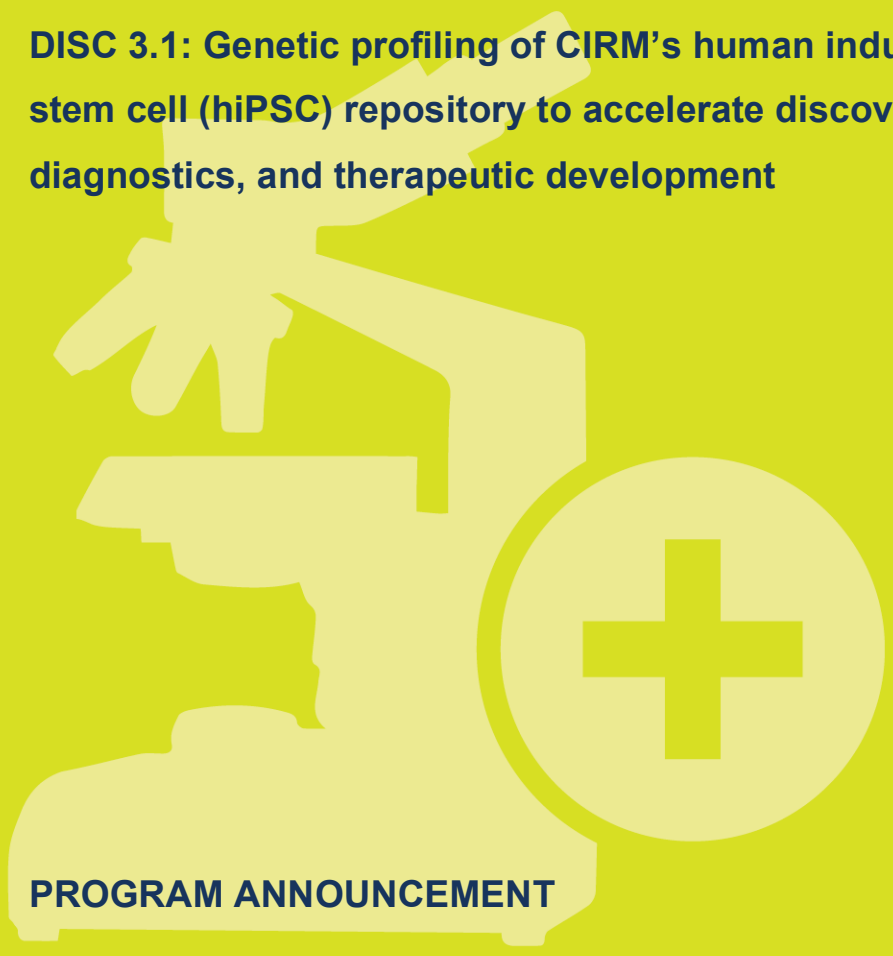
DISCOVERY

Partnering Opportunity for Discovery Stage Research Projects: The Challenge Award

DISC 3.1: Genetic profiling of CIRM's human induced pluripotent stem cell (hiPSC) repository to accelerate discovery, diagnostics, and therapeutic development



PROGRAM ANNOUNCEMENT

3.21.16

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DISC 3.1

Objective

The mission of California Institute for Regenerative Medicine (CIRM) is to accelerate stem cell treatments to patients with unmet medical needs.

The objective of the Discovery Program is to support exploratory research leading to the discovery of novel stem cell technologies to improve patient care.

The Challenge Award program will provide funding to address or overcome key challenges in the stem cell field that are preventing or slowing the discovery of promising new stem cell technologies that could be rapidly translated towards improving patient care. Key challenges will be defined periodically by CIRM and announced in advance of each funding cycle.

The challenge for the DISC 3.1 award is to enhance the value of CIRM's Human Induced Pluripotent Stem Cell (hiPSC) bank for disease modeling, target discovery, drug discovery, and development though the acquisition and addition of genetic data for up to 3000 disease-specific and control stem cell lines.

Project Deliverables

CIRM is creating a resource to accelerate the discovery and development of therapies for patients. The Institute's Human Induced Pluripotent Stem Cell Program is creating a bank of high quality disease-specific and control stem cell lines developed from thousands of individuals for use in disease associated allele discovery, drug screening, and drug safety assessment. iPS cell lines covering eleven genetically complex diseases, with accompanying clinical data, are banked by the Coriell Institute for broad distribution (catalog.coriell.org/1/CIRM). The first 300 lines in the repository were made available to the public in September 2015 and upwards of 3000 lines are anticipated to be available in 2017. In addition, several other resources will be available that were generated by the iPSC line producer Cellular Dynamics International (CDI) including 1) A downloadable single nucleotide polymorphism (SNP) dataset for each line based on the Illumina Infinium HumanCore-24 BeadChip. SNPs represented on BeadChip can be downloaded from ftp://webdata:webdata@ussd-ftp.illumina.com/Downloads/ProductFiles/HumanCore-24/v1-0/humancore-24-v1-0-manifest-file-a.csv; 2) Limited stocks of extracted DNA from hiPSC lines (~8μg per sample at ~50ng/μl concentration); and 3) Limited stocks

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of extracted DNA from parental cells used to generate iPSCs lines (~7.5μg per sample at ~50ng/μl concentration).

The eleven disease collections, plus controls, found in CIRM's iPSC bank include:

- Epilepsy
- Idiopathic Autism
- Cerebral Palsy
- Idiopathic Pulmonary Fibrosis
- Viral hepatitis C
- Nonalcoholic steatohepatitis (NASH)
- Idiopathic Familial Dilated Cardiomyopathy
- Sporadic Alzheimer's Disease
- Age-related macular degeneration
- Primary open angle glaucoma
- Diabetic retinopathy

The overall project deliverable of the DISC 3.1 Challenge Award is a comprehensive genetic profile of CIRM's Human Induced Pluripotent Stem Cell Bank to serve as a catalyst for further use in disease associated allele discovery, drug screening, and drug safety assessment. The project proposed to achieve this deliverable must adhere to the following requirements:

- Grantee must coordinate with CIRM, Coriell, and/or CDI to access iPSC lines or other resources listed above for genetic analyses.

- Grantee must analyze Illumina Infinium HumanCore-24 BeadChip datasets generated on all the banked lines (up to 3000). The goal of this analysis is to maximize the amount of data available to enable identification of alleles associated with disease, drug screening, and drug safety assessment (e.g. cardio or liver drug sensitivity). Lines where the same information is alternatively proposed to be obtained by whole genome sequencing are exempt from this requirement.

- All of the lines or specific disease subset(s) of the lines in the bank must be supplemented with other genetic profiling activities such as whole genome sequencing, exome sequencing or additional SNP assays. Specific disease lines and corresponding controls (in their entirety) can be profiled differently or more comprehensively with the appropriate rationale (e.g. exome sequencing would be informative and insightful for one disease collection but not provide useful information for another disease collection). If certain controls overlap multiple diseases with different profiling activities, a single supplemental profiling activity that covers all corresponding diseases is acceptable (e.g. sequencing that covers areas of SNP profiling).

- Genetic information must be transferred to Coriell to be displayed in its CIRM hiPSC Bank catalog. Data-sharing should be done in a suitable standardized format that is easily readable by the general research community. Grantee

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will work with CIRM and Coriell to achieve this outcome, which may include providing ready-to-share summaries, lists and/or tables of the main conclusions, etc.

- Raw data from collection activities such as sequencing must be deposited into a controlled access database (e.g., the database of Genotypes and Phenotypes, dbGaP) where outside scientists can apply to analyze the data. Grantee will work with CIRM and Coriell on how to deposit this data.

Award Information

How much funding will CIRM provide and for how long?

CIRM will fund a single award to develop, analyze and make available useful genetic information for all lines in the CIRM iPSC bank (up to 3000). Total funding available under this call is $2M. Direct project costs must be adequately justified and are subject to adjustment prior to the issuance of an award based on assessments by the Grants Working Group (GWG), the CIRM team, or by the Application Review Subcommittee of CIRM's Governing Board. The proposed project period must not exceed two years from the time of award start.

What activities will CIRM support?

CIRM resources will support the following activities under this opportunity:

✓ Activities that are necessary to collect and interpret information on hiPSC bank lines, including:

- ✓ Sample preparation (e.g., DNA extraction and/or library generation)
- ✓ Data collection (e.g., exon sequencing, SNP profiling)
- ✓ Data analysis (e.g. of existing SNP datasets for entire bank)
- ✓ Data formatting and transfer

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

- ✘ Characterization of cell lines outside of CIRM's hiPSC bank.
- ✘ A project where DNA sequencing and/or SNP analysis is not a core part of the project.
- ✘ Characterization where data cannot be shared with the outside research community.

How will funds be awarded?

- CIRM will disburse funds pursuant to a Notice of Grant Award

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Eligibility

What types of projects are eligible for partnering?

To be eligible, the proposed project must satisfy the following requirements:

(1) The applicant must propose work on all cell lines (up to 3000) within CIRM's hiPSC bank as outlined under Project Deliverables.

(2) The applicant must be ready to initiate work on the funded project within 120 days of approval. Given the urgency of CIRM's mission, the approved awardee must initiate work on the funded project within 120 days of approval and authorization for funding by the Application Review Subcommittee of the Independent Citizens' Oversight Committee.

(3) Co-funding is not required. If the project requires funding over and above that which CIRM provides to achieve the expected outcome, documentation demonstrating the commitment of funds to cover the required additional amount must be provided by the application deadline (e.g., copy of executed term sheet showing amount of co-funding, conditions and source).

(4) For-profit organizations must demonstrate solvency. For-profit organizations must provide documentation that shows 180 days cash on hand from date of application submission and the financial ability to meet the co-funding and contingency requirements for the term of the project. The determination of solvency will be made at CIRM's sole discretion.

Who can apply and where can funds be spent?

California Organizations

A California Organization is a for-profit or non-profit organization that employs and pays more than 50% of its employees in California.

For a California Organization, Allowable Project Costs include:

- Costs for activities conducted wholly in California; and
- Costs for activities conducted outside of California, provided that the California Organization exercises direction, supervision and control over the activities.

Non-California Organizations

A Non-California Organization is a for-profit or non-profit organization that employs and pays 50% or less of its employees in California.

For a Non-California Organization, Allowable Project Costs include:

- Cost of research activities conducted wholly in California; and
- Share of costs for research activities conducted outside of California that are directly required to support research conducted in California.

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Unallowable Costs

For both California Organizations and Non-California Organizations, Allowable Project Costs do **NOT** include the costs of activities performed by a separate out-of-state organization that retains intellectual property or publication rights in any intellectual property (e.g., invention, technology, data) arising out of the CIRM funded project.

CIRM may determine, in its sole discretion, whether an applicant is a California organization and whether the project activities are allowable.

The applicant must demonstrate by the application deadline a commitment of funds from other sources for non-allowable project activities that are necessary to achieve the goals of the application.

Who can serve as the Principal Investigator (PI)?

To be eligible, the PI 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 10 percent effort to working on the project
- Must be authorized by the applicant organization to conduct the research and assume the responsibilities of the PI

Schedule and Deadlines

Applications Due	March 30, 2016.
Grants Working Group (GWG) Review	Approximately 90 days post submission
ICOC Review and Approval	Approximately 150 days post submission
Award Start	Must start within 120 days of award approval

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Application Review Information

What is the process for evaluating an application?

Pre-submission Consultation

In accordance with CIRM's mission, the Institute is committed to helping develop promising stem cell-based technologies by partnering with world-class investigators. Therefore, prospective applicants are encouraged to contact CIRM before applying with questions or to discuss their project's eligibility.

Eligibility Review

CIRM will assess whether the proposed project meets eligibility requirements sought under this program. If CIRM determines, in its sole discretion, that an application does not meet the eligibility requirements of the program or that the submitted application is incomplete or contains false or inaccurate information, CIRM will notify the applicant of its decision, allow an opportunity to remedy, and if not remedied in a timely manner satisfactory to CIRM, terminate all further action on the application.

Scientific Review

The scientific merit of each application will be assessed by the GWG, which is composed of fifteen subject matter experts from outside California, seven patient advocate members of the ICOC, and the Chair of the ICOC. The list of scientific members who may participate in the GWG review can be found at http://www.cirm.ca.gov/WorkingGroup_GrantsReview. The composition of the ICOC can be viewed at http://www.cirm.ca.gov/GoverningBoard.

The fifteen participating scientists on the GWG will evaluate the applications and score them according to scientific and technical merit, applying the review criteria described below.

If the number of applications submitted in response to this request is significantly in excess of the number that the GWG can review in a single session, GWG members will conduct the review in two stages. In the first stage, reviewers will conduct a pre-review of applications to advance a subset of applications to second stage, the full GWG review described below. Those applications that are not advanced to the second stage will not be recommended for funding.

The Application Review Subcommittee will make final funding decisions giving consideration to the GWG recommendations and any CIRM team recommendations.

Consideration of Past CIRM Award Information (If Applicable)

The GWG may consider information from a previously funded and related CIRM award as part of its review. CIRM will provide the GWG with objective information regarding a related award that CIRM, in its sole discretion, deems relevant, including but not limited to achievement of specific milestones, data, and outcomes for a related CIRM award or awards.

A "related CIRM award" includes: (1) an award for which the applicant PI served as the PI, a co-PI, a co-investigator, or otherwise substantially participated in the conduct of the award; (2) an award involving the same research project or product; or (3) an award that includes overlapping team members.

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Confidentiality

CIRM's confidentiality and conflict screening rules apply to everyone who will have access to applications or who will attend any review meeting in which confidential information is discussed, including but not limited to CIRM team members, reviewers and members of the ICOC. (Per Gov. Code §6254.5(e), non-public records may be disclosed to government agencies under confidentiality agreements.)

How will the scientific merit of an application be evaluated?

Scientific and patient advocate members of the GWG will evaluate applications and the scientific members will score them based on the key questions below.

1. Does the project hold the necessary significance and potential for impact?

Is the proposed project likely to result in a maximum amount of useful genetic data that will enhance the value of CIRM's hiPSC bank for the identification of disease associated and drug sensitive alleles?

2. Is the rationale sound

Is the proposed project based on sound scientific and technical rationale? Is the preliminary data compelling and supportive of the proposed project? Are the proposed technologies efficient?

3. Is the project well planned and designed?

Is the project appropriately planned and designed to meet the project deliverables of this award? Is there a thoughtful plan in place for coordination amongst the investigators to generate DNA (if applicable) and to format and add the new genetic data to the Coriell searchable line specific clinical database? Is there a feasible plan to deposit data into a controlled access public database such as dbGaP? Are potential pitfalls identified and alternative approaches presented?

4. Is the project feasible?

Are the proposed milestones logical and the deliverables likely to be achieved within the proposed timeline? Is the proposed team appropriately qualified and staffed? Does the team have access to all the necessary resources to conduct the proposed activities? Is the budget appropriate for the research proposed?

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Application Components and Submission

How does one apply?

Applications must be completed and submitted online using the CIRM Grants Management Portal at https://grants.cirm.ca.gov. Any prospective PI must create a login in the system to access application materials and apply. Applications are available in the system only to the PI. A PI may submit only a single Challenge Award application.

Applications are due by 2:00 pm PDT on March 30, 2016.

What components does an application include?

The Grants Management Portal provides instructions for completing all the necessary components and submitting a final application. The application is designed to collect information necessary to appropriately evaluate the proposal and for CIRM to rapidly initiate an award if approved for funding. Applicants are required to indicate key personnel involved in the project, describe how the proposal addresses the objective of the partnering opportunity, provide a detailed plan of proposed activities, and prepare and justify an appropriate budget.

The main components of the application include the following key sections:

1. **Application Preview Page:** This section may serve as a basis for enabling GWG members select a subset of applications to advance to the second and final stage of review.

   Synopsis of key information including impact and summary of proposal, including when applicable:

   - DNA extraction and/or library generation
   - Genotyping platform
   - Data analysis
   - Data sharing

2. **Statement of Significance and Impact:** Description of how the proposed genetic analysis could enhance the value of CIRM's hiPSC bank for the identification of disease associated and drug sensitive alleles.

3. **Objective and Milestones:** A concise description of the project objective and project milestones (template provided), and criteria for success.

4. **Rationale:** Summary of the scientific and technical rationale for the proposed research including previous achievements or preliminary data using proposed genetic and analysis technologies.

5. **Research Plan**: A concise but detailed description of methods and techniques to be employed to achieve milestones and potential pitfalls and alternatives approaches.

6. **Data Sharing and Collaboration:** A description of the plans for sharing analyzed and raw data with the general research community, and plans for coordinating project activities with Coriell and any other key contributors.

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7. **Timeline**: Activities-based timeline for achieving project milestones.

8. **Principal Investigator and Team:** A description of the PI and team's expertise and experience.

9. **Resources and Environment:** A brief description of the resources available to the project and environment.

10. **References**

Who are Key Personnel?

In the application, we ask you to identify by name pertinent Key Personnel and their specific roles on the project. Key Personnel are defined as (1) the principal investigator or program director; or (2) any other person, including an independent consultant or an employee of a Subcontractor or Partner, who is expected to contribute to the scientific development or execution of the project in a substantive, measurable way *and* who is expected to: (a) receive or has been promised income, or anything else of value, of $10,000 or more per year for his or her contribution to the project or (b) contribute one percent (1%) or more effort to the proposed project. "Key Personnel" does not include a person who is expected to be involved in the proposed project but who does not satisfy conditions (1) or (2).

Individuals who do not meet the definition of Key Personnel may be supported with CIRM funds, but should not be identified by name in the application. Such unnamed personnel may be referenced indirectly by their role on the project (e.g., technician). The budget includes a line item for requesting support for unnamed personnel.

What should one know before preparing the budget?

Budgets must be justified in detail, including all subcontracts and consulting fees, including, if applicable, any additional costs that would be funded from another source. Allowable Project Costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy for Discovery and Translation Stage Programs. Generally, project costs for personnel, supplies, travel, equipment, and subcontracts may be claimed. Limits for specific cost categories must be observed.

What are Direct Facilities Costs?

Direct Facilities Costs are the general operating costs of the grantee's facilities attributable to housing all elements of the CIRM-funded project or activity. Facilities costs for non-profit applicant organizations are limited to the current applicable, federally negotiated rates for the organization as defined by the Office of Management and Budget (OMB) Circular A-21 or A-122. Facilities rates for for-Profit applicant organizations are limited to 35% of the direct project costs. Facilities rates are applied to direct project costs exclusive of the costs of equipment, tuition and fees, research patient care costs, as well as the costs of each individual subcontract, consultant, and service agreement in excess of $25,000. The facilities cost rates approved and in place at the time of the application are to be applied to the entire award project period.

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How much can an applicant claim for indirect costs?

For-profit organizations cannot claim indirect costs. For non-profit organizations, indirect costs will be limited to 20% of allowable direct research funding costs awarded by CIRM (i.e., project costs and facilities costs), exclusive of the costs of equipment, tuition and fees, research patient care costs, as well as the costs of each individual subcontract, consultant, and service agreement in excess of $25,000. The indirect cost rate budgeted at the time of application is to be applied to the entire award project period.

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Award Administration

Issuance of Award

A CIRM award is issued via a Notice of Grant Award (NGA), which is the formal contract that defines the terms and conditions of an award and documents the commitment of funds from CIRM. CIRM reserves the right to modify or establish funded project activities and the associated budget prior to issuance of the NGA. CIRM also establishes project milestones, success criteria and timelines for milestone achievement at its sole discretion after consultation with the PI and based on information provided in the application. CIRM may also review key contracts/agreements that are critical to the success of the project for compliance with CIRM's policies and regulations.

Payments and Reporting

Upon execution of the NGA, CIRM will issue an initial payment; subsequent disbursements will be made as outlined in the NGA. Continued CIRM funding is contingent upon timely scientific progress against milestones as outlined in the project milestones and timelines established under the NGA. Where project milestones are not timely met, CIRM reserves the right to either redirect resources to maximize the project outcome or, at its sole discretion, to suspend payment and/or terminate the project.

Grantees will be required to provide periodic written progress and financial reports to CIRM. CIRM will partner with the grantee to foster the success of the project. Grantees will have ongoing communication with the CIRM Program Officer throughout the duration of the award, typically meeting by teleconference and periodically in person.

No-Cost Extensions

Timely progress on funded projects is of critical importance to CIRM. Therefore, CIRM will consider a one-time, No-Cost Extension (NCE) request of no more than 6 months, submitted at least 30 days before the project end date. Such requests should properly justify how such an extension will advance the project towards its expected outcome, but Grantee should not assume CIRM will approve a NCE request.

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Contacts

For information and assistance with this program announcement please contact:

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Definitions

"California organization" means: An entity, regardless of profit status, that has >50% of its employees located in, and paid in, the state of California, and conducts the award activities from the California location.

"For-profit organization" means: a sole-proprietorship, partnership, limited liability company, corporation, or other legal entity that is organized or operated for the profit or financial benefit of its shareholders or other owners. Such organizations also are referred to as "commercial organizations".

"Non-profit organization" means: (1) a governmental entity of the state of California; or (2) a legal entity that is tax exempt under Internal Revenue Code section 501(c)(3) and California Revenue and Taxation Code section 23701d.

"Partner" means an organization that, in exchange for the right to the opportunity for a future financial return, has (1) agreed to provide matching funds for the proposed project or (2) entered into an agreement with the applicant organization relating to the commercialization of the proposed project. Partner does not include an organization that, like the National Institutes of Health, provides research funding to a proposed project but that does not have the right to a future financial return

"Subcontractor" means an organization (other than the applicant organization) that is expected to: (a) contribute to the scientific development or execution of the project in a substantive, measurable way *and* (b) receive $25,000 or more through the proposed project. "Subcontractor" does not include suppliers of widely available goods.

Appendix

CIRM Regulations

Grant awards made through this PA will be subject to all applicable CIRM regulations. These regulations can be found on CIRM's website at http://www.cirm.ca.gov/reg/default.asp.