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CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

DISC4: Pre-submission Informational Webinar Frequently Asked Questions

ADDITIONAL RESOURCES FOR APPLICANTS

- The Pre-submission form is available in the CIRM Grants Management Portal
- DISC4 Program Announcement (PA)
- Grants Administration Policy for Discovery, Translation, and Education Projects
- DISC4 Webinar can be found here on our website

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PROJECT SCOPE AND PROJECT ELIGIBILITY

1. **What is CIRM's ideal project for DISC4?**

   DISC4 awards were designed to support CIRM's strategic goal to identify novel, high-quality targets through a deliberate emphasis on disease mechanism research. The scope and structure of the DISC4 awards is flexible and intended to support teams pursuing ambitious, cross-disciplinary science across a wide range of disease areas and topics.

   Competitive DISC4 projects should articulate an ambitious scientific question with strong relevance to the understanding of human diseases. Projects should be well positioned to leverage innovations in stem cell or genetic research and meaningfully integrate different disciplines/technologies/specializations to address their core questions. The team should have a well-considered plan to accelerate translation of any new scientific insights that emerge into early therapeutic or biomarker development.

2. **What is an example of an acceptable use case for animal models?**

   We do not have examples of acceptable use cases. DISC4 proposals should be human-centered, but use of non-human models can be included if it would be highly impactful or necessary to achieve specific objectives. We invite applicants to consider relevant human tissue/models as alternatives where possible. If you believe your use case fits the scope of DISC4, please provide justification in your application.

3. **Ideally, how much of the project should focus on specific disease areas? Would developing a platform technology be suitable?**

   Research questions do not need to be focused on a specific disease or disease area. For example, projects might focus on common biological processes that impact multiple disease types and organ systems. Technology development and other research activities and approaches can be included in DISC4 proposals, as long as the project eligibility requirements are fulfilled.

4. **How does this program differ from DISC2, aside from increased budget/scope? Will the DISC2 Awards open in 2025?**

   The team composition, intent and expected outcomes are different. DISC4 supports large, multidisciplinary teams pursuing foundational research to elucidate disease mechanisms and discover novel targets. In contrast, DISC2 awards projects must be designed to culminate in the nomination of a therapeutic development candidate with demonstration of disease-modifying activity by the end of the award period.

   *DISC4 awards are **not** intended to support development of existing therapeutic or biomarker candidates. Major aims should not be focused on development activities, especially where study designs do not address current knowledge gaps beyond efficacy, safety and*

biodistribution readouts for a limited set of candidates. Proposals focused on developing a candidate will not be invited to submit an application.

CIRM does not currently anticipate offering DISC2 (Quest Awards) in the future but may, pending board approval, issue a new funding opportunity that would support a similar objective. Currently, investigators with interest in optimizing or advancing a therapeutic approach are encouraged to explore CIRM's new Preclinical Development Awards program.

5. **Should the proposal be structured as a program project grant where each PI/co-I is responsible for one project, or as a single project grant where multiple PI/co-Is interact with each other for each of the aims?**

   There are no requirements or restrictions on how the project should be structured. Each PI/co-I can be responsible for one project, interact, or work through a mixture of both scenarios. Regardless of the structure, the overall proposal should have significant added value as an integrated collaboration rather than as a series of independent projects.

6. **In what ways can stem cells can be incorporated into the approach? Can stem cells be considered primarily as tools, such as iPSCs for generating different cell types, or is the focus on stem cell biology and their use as therapeutics?**

   Yes. The project eligibility requirement (PA page 7) specifies that the "proposed project must include studies that employ human stem cells or genetic research as part of the central approach or hypothesis". Application of stem cells including patient derived stem cells as models or tools for studying biological phenomena is considered to satisfy this requirement.

7. **To what extent is CIRM is interested in understanding the mechanism of disease? Would DISC4 support purely mechanistic/discovery research, or should we include a possible route of translation?**

   Elucidating disease mechanisms is critical for identifying new targets and biomarkers, a key strategic goal that was defined in CIRM's Strategic Allocation Framework (See Goal 1). For this reason, the primary focus of DISC4 projects should be on generating novel foundational or mechanistic insights into disease biology as a basis for discovering new targets or biomarkers. Applicants are encouraged to consider incorporating elements in their overall proposal that could facilitate the progression of potential findings into future translational efforts, for example inclusion of validating studies in disease models etc. Applicants may elaborate on their plans for facilitating progression at both the pre-submission stage as well as the full application stage.

8. **Should DISC4 applications be focused on one disease or on multiple disease?**

   DISC4 was designed to support a wide range of research questions related to disease biology that would benefit from the integration of multiple disciplines. Applicant teams may focus on common biological processes across multiple disease indications or apply a range of different techniques and tools to deeply interrogate one disease.

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9. **What conditions are included within the preference topic? Are disorders of the eye and sensory systems, pain and CNS cancers included? Would pain mechanisms in peripheral diseases be considered preferred?**

   In FY25/26, the preference topic includes all diseases, disorders and conditions that result from or lead to abnormal function of the nervous system - brain, spinal cord, and peripheral nervous system, including the sensory, motor and autonomic nervous systems. This definition includes brain cancers, neurological injury, stroke, diseases of the retina, and pain amongst other conditions commonly considered as neurological disorders.

10. **Can we apply to CIRM if we are studying neurodegenerative diseases but have not yet used stem cells?**

    Applicants must include studies that employ human stem cells or genetic research as part of the central approach or hypothesis to be explored. Relevant preliminary data to support the major concepts, approaches, and team's ability and expertise to execute on the proposal should also be included. See the "Eligibility" section of the PA for additional information.

11. **Does this award support generating and validating patient-derived models, rather than hypothesis-driven studies?**

    A proposal does not have to be hypothesis-driven, as long as it meets the eligibility requirements to address knowledge gaps or bottlenecks in our understanding of human disease and includes studies that employ human stem cell or genetic research as part of the central approach. Creation of resources, such as new disease models, that can be useful to the broader scientific community is allowed, but the scope of the proposal should not be limited to deriving new cell lines, biobanking or model development alone.

12. **Does DISC4 support efforts for system digitalization, AI/ML collaborations?**

    Yes, AI/ML approaches or other computational components of projects are allowable, and requesting funds to support activities associated with these aims is allowed, including local data management, digitalization, and computing resources. You may also budget for funds to enable data sharing and collaboration.

13. **Are bioinformatics and genomics expected to be part of all DISC4 applications?**

    We expect DISC4 proposals to be expansive, multidisciplinary, and innovative, but there is no requirement to include genomics or bioinformatics. It is possible to have a project that satisfies the eligibility criteria and not have these elements.

14. **Can proposals focus on aging biology as a primary target, or must aging be studied in the context of specific age-related diseases?**

Proposals may focus on common biological processes that impact multiple diseases or organ/ systems, including the biology of aging, and do not have to be in the context of any specific disease. However, scientific reviewers will consider the potential significance and impact of the proposal in the context of advancing our understanding of human diseases (see review criteria p14 of PA).

15. **Is reverse translation within the scope of this award? If I already have a cell therapy target, but I would like to conduct studies to better understand the mechanism of action. Would that be within the scope of this award?**

    Yes. Reverse translation research is a valuable and complementary framework. Studies could be within scope if they are designed to contribute to our understanding of health and disease outside the context of a specific cell therapy candidate. If the knowledge resulting from the proposal is limited to supporting the clinical success of your therapeutic candidate, then the proposal would likely be deemed too product focused. CIRM supports preclinical and clinical development efforts through other award programs, please check out our website to find the most appropriate program for your goals.

16. **Is high-throughput screening (HTS) or other related techniques allowed?**

    There are no specific requirements, restrictions or preferences for research tools or approaches. Applicants are encouraged to propose the most impactful combination of research technologies or approaches relevant to their objective. They should ensure that all other project eligibility requirements are fulfilled (stem cell, genetic research, non-human models, unallowable activities, etc. see PA page 7-8).

17. **Are mechanistic clinical trials and/or a prospective observational clinical/biomarker studies allowable under the DISC4 mechanism?**

    The DISC4 program supports foundational disease biology research that may include reverse translational studies, including those using clinical samples or data, and basic research involving human subjects, provided the study is not subject to FDA oversight or regulation. Observational clinical studies may be allowable as a component of a project if they are aimed at achieving the expected outcomes of a DISC4 award and all necessary consents and institutional approvals are obtained.

    DISC4 will NOT support the conduct of clinical trials, whether interventional or mechanistic, that involve drugs, products, devices or other interventions subject to FDA oversight or regulation. Use of biosamples or data derived from such trials, however, would be allowable if all consents are in place.

    DISC4 will NOT support activities aimed at preclinical or clinical development of therapeutic candidates. Those activities are targeted by CIRM's PDEV and CLIN2 programs for which new PAs will be posted this month. Please sign up to receive email notification when those PAs are posted.

18. With regard to the "genetic" and "stem cell" requirements, does "genetic" modification have to occur in stem cells themselves?

All projects must include studies that employ human stem cells or genetic research as part of the central approach or hypothesis.

"Stem cells" include any progenitor and precursor cells that retain the ability to divide and give rise to differentiated cells. "Genetic research" is defined as studies that alter genomic sequences of cells (edit, remove or add DNA sequences); or introduces or directly manipulates nucleic acids (e.g., coding and non-coding RNAs, antisense oligonucleotides) in human cells.

Genetic research does not need to be applied to stem cells to meet the above requirement.

INDIVIDUAL AND TEAM ELIGIBILITY, ORGANIZATION ELIGIBILITY

19. Can there be overlap with a recently submitted DISC0?

No. CIRM will not consider pre-submissions that have scientific overlap with applications pending review or active awards. If the submitted DISC0 application is withdrawn, you may submit a DISC4 pre-submission that includes some elements of the DISC0 application.

20. How many co-investigators can be from the same institution? Are there any limits on co-investigators from different institutions?

The core team must include one principal investigator (PI) and at least four co-investigators (Co-Is). There are no limits to the number of Co-Is, but all Co-Is must adhere to the requirements listed in the PA. At least one Co-I must be based outside of the PI's organization. There are no limits to the number of institutions involved with any application.

21. Is DISC4 restricted to academic labs or can startups apply?

DISC4 is not restricted to academic labs. The focus of DISC4 is on foundational and mechanistic understanding of diseases with the expectation that these will be integrated into translational pathways in the future. We encourage any academic and/or for-profit team to apply or consider collaborating on a DISC4 application if their research aligns with the objectives of DISC4.

22. What do you mean by multi-institutional? Can different departments from the same university be considered?

At least 1 member of the core team must be employed by a different CA organization from that of the PI. Different departments within the same institution are not considered distinct institutions for this funding mechanism.

23. Can you give examples of 'relevant translational/industry expertise'?

To encourage the integration of multiple disciplines, at least one member of the applicant team (PI, Co-I, or Key person) must possess relevant translational/industry expertise, relevant clinical expertise and relevant bioinformatic and/or computational expertise.

There are no formal requirements or definitions for any of the above expertise requirements. These requirements may be fulfilled by any member of the broader team (Core members or key personnel). Invited teams will need to identify the team member that fulfills each requirement and provide a brief explanation in their full application. ***This is not required at pre-submission.***

In general, relevant translational/industry expertise should include experience that would help accelerate discoveries toward preclinical development. Examples may include experience advancing a therapeutic product, developing commercial strategies for products, or participating in discussions with regulatory bodies, etc.

24. What is CIRM looking for in a collaborative team? Do you emphasize expertise in the area of research or new perspectives and tools?

Either or both. We hope to support teams that are looking to integrate different disciplines, expertise, perspectives to address ambitious research questions in disease biology. Proposals may include efforts to develop or optimize new approaches and tools. Reviewers will "assess the extent to which the project cuts across silos or employs a unique synergy of technologies or disciplines to understand human disease." – see Review Criteria for Full Applications, on page 14 of the DISC4 PA.

25. Are out of state academic collaborators that would be co-inventors on IP or co-authors on publications acceptable?

An out of state collaborator can be a co-inventor, however the rights to the invention must be assigned to the Awardee Institution.

Out of state academic collaborators are encouraged to be co-authors on publications with the Award PI which will allow them to fall outside the independent publication restriction on allowable costs.

26. What are the IP obligations if a California based start-up receives part of a grant?

In general, a collaborator who receives CIRM funds and obtains ownership rights to inventions or data will have the CIRM IP Regulations, including, for example, revenue sharing, apply.

27. Can 2 or more members of a Core team (PI/Co-I) be from the same lab e.g. lab head and staff scientist ?

No. Each Co-I on a CIRM application must fulfill several requirements (see common requirements document) to be eligible for consideration for CIRM funding:

- *Must be an employee of a California-based organization and be accountable for the conduct of the proposed project to their California-based organization*
- *Must not currently have another application that is substantially similar or has overlapping activities pending review or approval under any CIRM opportunity*
- *Must meet the same institutional qualifications that would be expected of a PI*

Members of the DISC4 core team CANNOT be from the same lab since only one can be accountable for the conduct of the proposed project to their CA-based organization.

28. Can the project team include investigators outside of CA or outside of the US?

Non-CA-based investigators, including those outside the US, are not eligible to serve as PI or Co-I on DISC4 awards. However, DISC4 applicants are allowed to budget grant funds to support a non-CA-based collaborator through a grant subcontract, provided the out-of-state organization DOES NOT retain the intellectual property or independent publication rights of any intellectual property (e.g., invention, technology, data) arising out of the CIRM-funded project.

Optionally, collaborating non-CA investigators and organizations may contribute research activities or unique resources to the overall project at no cost to the team (in-kind contribution). If qualified as matching funds, these contributions would allow the applicant team to request additional CIRM funding. Applicants should refer to the section on "Matching funds" in the PA (page 7) to learn more.

29. Can the PI or a member of the core team be someone with no background in regenerative medicine?

Yes. The DISC4 program is intended to bring together different expertise and approaches to generate novel insights. There is no requirement for core team members to have a background in regenerative medicine. Applicant teams should ensure, however, that the appropriate leadership and expertise is in place to achieve stated objectives.

Note: to encourage cross-disciplinary proposal, the broader applicant team (Core Team and Key Persons) must include members with specific relevant expertise (see PA page 8) and include an experienced Data Project Manager (Full Application only).

BUDGET, AWARD DURATION, AND AWARD NUMBERS

30. How do I determine whether CIRM considers a cost allowable?

When not otherwise specified by CIRM regulations, CIRM applies the Office of Management and Budget cost allocation principles including the determination of whether costs are 1) reasonable, 2) allocable, 3) consistently treated, and 4) adhering to any other limitations set

forth by the PA/RFA or Notice of Grant Award. For more information, see the NIH Cost Principles. CIRM encourages grantees to use these cost principles to make their own determinations on cost allowability given CIRM cannot make a judgment on every cost scenario.

Allowable project expenses encompass, yet are not restricted to: personnel salaries, fringe benefits, specified supplies, tuition and fees, research animal expenditures, consulting fees, itemized clinical study outlays (encompassing research patient care costs), travel-related disbursements, project-related equipment, publication expenses, service agreements, subcontracts, and delineated administrative costs necessary for executing the endorsed project.

Please see the Grants Administration Policy and FAQ on Allowable Project Costs for more information.

31. Is there a resolution for the indirect costs of subawards not going into the direct cost budget of the primary institution?

The DISC4 awards supports up to $13,000,000 total costs. The total cost cap is inclusive of all direct, facilities, and indirect costs from the prime applicant and subcontractors.

32. Does the subrecipient need to follow CIRM's Facility Cost / IDC policy, or can they apply their own indirect cost rate?

Your subcontractor would include the full amount of overhead they are eligible for under CIRM regulations as part of their subcontract budget. The full cost of the subcontract budget (direct+ indirect) is entered in the prime budget as a direct cost. Our funding calculator will automatically exclude the amount of any subcontract over $25,000 from generating F&A to the prime applicant.

33. Can we have international collaborators so long as they aren't co-I nor "retain intellectual property or independent publication rights"?

Non-CA collaborators, including international collaborators, cannot be listed as a Co-I. They can be listed as key personnel or subcontractors, provided the out-of-state organization DOES NOT retain the intellectual property or independent publication rights of any intellectual property (e.g., invention, technology, data) arising out of the CIRM-funded project.

34. Can matching funds be used to support equipment purchase/support?

As outlined in the PA, eligible matching fund contributions must take the form of either:

(i) Unique resources that will be leveraged by the project team e.g. cell-lines, biosamples, research/computational resources, etc.; or

(ii) Independently funded activities undertaken during the award period to generate data or resources that will be leveraged by the project team during the award period.

Matching fund contributions should be provided by a non-CIRM source. Equipment or other forms of contribution may be allowed if they satisfy any of the above conditions.

PRE-SUBMISSION AND REVIEW PROCESS

35. How binding is the Pre-Submission proposal?

The project described in the full application should largely reflect the project that was presented in the pre-submission proposal. During the formal eligibility assessment of full applications, CIRM will verify that this is the case. As invited teams will have the opportunity to consult with CIRM program officers during the preparation of their full applications, they will have the opportunity to discuss any changes that they anticipate and CIRM will advise whether the changes are significant enough to preclude invitation.

36. How will the Pre-submission forms be evaluated?

Pre-submissions are evaluated and ranked by CIRM Science Officers according to criteria described in the PA (page 10), including alignment with the preference topic. The goal is to identify the proposals that are most aligned with the objectives of this program to move forward to a formal scientific/merit review. Pre-submissions are not evaluated for feasibility, scientific merit or the composition of the team.

37. How will Neurological Diseases be prioritized? At what stage of the review process?

Neurological conditions and diseases of the brain, spinal cord or peripheral nervous system are prioritized at the pre-submission stage. Proposals that include these conditions as part of its main focus, including as part of a cross-disease proposal will receive a scoring advantage. If invited, all full applications will be scored on an equal footing by scientific experts of the Grants Working Group according to the review criteria described in the PA, without regard to research topic.

38. Are there priority neurological diseases (e.g. more priority in more prevalent vs. more rare diseases)?

No preference or priority will be specifically given to the study of diseases of higher prevalence at the pre-submission stage. However, scientific experts of the Grants Working Group are asked to consider a project's potential for broader impact (see Review Criteria: Significance, PA page 14).

39. Is the CNS/PNS preference designed to fill a quota, or will CNS/PNS projects get advantaged regardless of the number of pre-submissions?

There is no predetermined quota for invitations or approved awards in the preference area. Pre-submissions that align with the preference topic will receive an additional weight to their score. (see page 10 of PA for other alignment criteria). The total number of submissions

invited representing the preference area or non preference area will depend on the number, type and program fit of received pre-submissions.

CONTACT AND OTHER RESOURCES

40. What do new applicants need to know about the CIRM application process?

As a first-time applicant, you should look through the resources at the top of our FAQ. You should also be familiarized with Authorized Institutional Officials (AOOs), the individual with the signature authority for an institution that is submitting a full application ***(not required at pre-submission****). The AOO must be "cleared" by our Grants Management Team before the final application is considered submitted, which can take up to a week. The submission process takes place in 2 steps: the PI will submit their application first, which is then routed to the AOO. The approved AOO must log in and co-submit through their own interface.*

There may be significant differences in application form and templates between CIRM programs and NIH or other funding agencies. First time applicants are advised to familiarize themselves with CIRM application portal and upload templates and other material well ahead of the deadline.