CALIFORNIA'S STEM CELL AGENCY

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

PA 14-01: CIRM Accelerated Development Pathway

I. Purpose

Through the Disease Team (Disease Team Research or Therapy Development) and Strategic Partnership Award programs, the California Institute for Regenerative Medicine (CIRM) currently supports a number of development programs in stem cell research that will include an early phase clinical trial. In appreciation of the urgency of CIRM's mission to bring stem cell therapies to the people of California, and in accordance with CIRM's 2012 Strategic Plan and with a strong recommendation from CIRM's Scientific Advisory Board, CIRM is focused on identifying and accelerating development of high-potential programs, particularly those that may demonstrate clinical proof of concept during, or before, the year 2017. To accomplish this goal, the Agency has been authorized by the Independent Citizen's Oversight Committee (ICOC) to invite its current grantees in these programs (Disease Team and Strategic Partnership), who are already funded to conduct a clinical trial, to compete for recommendation into an Accelerated Development Pathway, and to provide a pathway for future grantees to participate in the program.

The aim of this program is to provide selected applicants who are making rapid progress with additional resources and financial support to accelerate their stem cell-based therapy towards demonstrating evidence of an acceptable safety profile and clinical proof of concept. An applicant team will be asked to propose new, complementary activities that reflect their early progress and which, if conducted concurrently with the on-going funded project, could significantly accelerate and advance their program, yet cannot be pursued without disrupting their original timeline and budget. For example, a team could propose additions to an ongoing CIRM-funded clinical trial that would accelerate development decisions such as including the testing of a biomarker they identified in correlated research work or adding a patient group based on data from an unblinded safety study. Other examples of accelerating activities could include changes in manufacturing processes or delivery devices, based on novel ideas that emerged from the activities of the initial award or related research, that could require comparability studies to facilitate development of the candidate therapeutic. In addition, the Accelerated Development Pathway would also consider the possibility of funding a future clinical trial to demonstrate clinical proof of concept in the approved therapeutic indication, subject to satisfaction of milestones and conditions. The applicant must indicate how the proposed new activities arise from related development activities and

demonstrate how they will change, augment, and accelerate the goals of the original grant.

For those programs that apply and are not recommended for inclusion into the Accelerated Development Pathway, this review process is not intended to be a mechanism for modifying their current award and funding structure.

For future grantees, and current grantees whose projects are not yet mature enough for the Accelerated Development Pathway, CIRM expects to offer future opportunities to compete for selection into the Accelerated Development Pathway.

II. Objectives and Scope

A. Objective

The objective of the Accelerated Development Pathway is to advance development of projects with a stem cell-based therapeutic in the CIRM Disease Team and Strategic Partnership portfolio, particularly those that have the potential to reach clinical demonstration of an acceptable safety profile and proof of concept during, or before, 2017.

Grantees that are recommended by the CIRM Grants Working Group (GWG) and approved by the ICOC to enter the Accelerated Development Pathway will have additional access to guidance from the CIRM Scientific Staff and CIRM's external regulatory, development and business advisors. By permitting grantees to engage in high impact development activities concurrently, rather than sequentially, and by committing to subsequent clinical trial support, this program will provide a streamlined, expedited pathway for the funding of key development activities that could accelerate reaching clinical proof of concept.

Disease Team (Disease Team Research or Therapy Development) and Strategic Partnership awardees that apply for recommendation into the Accelerated Development Pathway will be asked to provide descriptions of, and budgets for, additional key development activities that could accelerate their progress toward demonstration of clinical safety and proof of concept for the funded therapeutic candidate and clinical indication. The new activities proposed would be expected to fall outside the work plan described in their approved award (e. g., the "Parent Award"), yet would be identified as a means to advance and support the strength and overall progress of their development program. In addition, applicants that are funded to conduct an early phase clinical trial which is primarily assessing safety endpoints, may propose a follow-on clinical trial designed to demonstrate clinical proof of concept. Any funding for Accelerated Development activities will be dependent on meeting agreed-upon milestones and providing sufficient justification for proposed activities, and would require that the additional activities could not be accommodated by redirection of funds from a team's current Parent Award.

For recommendation into the Accelerated Development Pathway, CIRM aims to identify project teams that are currently funded to conduct a clinical trial to support the development of a stem cell-based therapeutic which has the following:

1. The potential to have a major clinical impact for patients (e.g., addresses an unmet medical need, fills a void in medical care or may substantially improve patient outcomes).
2. The support of a clear and realizable Development Plan with realistic timelines.
3. Management by a strong, credible team with expertise and experience in product development and a track record with CIRM that demonstrates the ability to execute on plans.
4. Addresses a disease or injury type for which there is the ability to measure a treatment effect on an accepted clinical endpoint or biomarker of activity relevant to the disease (e.g., a signal of sufficient strength to progress a project into a pivotal, registrational clinical trial).
5. A strong scientific, operational and business case to support the proposition that additional resources will accelerate the project.

B. Scope

The Accelerated Development Pathway Program (PA 14-01) is directed to those teams that currently hold an active Disease Team (Disease Team Research or Therapy Development) or Strategic Partnership Parent Award that includes funding for an early phase clinical trial. Applications will only be accepted at this time from those grantees who already hold a Disease Team or Strategic Partnership Parent Award that meets this description.

Funding under the Accelerated Development Pathway may only be used to support activities using the therapeutic candidate approved for funding under the original Disease Team or Strategic Partnership Parent Award. New, additional activities proposed in the current application should fall outside the plans of the Parent Award and would be expected to accelerate the program so as to meet the objective of demonstrating an acceptable clinical safety profile and evidence for proof of concept. Activities would be projected to enhance the attractiveness of the therapeutic program for external investment, partnering or commercialization. These may include, but are not limited to, the activities listed below:

- Introduction of additional endpoints into the design of a funded clinical trial, such as imaging assessments or monitoring immune responses, that would provide data essential to demonstration of clinical proof of concept and could better inform decisions for subsequent pivotal clinical testing on a registration pathway.

- Inclusion and initiation of additional clinical sites to accelerate enrollment of an on-going clinical trial.

- Conducting supporting clinical or nonclinical studies to incorporate additional biomarkers or assays designed to correlate treatment effects with a clinically meaningful outcome or to identify relevant subsets of patients for further examination.

- A follow-on clinical trial designed to demonstrate clinical proof of concept, if the initially-funded clinical trial was focused primarily on assessing safety.

- A follow-on clinical trial that focuses on a different candidate patient population in the funded therapeutic indication, or focuses on a closely related therapeutic indication (e.g., that would not require a re-evaluation of rationale and impact), or uses an improved delivery method.

- Accelerated development and qualification of a medical device for improved and/or more efficient delivery of the product to be administered in the approved clinical trial.

- Process development activities that could enhance further development of the therapeutic candidate, such as optimization of cGMP production or development and validation of a potency assay.

- Manufacturing improvements or scale-up activities designed to increase efficiency and/or decrease costs associated with manufacturing the stem cell therapeutic.

- Supporting studies to demonstrate comparability or “bridging” of an optimized therapeutic candidate into the development pathway, following manufacturing scale-up or process improvements.

Activities that fall outside the scope of the Accelerated Development Pathway include the following examples:

- Phase 3 clinical studies.

- cGMP manufacturing for Phase 3 studies.

- Clinical trials using second generation candidate molecules or compositions.

- Clinical trials testing the candidate in a different therapeutic area (e.g., one which would require re-evaluation of rationale and impact).

- Non-interventional clinical studies; clinical studies not involving administration of the proposed therapeutic; or research studies using samples not from subjects of the proposed clinical studies.

- Development and qualification of a medical device for the delivery of a product other than the therapeutic agent proposed in the funded project .

- Development activities that are the subject of a definitive funding obligation by a third party, such as an agreement with a biopharmaceutical partner.

III. Award Information

Applications will only be accepted from those Disease Team and Strategic Partnership awardees who are already funded to conduct a clinical trial under an active CIRM grant, and who will have participated in at least one assessment by a group of external experts, the Clinical Development Advisory Panel (CDAP), prior to review of the applications by the GWG. Submitted applications will be reviewed by the GWG, according to review criteria described in Section VII, and programs will be recommended to the ICOC for inclusion in the Accelerated Development Pathway.

For those applicants that are accepted into the Accelerated Development Pathway following GWG review and ICOC approval, the teams will gain additional access to scientific, development, regulatory, and business advice from CIRM staff and consultants, as needed, to facilitate progress and address development issues that may arise. For academic applicants, this may include engaging their technology transfer offices in a supportive role to advance the team's efforts. The teams will be expected to work actively with CIRM Science Staff and the CDAP to further define areas for potential acceleration of their development plans, while maintaining progress and good standing on their agreed-upon milestones. In addition, the teams in the Accelerated Development Pathway that are successfully meeting their agreed-upon milestones will have access to additional funding for in-scope activities (as described in Section II.B) that are necessary to accelerate the development of their stem cell-based therapeutic. Additional financial support will be through two potential forms: Supplements to the related, active Disease Team or Strategic Partnership award (e.g., the Parent Award); and/or a new award to support an approved clinical trial.

Under this Program Announcement, CIRM intends to commit up to $200 million in future funding to facilitate timely progression of designated Disease Team and Strategic Partnership programs to clinical demonstration of safety and proof of concept. Applicants to the Accelerated Development Pathway will be asked to propose for GWG review additional in-scope activities, such as those described in Section II, and a supporting budget for each, with a clear description of how the additional activities would accelerate their development programs. Review criteria are described in Section VII. For each team accepted into the Accelerated

Development Pathway, CIRM will set aside up to a maximum cap per project team of $25 million in total cost funding. Pursuant to this Program Announcement, on an activity-based need and with adequate budget justification, CIRM will consider issuing awards to fund recommended activities that will accelerate a team's progress toward demonstration of clinical proof of concept. Awards for activities funded through the Accelerated Development Pathway will be made in the form of Supplements to the Parent Award, or, in the case of a follow-on clinical trial, as a new award, as follows: up to a maximum of $5 million for manufacturing improvements, up to a maximum of $10 million for key development activities, and up to a maximum of $20 million to conduct a follow-on clinical proof of concept trial, with a cumulative cap per project of $25 million. The Accelerated Development Pathway is intended to streamline access to future funding and facilitate progress toward the objective of demonstrating clinical proof of concept and an acceptable safety profile of a stem cell-based therapeutic. Where a proposed activity will justifiably cost more than the CIRM maximum allotment, the applicant is expected to specify in the activity-based budget the non-CIRM funded cost and describe the source of funding in the budget justification.

For teams accepted into the Accelerated Development Pathway program, the CIRM Science Office and CDAP will continue to assess progress and milestones. Prior to a release of funds from the approved Accelerated Activities budget for a team, CIRM reserves the right to negotiate funded project activities, additional milestones, success criteria, timelines and budgets; members of the CDAP may be consulted, as needed, to help a team prioritize activities. Project progress for all successful applicants in the Accelerated Development Pathway will continue to be evaluated by the CDAP at key milestones and decision points such as the transition from IND filing to initiation of a clinical trial, and the transition from a safety trial to a proof of concept clinical trial. In addition, teams would be expected to continue sharing information with CIRM regarding their interactions with external regulatory agencies and review boards, as required to achieve the project's Development Plan.

CIRM recognizes that development programs for stem cell-based therapies are subject to many unique challenges, and may encounter unexpected delays. As a result of such a challenge or delay, if a project in the Accelerated Development Pathway program appears to no longer be likely to achieve clinical proof of concept during the proposed time frame, CIRM may determine that the Grantee would no longer be a participant in the Accelerated Pathway program but will continue only in its Disease Team or Strategic Partnership Parent Award agreement. Subject to the terms of the Parent Award and providing that the team remains in good standing, compliant with the regulations and requirements of the Disease Team and Strategic Partnership programs, the funding structure and requirements of the Parent Award would remain in place. However, access to the supplemental resources and funding associated with the Accelerated Development Pathway would no longer be available to the grantee.

IV. Award Mechanism

The mechanism by which funding is awarded under the Accelerated Development Pathway, will be in the same form as the related, active Disease Team or Strategic Partnership award (e.g., the Parent Award). For example, if the Parent Award is a grant, the supplement will be in the form of an amendment to the grant. If the Parent Award is a loan, then the supplement will be in the form of an amendment to the loan. However, funding approved for a subsequent clinical trial will be in the form of a new award, as opposed to a supplement to the existing Parent Award. In this instance, a for-profit grantee may elect (at the time of application) to have the award made in the form of a grant or a loan. Payments will be disbursed in accordance with a schedule set forth in the Grantee's Notice of Grant Award.

V. Eligibility

A. Project Eligibility

Eligible projects are those Disease Team and Strategic Partnership grantees that are already funded to complete a clinical trial, and who will have participated in at least one CDAP assessment of their program prior to the GWG review. At this time, applications will only be accepted from teams meeting these criteria, with current awards under the following RFAs:

RFA 09-01: CIRM Disease Team Research Awards (DR1)
RFA 10-05: CIRM Disease Team Therapy Development Awards (DR2)
RFA 12-05: CIRM Strategic Partnership I Awards (SP1)
RFA 12-09: CIRM Strategic Partnership II Awards (SP2)
RFA 13-01: CIRM Disease Team Therapy Development III Awards (DR3)

For future grantees, and current grantees whose projects are not yet mature enough for the Accelerated Development Pathway, CIRM expects to offer future opportunities to compete for selection into the Accelerated Development Pathway.

B. Institutional Eligibility

The applicant organization must be the grantee organization on the Parent Award.

C. Principal Investigator (PI) Eligibility and Percent Effort

It is CIRM's expectation that the PI and Co-PI (if applicable) on the existing Disease Team or Strategic Partnership Parent Award will remain in place if a program is entered into the Accelerated Development Pathway. The PI and Co-PI (if applicable) must have an M.D., Ph.D. or equivalent degree, and must be authorized by the applicant institution to conduct the proposed research in California. The current PI and Co-PI are expected to commit at least the percent effort committed

under their Parent Award to any activities awarded additional funding under the Accelerated Pathway program.

D. Co-Funding Requirements

Some eligible Parent Awards include a co-funding requirement that the Grantee match a portion of CIRM funding. If CIRM issues a supplement to a Parent Award that has a "matching" requirement, the same co-funding requirement will apply to the Accelerated Pathway supplemental funding. However, confirmation of matching funding would not be required until the activation of the Accelerated Pathway supplemental funding. If CIRM issues a new award for new clinical trial, and the Parent Award has a co-funding requirement, the Grantee will be required to provide matching funds equal to at least one- third (1/3) of the costs of the new award. The co-funding requirement may be satisfied, in part, through the provision of services, to the extent they are demonstrated to reduce the overall cost of the clinical trial. Such determinations will be made by CIRM Staff.

The co-funding requirement, when applicable, is intended to encourage early engagement with funding sources that might support later stages of the Development Plan. Transition to external funding for Phase 3 should be easier if that external funder has been involved in earlier stages of development, and a smooth transition should accelerate progress toward a Biologics License Application (BLA) or a New Drug Application (NDA). An applicant subject to this requirement may request an Extraordinary Exception (see next section) to be allowed to submit an application which does not meet the co-funding requirement. Reviewers will be instructed to consider the absence of co-funding in their assessment of feasibility.

As noted above, these considerations only apply to applicants whose Parent Award has a co-funding requirement.

E. Extraordinary Exceptions

In extraordinary circumstances, the President of CIRM has the discretion to permit exceptions to requirements or limitations in Section V. The exercise of such discretion will be only in exceptional cases where the applicant has demonstrated that such an exemption would preserve an important research opportunity or make a critical contribution to one of CIRM's mission objectives. Exceptions must be consistent with the intent and objectives of this Program Announcement and the requirements of Proposition 71 and California state regulations, or they will not be considered.

VI. Application and Evaluation Process

A. Application Review Process

Submission of an application for the Accelerated Development Pathway (PA 14-01) involves a two-step process. Eligible applicant teams that wish to apply for the CIRM Accelerated Development Pathway must first submit a non-binding letter of intent (LOI). Applicants will be notified if their LOI is **NOT** accepted. In the second step of the process, eligible applicants will submit a full application. Applications will only be accepted from applicants that have submitted an LOI that was accepted by CIRM.

As described in this Program Announcement, the application (see Section VIII) will include both a proposal for activities that could accelerate the team's progress, and an accompanying budget for each proposed activity. Applications will be reviewed by the CIRM Grants Working Group (GWG). The GWG is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's Governing Board (the ICOC), and the Chair of the Governing Board. The list of scientific members who may participate in the GWG review can be found at http://www.cirm.ca.gov/GrantsWkgGrpMembers. The composition of the ICOC can be viewed at http://www.cirm.ca.gov/GoverningBoard.

The fifteen participating scientists on the GWG will review the applications and score them according to scientific and technical merit, applying the review criteria described in Section VII. If the GWG feels that an application for the Accelerated Development Pathway would score more favorably if certain proposed new activities were removed from the application, the GWG may consider a motion to remove such activities and the associated funding request before scoring the application. The entire GWG will make recommendations regarding applications to be selected for participation in the Accelerated Development Pathway Program and an associated maximum funding budget for each team, based on the justified activities proposed in the application that are designed to accelerate progress to achieving clinical proof of concept and establishing an acceptable safety profile for a stem cell therapeutic. The ICOC's Application Review Subcommittee will make final decisions on which applicants may participate in the Accelerated Development Pathway program and an allowable budget for each team, based on the GWG recommendations, CIRM Staff recommendations and a programmatic review.

CIRM's confidentiality and conflict screening rules will apply to everyone who will have access to applications or who will attend the review meeting, including CIRM staff and external reviewers and members of the CDAP. (Per Gov. Code §6254.5(e), non-public records may be disclosed to government agencies under confidentiality agreements). The policies, procedures and laws that address confidentiality of records submitted to CIRM are described in Section XII.

VII. Review Criteria

The GWG will be asked to evaluate applications for the degree to which they achieve CIRM's priorities for this Program Announcement; namely, to identify project teams for acceleration that, with additional resources, have the potential to demonstrate an acceptable safety profile and clinical proof of concept for a stem cell-based therapeutic during, or before, 2017. In preparing this Program Announcement, CIRM has determined that the research solicited through the Accelerated Development Pathway program is not likely to receive timely or sufficient federal funding, unencumbered by limitations that would impede the aims of this Program Announcement.

Reviewers will be asked to assess the scientific and technical merit of applications for inclusion into the Accelerated Development Pathway based on the review criteria listed below. In addition, though not required at the time of this application, demonstration of funding secured from additional sources or through a partnership with an established pharmaceutical or biotechnology company to support the proposed new activities would be a positive consideration.

Clinical Competitiveness and Impact of the Proposed Therapy

Applications will be assessed for the extent to which they support the development of a therapeutic candidate that could have a significant and timely clinical impact on the target disease/injury and would offer advantages over current therapies on the market or in late stage development. Activities proposed in the application should demonstrate an acceptable safety profile and clinical proof of concept endpoints for the therapeutic candidate, based on objective, clinically meaningful and relevant measures.

Relevance of the Therapeutic to Regenerative Medicine

Applications will be assessed for the overall relevance of the project to stem cell-based and regenerative medicine and the body of evidence that the therapeutic has a strong and compelling stem cell connection.

Strength of the Development Program

Applications will be assessed for the quality of the Development Plan to End-of-Phase 2 (defined herein as completion of clinical studies providing sufficient information on safety, efficacy and dose to enable the transition to Phase 3) and the extent to which it describes a clear, well-designed, efficient and achievable path to advance the therapeutic candidate towards commercialization and patient use. A successful development program would be expected to benefit and advance the stem cell-based field of regenerative medicine.

Proposed Activities for Acceleration of the Development Program

Each additional activity proposed in the application will be assessed for its suitability, potential to add value, and effectiveness to accelerate the development program toward clinical proof of concept. The appropriateness of the proposed budget for each activity will also be considered. Additional activities may reflect an approach, technology or innovation that enables the project to advance more rapidly and effectively towards key milestones and objectives. Proposed activities should be well-justified, focused and integral to the core objective of achieving clinical proof of concept with the intended candidate in the therapeutic area identified in the Parent Award. Any new clinical trials proposed should provide timely evidence of safety and clinical proof of concept, based on objective, biologically quantifiable endpoints and clinically meaningful, well-established measures.

Feasibility of Proposed Activities for Acceleration of the Development Program

Each additional activity proposed will be assessed for its feasibility, probability to succeed and likelihood to achieve meaningful results. Proposals should appropriately reflect the resources (including allocation of funds), personnel and/or technologies required to implement and complete activities within the proposed time line.

Qualifications of Development Team

The applicant team will be assessed for whether it has the relevant experience, knowledge, and personnel, including access to appropriate regulatory expertise and process development/manufacturing expertise, to carry out the proposed new activities while maintaining and/or accelerating activities required to achieve milestones associated with the Parent Award.

Progress on Parent Award and Effective Program Leadership

Grantees will be assessed for their progress to date on achieving milestones in the Parent Award, their ability to address challenges in a timely and effective manner, and their demonstrated success at implementing and executing on plans.

VIII. Application Procedure

Applications will only be accepted from those Disease Team (Disease Team Research or Therapy Development) and Strategic Partnership awardees who are already funded to conduct a clinical trial under an active CIRM grant and meet the other eligibility criteria defined in Section V. Submission of an application for the

Accelerated Development Pathway (PA 14-01) involves a two-step process. Eligible applicant teams that wish to apply for the CIRM Accelerated Development Pathway must first submit a non-binding letter of intent (LOI). Applicants will be notified if their LOI is **NOT** accepted. In the second step of the process, eligible applicants will submit a full application. Applications will only be accepted from applicants that have submitted an LOI that was accepted by CIRM.

A. Letter of Intent (LOI) Submission Instructions

A non-binding Letter of Intent (LOI) indicating plans to submit an application for the Accelerated Development Pathway must be received by CIRM no later than 5:00 pm PDT on March 24, 2014 via the Grants Management Portal (https://grants.cirm.ca.gov). It is the applicant's responsibility to meet this deadline; no exceptions will be made.

B. Application Forms

Application forms for the Accelerated Pathway will be available via the Grants Management Portal at https://grants.cirm.ca.gov in early March, 2014. The application for the CIRM Accelerated Development Pathway consists of **at least eight parts to be submitted by the applicant**, described in detail, below:

Part A: Application Information Form
Part B: Proposal for Accelerated Development Plan
Part C: Biographical Sketches for Key Personnel and Letters of Support
Part D: Activities-Based Budget to Support Accelerated Development Plan
Part E: FDA Correspondence
Part F: Updated Clinical Protocol for Trial Funded in Parent Award
Part G: Updated Investigator Brochure for Trial Funded in Parent Award
Part H: Clinical Protocol for Follow-on Clinical Trial (if applicable)
Part I: Investigator Brochure for Follow-on Clinical Trial (if applicable)
Part J: Updated Intellectual Property and Licensing Agreements

In addition, CIRM will provide the GWG reviewers with copies of the applicant team's most recent Progress Report for the Parent Award, and the briefing document and questions to the team that were prepared for the team's most recent CDAP interaction.

Part A: Application Information Form (Web-based form)

1. **Public Abstract** (up to 3000 characters)
   Briefly describe the proposed therapeutic candidate and summarize the scientific rationale for the proposed intervention in the target disease/injury. The abstract will become public information and will be

available online; do not include proprietary, identifying or confidential information.

2. Statement of Benefit to California (up to 3000 characters)
Briefly describe how the proposed project will benefit the State of California and its citizens. The Statement of Benefit will become public information and will be available online; do not include proprietary, identifying or confidential information.

3. Key Personnel
List all key personnel and their roles on the proposed accelerating activities in the relevant sections of Part A (and include biographical sketches for key personnel in Part C). Clearly identify the roles of key personnel on activities proposed in this application to accelerate progress. Key personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive way, regardless of whether they receive salaries or compensation under the grant. Key personnel may include any staff, collaborators, or consultants who meet this definition. Key personnel who are not part of the applicant organization should be listed; for example, list the key lead investigator for each clinical site, even if he/she will be compensated as part of a subcontract.

4. Related Business Entities
To comply with the Conflict of Interest policies under which CIRM operates, all applicants must provide information on related business entities for any application that, if awarded, would fund a for-profit organization either as: 1) the applicant organization; 2) a subcontractor or 3) the employer of a consultant or subcontractor. If the application does not seek funding for any such for-profit organizations, indicate that in this section of the form. If for-profit funding is sought, include the following for each such for-profit organization to be funded:

- A list of any parent organization that owns 50% or more of the for-profit's voting shares;
- A list of all subsidiaries in which the for-profit owns 50% or more of the voting shares; and
- A list of all other related business entities (i.e., entities with which the for-profit shares management and control, or shares a controlling owner).

5. Budget (included in Parts A and D)
Provide all budget information requested in the budget sections of Part A and Part D. Detail key development activities proposed in this application and their associated costs. Justifiable costs include direct project costs, direct facilities costs and indirect costs.

6. Budget Justification

Specify and provide well-justified budgets that align with the sequence of when activities will be conducted and clearly identify the expected duration of proposed new activities. Include costs for each proposed new activity in a modular manner. Describe budgets that include costs anticipated to be funded by CIRM through this Accelerated Pathway funding source, and activities that could be co-funded either by self-funding or through third parties.

Part B: Proposal for Accelerated Development Plan (MS Word template)

1. Updated Target Product Profile (up to 2 pages; use TPP template provided). Update the TPP for the proposed therapeutic candidate. The TPP provides the aspirational attributes of the product to help define success and inform the proposed label. The TPP should articulate the overall intent of the therapeutic development program, and the studies proposed within this application should be designed to collect data that will support the TPP. The TPP should provide the optimal profile (ideal) and the threshold profile (minimally acceptable to differentiate from current and future competing products), and identify criteria (metrics) for key decisions in the development process. It is a comprehensive outline of product specifications with respect to safety, effectiveness, quality, clinical evaluation, nonclinical evaluation, regulatory requirements and commercial factors (e.g., market advantage and target differentiation). The TPP is a dynamic document that should be continually refined as data evolve, and that will ultimately become the product label.

Provide the desired attributes/claims of the therapeutic for the following: indication, target activity, patient profile, efficacy endpoints, safety/contraindications, dose/regimen, dosage form and route of delivery. The FDA released the draft guidance document "Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool" which may be a helpful resource for developing a TPP. It is available from the FDA's website (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf).

2. Updated Clinical Competitiveness and Impact (up to 3 pages). Explain how the proposed project and accelerated activities will advance the field of stem cell-based or regenerative medicine. Summarize the current standard of care and competitive landscape for treatment of the target disease/injury; highlight changes in the field that have occurred since the Parent Award application was submitted which could affect development and commercialization of your proposed therapeutic. Describe how the proposed stem cell-based

therapy could lead to a significant improvement in patient care compared to existing therapies or to other therapies currently in late-stage development. Describe the pharmacoeconomic rationale for the proposed therapeutic.

3. **Updated Development Plan to End-of-Phase 2** (up to 3 pages). Summarize the Development Plan to End-of-Phase 2 (defined herein as completion of clinical studies providing sufficient information on safety, efficacy and dose to enable the transition to Phase 3) for the proposed therapeutic candidate and provide a high-level timeline highlighting key nonclinical, clinical, CMC, regulatory and other milestones and major decision points. Describe how proof of concept endpoints or proposed biomarkers of activity will objectively measure success and how they will inform your activities to enable the transition to Phase 3. Discuss your plans for moving the stem cell-based therapeutic toward commercialization and enhancing the attractiveness of the program for partnering or future investments. Identify key decision points and indicate the success criteria that will be used to inform future development.

4. **Updated Project Plan for Remaining Milestones and Timeline** (up to 3 pages, including a timeline displayed in Gantt chart format or the equivalent). Provide a high-level review of progress and summarize the remaining, agreed-upon milestones under your Disease Team or Strategic Partnership Parent Award. If the program is currently enrolling patients in a clinical trial, include updated information regarding rates of patient enrollment and accrual. Summarize challenges and possible risks to continued progress and your mitigation strategies to address these issues.

5. **Proposal for Acceleration of Development Pathway** (up to 8 pages, including a timeline for additional proposed activities, displayed in Gantt chart format or the equivalent). Consider your Development Plan to End-of-Phase 2, the current Project Plan, and review your team's progress and limitations to suggest areas that might be accelerated through additional consulting or resources. Consider how progress in the field may suggest new ways to address proof of concept for the proposed therapeutic and specify how decision making would be informed by amended activities for the funded clinical trial, or addition of key clinical or nonclinical activities.

   Identify and propose key clinical and nonclinical activities that would facilitate progress toward demonstrating clinical proof of concept. Present each new activity in a modular manner to include the requested funding that it would require and the timeframe across which the proposed new activity would be conducted. Specifically indicate

how each new activity proposed will augment and accelerate the work approved in the Parent Award; indicate the acceleration effects in parallel, or as an overlay, on an accelerated timeline (displayed in Gantt chart format or the equivalent). Use the activities-based budget spreadsheet in Part D to illustrate the additional funding support for each additional activity proposed. Clearly identify activities that are currently funded, or could be funded, under the existing Parent Award and distinguish them from proposed activities for acceleration that would require additional funding. Explain why the proposed additional activities could not be accommodated by redirection of funds from the current Parent Award.

6. **Clinical Protocol Synopsis for Follow-on Clinical Trial** (if applicable; up to 8 pages; use the Clinical Protocol Synopsis template provided). Required for projects that propose conducting an additional clinical trial to accelerate their development pathway. Provide the full clinical protocol for a proposed additional clinical trial in Part H (submit draft if the final is not available).

Part C: Biographical Sketches for Key Personnel and Letters of Support
For the key personnel listed in Part A, provide a two-page biographical sketch using the template provided. The biographical sketch should highlight relevant experience, in particular, team leadership, conduct of clinical studies and/or contribution to regulatory filings for product development. Include relevant publications, patents or patent applications. Include a biographical sketch for the PI and for functional area heads and/or members of the development core team (including the individuals responsible for overseeing clinical, clinical operations, regulatory, CMC, data management and translational research activities), as well as the lead clinical investigator at each proposed site.

Part D: Activities-Based Budget to Support Accelerated Development Plan
In the activities-based budget spreadsheet (provided), detail key activities proposed to support the Accelerated Development plan, and their associated costs. Include costs anticipated to be funded by CIRM through this Accelerated Pathway funding source, and activities that could be co-funded either by self-funding or through third parties. Proposed budgets should align with the current Development Plan and support only those additional activities that would be within the scope of activities described in Section II. Justifiable costs include direct project costs, direct facilities costs and indirect costs. In general, CIRM funding must be used to support research in California.
Please see the requirements for your Disease Team or Strategic Partnership award for additional information regarding allowable costs.

Part E: FDA Correspondence. Provide copies of regulatory correspondence with the FDA that has occurred subsequent to the original application.

Part F: Updated Clinical Protocol for Trial Funded in Parent Award. If final is not available, submit draft. If additional endpoints are proposed in this application that would modify the funded clinical trial, clearly delineate proposed supplementary activities from the funded clinical activities.

Part G: Updated Investigator Brochure for Trial Funded in Parent Award. If final is not available, submit draft.

Part H: Clinical Protocol for Follow-on Clinical Trial (if applicable). Required for projects that propose conducting an additional clinical trial to accelerate their development pathway. If final is not available, submit draft.

Part I: Investigator Brochure for Follow-on Clinical Trial (if applicable). Required for projects that propose conducting an additional clinical trial to accelerate their development pathway. If final is not available, submit draft.

Part J: Updated Intellectual Property and Licensing Agreements. Provide an updated description of intellectual property assets (patent applications and patents, regardless of whether CIRM funded) which are critical to commercialization of the therapeutic under development. Include any challenges and pending litigation to same; identify any potentially blocking intellectual property. Provide copies of license agreements or other contracts that (1) provide rights to technologies/materials required to commercialize the therapeutic, 2) out-license any background intellectual property needed for the commercialized therapeutic, and/or 3) impose financial or other burdens on the commercialized therapeutic.

C. Application Submission Instructions

All applicable parts of the Accelerated Development Pathway application must be submitted together and received by CIRM no later than 5:00 pm PDT on April 28, 2014 via the Grants Management Portal (https://grants.cirm.ca.gov). It is the applicant's responsibility to meet this deadline; no exceptions will be made.

D. Submission of Supplemental Information

If necessary, the PI may submit limited supplemental materials that provide critical new information related to their research proposal after the application deadline but **not later than 5:00 pm PDT on June 5, 2014**. Supplementary materials will not be accepted after this deadline. CIRM will accept a one-time-only submission of

materials from the PI only if it meets the submission deadline and conforms to the requirements described herein. Accepted submissions will be forwarded to reviewers for their consideration.

The submission of supplemental materials should be in the form of a one-page letter addressed to the Associate Director of Review and submitted via email to gsambrano@cirm.ca.gov. The body of the letter may not exceed 500 words and should briefly describe the type of information submitted and when the information became available. The following materials qualify for submission of supplemental materials and would be contained within the one-page letter:

1. Specific citation(s) to journal publications related to the proposed project that were published or accepted for publication after the application submission deadline. You may briefly describe the significance of the publication(s) to the proposal in the cover letter.
2. Confirmation of funding secured from other sources
3. Notification of regulatory (e.g., IND, IDE) filings or approvals or lifting of clinical holds that occurred since the application submission deadline.
4. Notice of patent application(s) filed; notice of allowance received or patent(s) issued; or notice of license(s) to relevant intellectual property (granted or received) since the application submission deadline.
5. Identification of any challenges to relevant patents; updates to any pending litigation; or notification of newly initiated litigation.

The letter may not be used to describe any additional data or experiments. Changes in scope, experimental approach, or research design are not allowed in this document.

E. Opportunity for Clarification of Submitted Information

Critical questions raised by GWG reviewers regarding information submitted in the application will be forwarded to applicants prior to the scientific review meeting. Applicant responses will be in writing and will be made available to the GWG before the review meeting.

IX. Schedule of Deadlines and Reviews

Letters of Intent (LOI) Due	5:00 pm (PDT), March 24, 2014
Applications Due	5:00 pm (PDT), April 28, 2014
Supplemental Information Due	5:00 pm (PDT), June 5, 2014
Review of Applications by Grants Working Group (GWG)	Summer, 2014
Review and Approval by ICOC	Quarter 3, 2014

X. Contacts

For information about this PA:

Catherine Priest, Ph.D.
Science Officer
California Institute for Regenerative Medicine
Email: cpriest@cirm.ca.gov
Phone: (415) 396-9805

For information about the review process:

Gilberto R. Sambrano, Ph.D.
Associate Director, Review
California Institute for Regenerative Medicine
Email: gsambrano@cirm.ca.gov
Phone: (415) 396-9103

XI. CIRM Regulations

Funding made through this PA will be subject to CIRM regulations. These regulations can be found on CIRM's website at http://www.cirm.ca.gov/reg/default.asp. CIRM regulations include the following:

A. CIRM Grants Administration Policy

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP) and the GAP for For-Profit Institutions (For-Profit GAP) serve as the standard terms and conditions of grant awards issued by CIRM. All research conducted under this award must comply with the stated policy. Progress reports of research, as required by the GAP, are important to CIRM: Funding from year to year will depend on adequate scientific progress as outlined in the grant application timeline. CIRM's GAP is available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#GAP.

B. CIRM Loan Administration Policy

CIRM's Loan Administration Policy (LAP) will apply to awards made in the form of a loan. For additional information on the loan program, consult the CIRM LAP, available at: http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants.

C. Intellectual Property Regulations

CIRM has adopted intellectual property and revenue sharing regulations for non-profit and for-profit organizations. By accepting a CIRM Grant, the Grantee agrees to comply with all such applicable regulations.

D. Human Stem Cell Research Regulations

As reflected in CIRM's GAP, CIRM has adopted medical and ethical standards for human stem cell research (Title 17, California Code of Regulations, sections 100010-100110 available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#standards). All research conducted under this award will be expected to comply with these standards. This information can be found on the CIRM website.

E. California Supplier Regulation

CIRM has adopted a regulation to implement the requirement in Proposition 71 that grant and loan recipients make a good faith effort to achieve a goal of purchasing more than 50% of their goods and services from California suppliers (Title 17,California Code of Regulations, section 100502). Grant and loan recipients are required to comply with this standard.

F. Clinical Trial Registration

CIRM requires that any clinical trial funded under any of its funding programs be listed on http://clinicaltrials.gov/. CIRM will also require awardees to share the results, at the completion of their studies for the benefit of the field.

XII. Confidentiality of Submissions to CIRM

CIRM protects the confidential information it receives from applicants and grantees to the maximum extent permitted by law. That protection is embodied in a number of laws and policies, described below, and applies to the confidential information submitted by all applicants and grantees. CIRM does not enter into separate non-disclosure agreements with individual applicants or grantees.

A. CIRM Employees

CIRM employees are subject to the confidentiality requirements identified in a CIRM policy known as the "Incompatible Activities Statement." By law (Cal. Gov. Code § 19990), state employees are prohibited from engaging in activities identified by their employing agencies' Incompatible Activities Statements. CIRM employees are also subject to the confidentiality provision in the CIRM Employee Handbook. All

employees sign statements acknowledging receipt of the Incompatible Activities Statement and the CIRM Employee Handbook.

Excerpt from Incompatible Activities Statement:

> No employee shall utilize his or her status as a CIRM employee to acquire access to confidential information other than on behalf of the CIRM.
>
> Additionally, no employee shall use such information for private gain or advantage or provide confidential information to persons to whom issuance of this information has not been authorized.

Excerpt from Employee Handbook

> All records and information relating to CIRM and its activities are confidential and employees must, therefore, treat all matters accordingly. No CIRM or CIRM related information, including without limitation, documents, notes, files, records, oral information, computer files or similar materials (except in the ordinary course of performing duties on behalf of CIRM) may be removed from CIRM without the President's authorization. Additionally, the contents of CIRM's records or information otherwise obtained in regard to CIRM activities may not be disclosed to anyone, except where required for an official purpose or by law. Employees must not disclose any confidential information, purposefully or inadvertently through casual conversation, to any unauthorized person inside or outside CIRM. Employees who are unsure about the confidential nature of specific information must ask their supervisor for clarification. Employees will be subject to appropriate disciplinary action, up to and including dismissal, for purposefully or accidentally, revealing information of a confidential nature.

B. Clinical Development Advisory Panel

Members of CIRM's Clinical Development Advisory Panel (CDAP) sign contracts that include the following provision:

> Advisor shall keep confidential any information provided by CIRM or any information conveyed orally to Advisor by CIRM with oral notification of its confidentiality (the "Confidential Information"). Advisor agrees to maintain the secrecy of CIRM's Confidential Information and agrees not to use it except in performing the Services under this Agreement and not to disclose it to anyone outside CIRM or anyone within CIRM's organization who does not have a need to know it to perform under this Agreement. This non-disclosure provision shall not apply to any of the following:
>
> 1. Information which Advisor can demonstrate by written records was known to him or her prior to the effective date of this Agreement;

2. Is currently in, or in the future enters, the public domain other than through a breach of this Agreement or through other acts or omissions of Advisor; or
3. Is obtained lawfully from a third party.

C. Grants Working Group

The Grants Working Group (GWG) reviews grant applications. All members sign statements guaranteeing confidentiality, at the time of their appointment, and again prior to accessing application materials for each grant round.

D. Public Records Act

As a state agency, CIRM is required to allow public access to certain categories of documents held by the agency. The Public Records Act (California Government Code section 6250 et seq.) exempts certain categories of documents from public disclosure. As relevant here, agencies are not required to release trade secrets, as defined by section 3426.1(d) of the Civil Code:

> "Trade secret" means information, including a formula, pattern, compilation, program, device, method, technique, or process, that (1) Derives independent economic value, actual or potential, from not being generally known to the public or to other persons who can obtain economic value from its disclosure or use; and (2) Is the subject of efforts that are reasonable under the circumstances to maintain its secrecy.

In addition, CIRM operates under special Public Records Act exemptions included in Proposition 71, the ballot initiative that created CIRM. Proposition 71 (Health & Safety Code, **§** 125290.30(e)(2)(B)-(C)) exempts from disclosure:

1. Records containing or reflecting confidential intellectual property or work product, whether patentable or not, including, but not limited to, any formula, plan, pattern, process, tool, mechanism, compound, procedure, production data, or compilation of information, which is not patented, which is known only to certain individuals who are using it to fabricate, produce, or compound an article of trade or a service having commercial value and which gives its user an opportunity to obtain a business advantage over competitors who do not know it or use it.

2. Prepublication scientific working papers or research data.

PA 14-01: CIRM TARGET PRODUCT PROFILE (TPP) TEMPLATE

TARGET PRODUCT PROFILE for	
<Delete this text and type Name of your Product/Therapy here>	
INDICATION: ***Disease or condition for which your product/therapy will be indicated***	
Optimal indication and decision criteria < Delete and type your text here>	***Minimally acceptable indication and criteria*** < Delete and type your text here>
BIOLOGICAL ACTIVITY: ***Biological activity of your product/therapy***	
Optimal biological activity and decision criteria < Delete and type your text here>	***Minimally acceptable biological activity and criteria*** < Delete and type your text here>
EFFICACY: ***Proposed efficacy endpoints for your product/therapy***	
Optimal efficacy endpoints and decision criteria < Delete and type your text here>	***Minimally acceptable efficacy endpoints and criteria*** < Delete and type your text here>
SAFETY/CONTRAINDICATIONS*:* ***Potential safety risks associated with your product/therapy***	
Optimal safety profile and decision criteria <Delete and type your text here>	***Minimally acceptable safety profile and decision criteria*** <Delete and type your text here>
DOSE/REGIMEN: ***Briefly describe the proposed dose and dosing regimen of your product/therapy.***	
Optimal dose and dosing regimen and decision criteria <Delete and type your text here>	***Minimally acceptable dose and dosing regimen and decision criteria*** <Delete and type your text here>
DOSAGE FORM/ROUTE OF DELIVERY: ***Briefly describe the proposed dosage form and route of delivery for your product/therapy.***	
Optimal dosage form and route of delivery and decision criteria <Delete and type your text here>	***Minimally acceptable dosage form and route of delivery and decision criteria*** <Delete and type your text here>

PA 14-01: CIRM CLINICAL PROTOCOL SYNOPSIS TEMPLATE

STUDY TITLE
Provide full title of the study
CLINICAL PHASE
Specify clinical phase (1, 2a)
STUDY OBJECTIVES
Provide a brief description of the study objectives e.g., why is the study being done, what is the intent? E.g., safety, feasibility *Primary Objectives:* *Secondary Objectives:* *Exploratory Objectives:*
STUDY RATIONALE
Summarize the rationale for testing the proposed therapy
STUDY POPULATION
Briefly describe the study population and explain the rationale for choosing this population
MAIN INCLUSION/EXCLUSION CRITERIA
Specify the main inclusion/exclusion criteria and explain the rationale.
PRIMARY ENDPOINT (S)
Describe the Primary Endpoint(s) and the set of measurements used to address the objectives
SECONDARY & EXPLORATORY ENDPOINTS
Describe the Secondary & Exploratory Endpoint(s) and measures that will address them
STUDY DESIGN
Summarize the study design, including type of study, number of arms, controls or comparators
SUBJECT NUMBER
Provide the total number of study subjects, the number per study arm, and justification
TREATMENT DURATION
Specify the length of the treatment period
DURATION OF FOLLOW UP
Specify the length of the protocol-specified follow up period

DOSE LEVEL (S) AND DOSE JUSTIFICATION
Specify the dose level(s), number of doses, and dosing frequency. Summarize how dosing was determined
ROUTE OF DELIVERY
Specify how the doses will be delivered
DATA and SAFETY MONITORING PLAN (DSMP)
Summarize the Data and Safety Monitoring Plan. Describe measures that will be implemented to minimize risk to study subjects e.g. specific inclusions/exclusions; plans to ensure medical intervention in the case of an adverse event for subjects; plans for surveillance, detection and management of specific adverse events that might or could occur; potential use of an Independent Safety Monitor or Data Safety Monitoring Board (DSMB)
STOPPING RULES
Specify stopping rules
IMMUNE MONITORING & IMMUNOSUPPRESSION
Describe and justify the plan for immunosuppression and immune monitoring (if applicable)
SUPPORTING STUDIES
Summarize supporting studies that are part of this clinical study (e.g. imaging, biomarker analyses, cell phenotyping, genotyping, gene expression analyses), that will provide critical additional data to address the objectives of this RFA or inform decisions on continued clinical testing. Include: *Objectives and rationale* *Sample collections (specify type, frequency)* *Testing methodology* *Data analysis* *Special considerations*
ASSAYS/METHODOLOGIES
Briefly describe any specialized assays or methodologies that will be used in this clinical study or supporting study/studies. (Provide a more detailed summary of assay methods and summarize assay qualification/validation in Part D). Indicate where specialized testing will be conducted
STATISTICAL ANALYSIS PLAN
Summarize the Statistical Analysis Plan or describe how the data will be analyzed
OUTCOME CRITERIA
Describe criteria that would define whether you would or would not move forward with the subsequent development plan, based upon primary and designated secondary objectives

RISKS
Identify potential risks and mitigation strategies (e.g. need for and risks associated with long term immunosuppression)
CLINICAL SITES
Indicate the number of clinical sites that will participate in the study. Summarize the criteria for site selection. Provide a list of proposed sites with a brief description of the site's experience and capabilities in the conduct of clinical research.
CLINICAL OPERATIONS PLAN
Summarize the plan for managing the conduct of the clinical study. Describe plans for training clinical investigators and personnel at clinical sites and the plan for oversight and monitoring of clinical sites. Indicate who will be responsible for management and sign off of clinical operations activities.
ENROLLMENT
Describe the enrollment strategy and provide a timeline showing enrollment projections Describe plans for inclusion of women and minorities
LONG TERM FOLLOW UP
Describe requirements and plans for long term follow up and indicate how these will be supported
TIMELINE
Provide a timeline for completion of the study and indicate relevant milestones