GWG Recommendations for Applications Submitted to the CLIN Program

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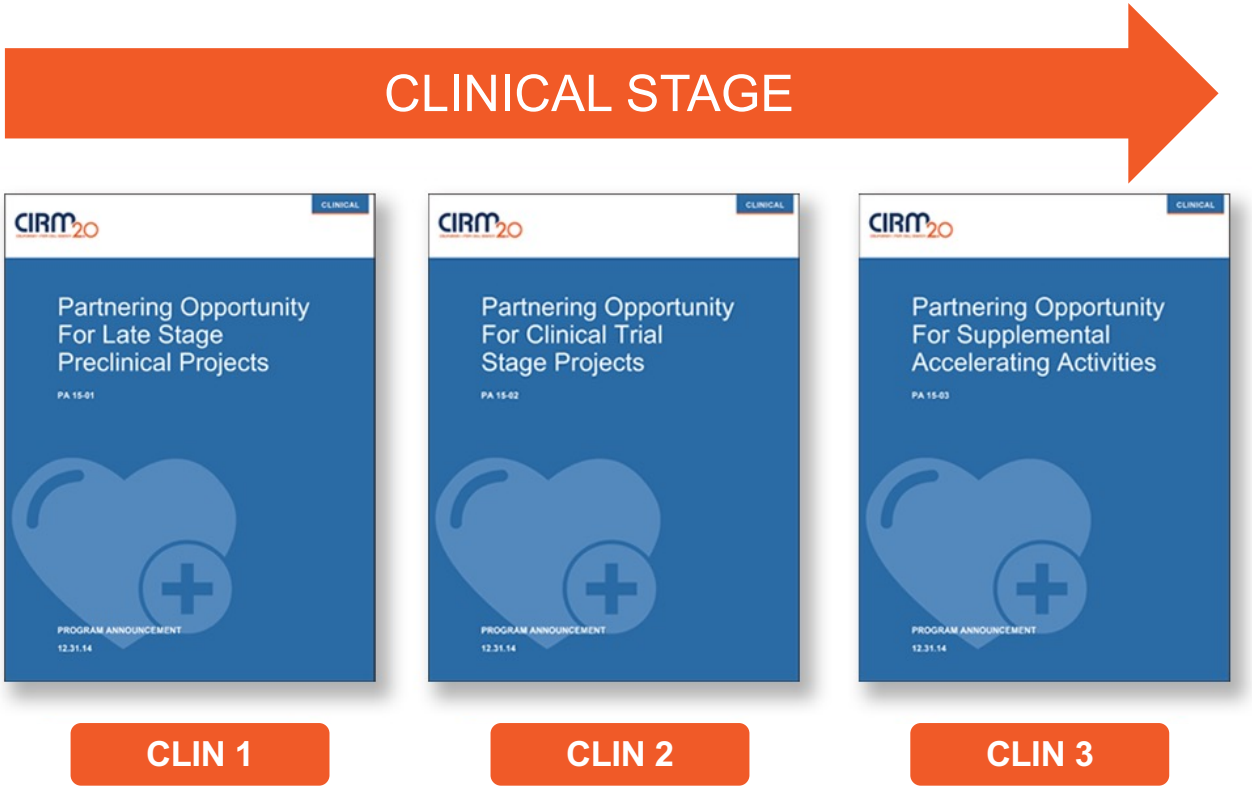
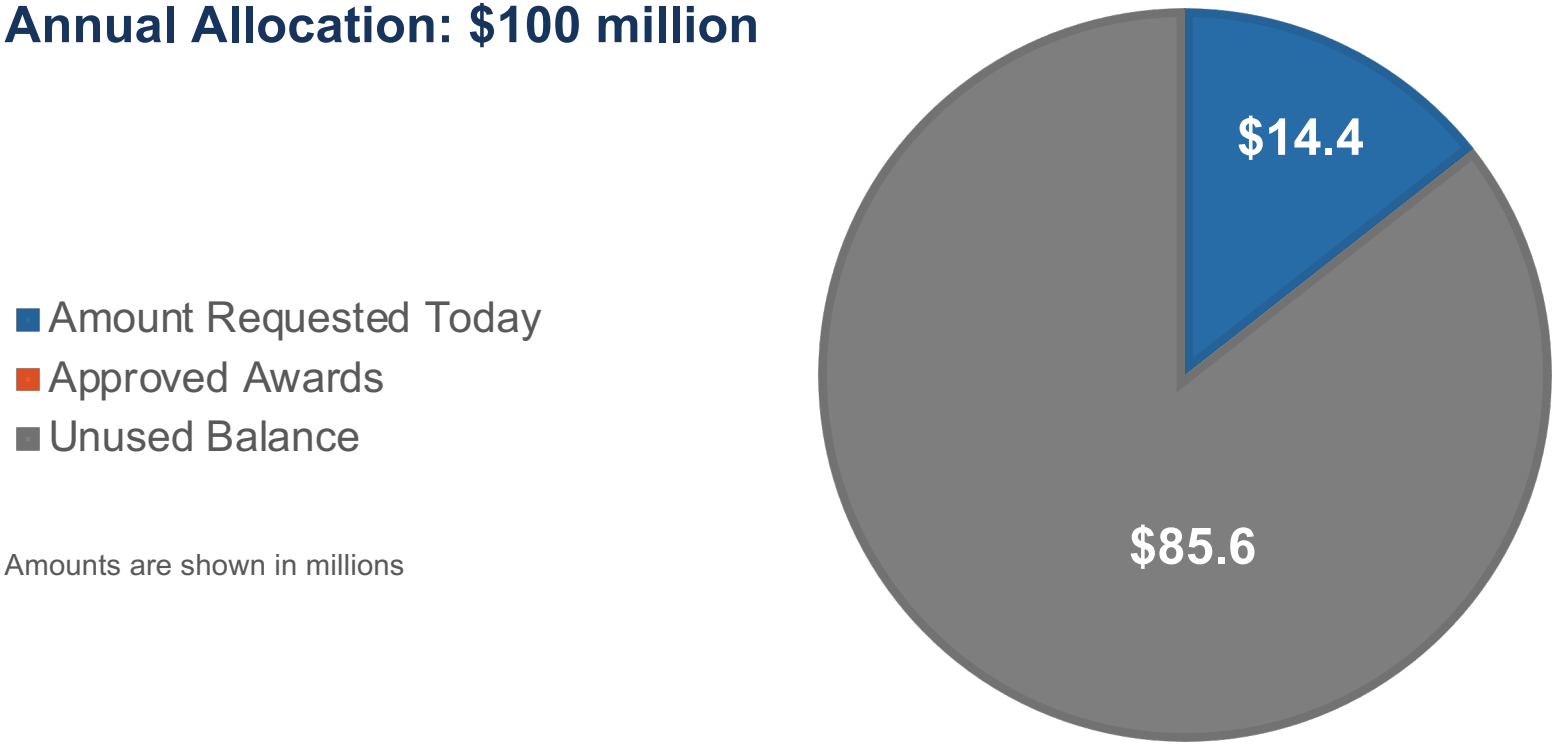
CIRM
CALIFORNIA'S STEM CELL AGENCY

Clinical Stage Programs



Jan-Jun 2021 Clinical Budget Status

Annual Allocation: $100 million



Amounts are shown in millions

Review Criteria

1. Does the project hold the necessary significance and potential for impact? (i.e., what value does it offer; is it worth doing?)

2. Is the rationale sound? (i.e., does it make sense?)

3. Is the project well planned and designed?

4. Is the project feasible? (i.e., can they do it?)

5. Does the project address the needs of underserved communities? NEW

Scientific Scoring System for Clinical Applications

- **Score of "1"**

  Exceptional merit and warrants funding.

  May have minor recommendations and adjustments that do not require further review by the GWG

- **Score of "2"**

  Needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.

  GWG should provide recommendations that are achievable (i.e., "fixable changes") or request clarification/information on key concerns.

- **Score of "3"**

  Sufficiently flawed that it does not warrant funding and the same project should not be resubmitted ***for at least 6 months****.*

Applications are scored by all scientific members of the GWG with no conflict.

New Elements in CIRM Application Review

- Gene Therapy
- Data Sharing
- Addressing the Needs of Underserved Communities
- Diversity, Equity and Inclusion

New Elements in CIRM Application Review

- **Addressing the Needs of Underserved Communities**
  - **This section describes the applicant's plan for outreach and enrollment of a diverse patient cohort that accounts for racial, ethnic and gender diversity**
  - **The section is evaluated as part of the overall project and incorporated into the scientific merit score (1,2 or 3)**
- **Diversity, Equity and Inclusion**
  - **This section describes how the applicant team incorporates diverse perspectives and experiences to improve the project through the composition of the team and/or any other approaches**
  - **This section is evaluated and scored by patient advocate members and represented in the DEI score (0-10)**

Addressing Needs of the Underserved

- CIRM clinical trial (CLIN2) projects are required to include a plan for outreach and inclusion of minority and underserved populations in their studies.
  - Public Law 103-43 requires that women and minorities be included in all clinical research studies, as appropriate for the scientific goals of the work proposed.
  - California Health and Safety Code requires that any organization conducting clinical research using State funds shall ensure inclusion of women and minorities in studies.
- Discovery and translational applicants are also required to address how their overall study plan and design has considered the influence of race, ethnicity, sex/gender diversity.
- Given its importance, **CIRM has created a new (5th) review criterion** to incorporate this element into the evaluation and scoring of applications.

Addressing Needs of the Underserved

Application Instructions

Describe the plan for outreach and study participation by underserved and disproportionately affected populations. Describe the planned distribution of subjects by sex/gender, race and ethnicity. Provide the rationale for the study population selection criteria and justification for the proposed exclusion of any group(s) at risk for the disease/condition under study. The GWG and CIRM's governing board will evaluate these plans as a review criterion in making funding recommendations. Priority will be given to projects with the highest quality plans in this regard.

Addressing Needs of the Underserved:

GWG 5th Review Criterion

5. Does the project serve the needs of underserved communities?

- Does the proposal provide a clear and robust plan for outreach and study participation by underserved and disproportionately affected populations?
- Does the proposal adequately address the planned distribution of subjects by sex/gender, race and ethnicity?
- Does the proposal provide an appropriate rationale for the study population selection criteria?
- Does the application provide adequate justification for the proposed exclusion of a group(s) at risk for the disease/condition under study?

The evaluation questions align with guidance from NIH regarding the review of clinical trial proposals and inclusion of subjects on the basis of sex/gender, race, ethnicity and age. Evaluation is from a scientific and patient perspective.

Diversity, Equity and Inclusion in Research

New Element for Evaluation by Patient Advocate Members

- This is a more holistic view of diversity and inclusion in the composition of the research team and approaches to incorporate perspectives and experience that may inform or improve their research proposal.

- This section will be evaluated and scored only by patient advocate members of GWG and reported to ICOC in the review summary.

Diversity, Equity and Inclusion in Research

Application instructions

Describe how the research team has or will incorporate diverse and inclusive perspectives and experience in the implementation of the research project, including, for example, the inclusion of team members from different socio-economic backgrounds and team members who are the first in their family to attend college.

Diversity, Equity and Inclusion in Research

By State law, CIRM is prohibited from taking race, ethnicity, national origin, or gender into account in making grant decisions.

- Evaluation of this section cannot be solely based on or make sole reference to race, ethnicity, national origin, or gender.
- Evaluation should focus on other factors such as socio-economic background or those who are the first in their family to attend college.
- Evaluating demographic information for scientific purposes, as in the 5th review criterion, would not violate the prohibition.

Diversity, Equity and Inclusion in Research

Scoring:

- Patient advocate members will score the DEI section on a scale of 0-10, with 10 being the best possible score.
- Comments from patient advocate members will also be captured in the Final Score page during the review.
- As this process is new, we anticipate improvements will be made as we learn what works best to evaluate DEI.

Resubmitted Applications

- The two applications presented today originally applied in August 2020 and received a score of “2” with no CIRM funding available
- Revised submission of the applications could not occur until CIRM re-established funding opportunities under Prop 14
- Therefore, new elements of data sharing and DEI where not components of the original application and review
- However, the applicants submitted supplementary information to address these areas

CLIN2-12149: Antibody Therapy that Targets Leukemia Cancer Stem Cells

Therapy	Antibody targeting leukocyte immunoglobulin-like receptor B4 (LILRB4)
Indication	Acute myeloid leukemia (AML) with monocytic differentiation and chronic myelomonocytic leukemia (CMML)
Goal	Complete a phase 1 clinical trial
Funds Requested	$6,000,000 ($3,130,454 Co-funding)

Maximum funds allowable for this category: $8,000,000

CLIN2-12149: Background Information

Clinical Background: About 20,000 new cases of acute myeloid leukemia (AML) are diagnosed each year in the US with a 5-year survival rate of ~29%. Chronic myelomonocytic leukemia (CMML) has an incidence of about 4/million people but 15-30% of cases advance to AML.

Value Proposition of Proposed Therapy: The proposed therapy targets myelomonocytic and monocytic AML (~30% of AML) and CMML. Some therapeutic options for AML are not effective in this subpopulation of patients and the proposed therapy offers a new and potentially effective option.

Why a stem cell project: The proposed therapeutic candidate targets cancer stem cells as a primary mechanism of action.

CLIN2-12149: Related CIRM Portfolio Projects

Although CIRM supports several projects that broadly impact leukemias and lymphomas, there are no currently active clinical trial projects for AML in CIRM's portfolio.

There have been two previous trials supported that are related to AML but none specifically targeting myelomonocytic or monocytic AML.

CLIN2-12149: Previous CIRM Funding

Applicant does not have previous CIRM funding

CLIN2-12149: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Scientific Score	GWG Votes
1	11
2	1
3	0

DEI Score: 10

CIRM Team Recommendation: Fund (concur with GWG recommendation)

Award Amount: $6,000,000*

*Final award shall not exceed this amount and may be reduced contingent on CIRM's final assessment of allowable costs and activities.

CLIN2-12153: CAR-T Cell Therapy for Pediatric Brain Tumors

Therapy	Autologous chimeric antigen receptor T cells derived from naive/memory T cells and engineered to target an antigen on pediatric malignant brain tumors
Indication	Recurrent/refractory malignant pediatric brain tumors that express the tumor-associated antigen
Goal	Complete a phase 1 trial
Funds Requested	$8,401,309 ($0 Co-funding)

Maximum funds allowable for this category: $12,000,000

CLIN2-12153: Background Information

Clinical Background: Brain tumors are the leading cause of solid tumor cancer death in children between the ages of 0-14 and the second most common cancer in children (after leukemia).

Value Proposition of Proposed Therapy: The prognosis for pediatric patients with aggressive brain tumors is very poor; often just a few months. The proposed CAR-T therapy offers the possibility of improved patient outcomes including tumor shrinkage and regression. The approach would provide a therapeutic option with improved tolerability and fewer side effects than the current standard of care.

Why a stem cell project: The therapeutic candidate contains memory T stem cells

CLIN2-12153: Related CIRM Portfolio Projects

Application/ Award	Project Stage	Project End Date	Indication	Candidate	Mechanism of Action
Current Application	Phase 1 clinical trial	~Nov 2023	Pediatric gliomas	CAR-T cell therapy	Chimeric antigen receptor T cells engineered to target tumor cells in pediatric gliomas
CLIN2	Phase 1 clinical trial	Nov 2021	Malignant glioma	CAR-T cell therapy	Chimeric antigen receptor T cells engineered to target tumor cells
CLIN2	Phase 1 clinical trial	Aug 2022	HER-2 positive brain metastases	CART-T cell therapy	Chimeric antigen receptor T cells engineered to target HER-2 positive tumor cells that have metastasized to the brain

CLIN2-12153: Previous CIRM Funding

Project Stage	Project Outcome	Project Duration	Award Amount	Milestones*
Phase 1 clinical trial (Active)	Safety, feasibility	Nov 2017 – Nov 2021	$12,753,854	**OM1-OM4:** Enrollment and dosing of proposed patients (Achieved on time) **OM5: Interim analysis of data** (On track)
Translational (Closed)	Proof of concept and feasibility of GMP-compatible production	Mar 2013 – Aug 2016	$5,217,004	6 milestones proposed and 6 milestones completed. 4 publications reported by grantee. Study progressed to phase 1 clinical trial

CLIN2-12153: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Scientific Score	GWG Votes
1	11
2	4
3	0

DEI Score: 9

CIRM Team Recommendation: Fund (concur with GWG recommendation)

Award Amount: $8,401,309*

*Final award shall not exceed this amount and may be reduced contingent on CIRM's final assessment of allowable costs and activities.