GWG Recommendations for Applications Submitted to the CLIN Program

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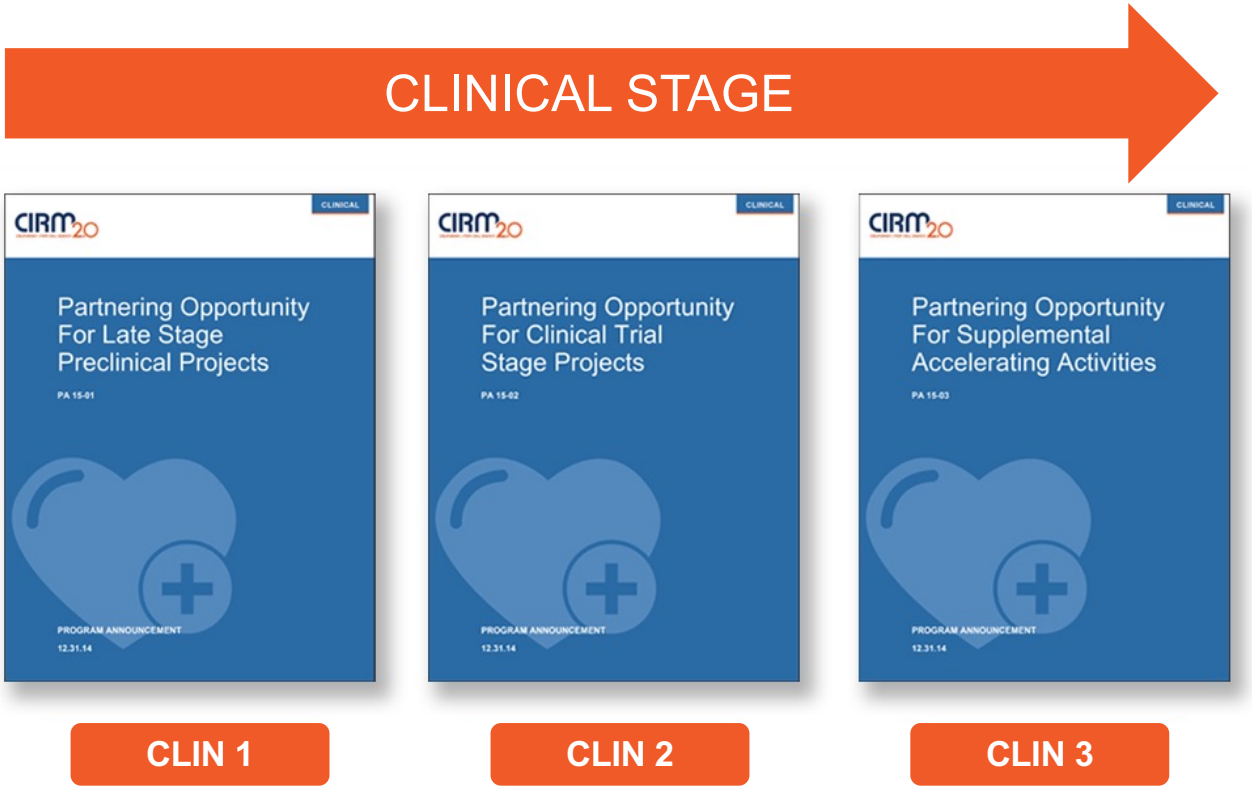
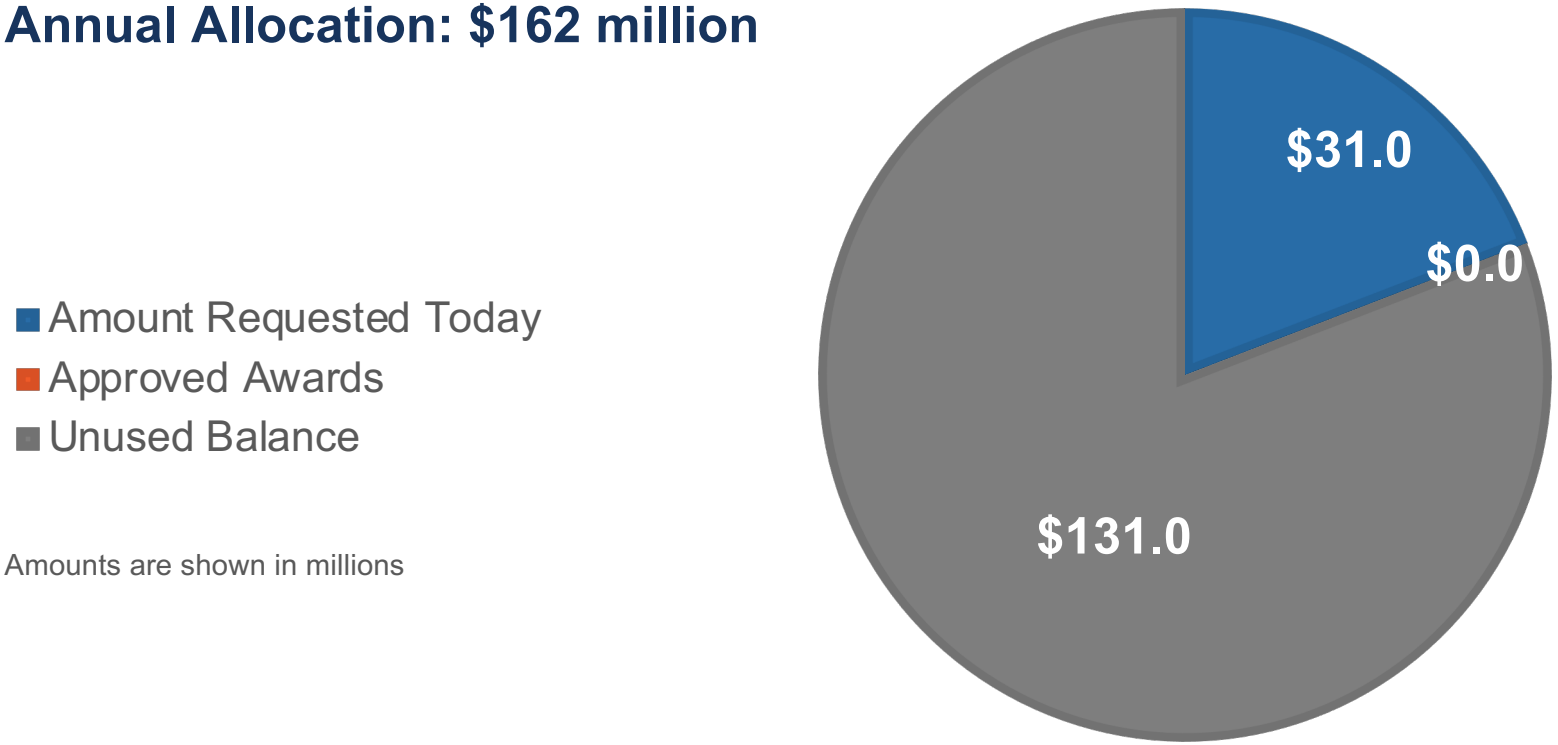
CIRM
CALIFORNIA'S STEM CELL AGENCY

Clinical Stage Programs



2021/22 Clinical Budget Status

Annual Allocation: $162 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?

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.

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/nurse members of the Board (appointed to the GWG) and shown in the DEI score (0-10)**

CLIN2-12379: Cell Therapy for Chronic Ischemic Subcortical Stroke

Therapy	hESC-derived neural stem cells
Indication	Subcortical stroke patients with chronic motor deficits
Goal	Complete a phase 1/2a trial to assess safety and initial efficacy
Funds Requested	$11,998,988 (co-funding: $0)

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

CLIN2-12379: Background Information

Clinical Background: Every year, more than 795,000 people in the United States have a stroke. About 610,000 of these are first or new strokes. About 185,000 strokes—nearly 1 of 4—are in people who have had a previous stroke.

Value Proposition of Proposed Therapy: The current standard of care is neurorehabilitation following stroke. However, patients experience a decline in function and live with some neurological impairment or disability. The proposed allogeneic cell therapy may promote recovery and improved motor function.

Why a stem cell project: The therapeutic candidate is a human embryonic stem cell-derived neural stem cell product.

CLIN2-12379: Similar CIRM Portfolio Projects

No other currently active projects in the CIRM portfolio for stroke.

CLIN2-12379: Previous CIRM Funding to Applicant

Project Stage	Indication	Project Outcome	Project Duration	Award Amount	Milestones*
IND-enabling (Closed)	Subcortical Ischemic Stroke	Preclinical studies, IND filing	Aug 2017 – Jan 2021	$5,300,000	**M1-M2**: Preclinical safety/toxicity, manufacturing filing (Achieved with minor delays) **M3**: File IND (Achieved with minor delays) **M4:** Clinical start up activities (Achieved with minor delays)
IND-enabling (Closed)	Subcortical Ischemic Stroke	Pre-IND meeting	Feb 2010 – Mar 2015	$17,244,851	**M1-M3:** Proof of concept studies (Achieved on time) **M4-M6:** Pilot safety, manufacturing (Achieved with minor delays) **M7-M8:** Pre-IND meeting (Achieved on time) **M9-M12:** Pivotal studies and IND filing (Not completed)
Studies on basic mechanisms	Subcortical Ischemic Stroke	Candidate characterization	Aug 2014 - Jul 2017	$1,178,370	**M1-M3:** Investigate effects of candidate on inflammatory response, recovery, and plasticity (Achieved on time)

CLIN2-12379: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Scientific Score	GWG Votes
1	11
2	0
3	1

DEI Score: 9

CIRM Team Recommendation: Fund (concur with GWG recommendation)

CIRM Award Amount: $ 11,998,988*

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

CLIN2-12595: CAR-T Cell Therapy for Brain and Spinal Tumors (Gliomas)

Therapy	Autologous CAR-T cell therapy
Indication	Diffuse Intrinsic Pontine Glioma (DIPG), Spinal Diffuse Midline Glioma (DMG)
Goal	Complete a phase 1 trial to assess safety and dosing
Funds Requested	$11,998,310 (co-funding: $0)

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

CLIN2-12595: 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 and radiotherapy only provides temporary improvement. The proposed CAR-T therapy offers the possibility of improved patient outcomes including an improvement in neurological deficits.

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

CLIN2-12595: Similar CIRM Portfolio Projects

Application/ Award	Project Stage	Project End Date	Indication	Candidate	Mechanism of Action
CLIN2	Phase 1 clinical trial	Dec 2023	Malignant pediatric glioma	CAR-T cell therapy with lymphodepletion	Chimeric antigen receptor T cells engineered to target tumor cells combined with lymphodepletion of patients to enhance effectiveness
CLIN1	IND-enabling studies	Dec 2021	Glioblastoma/ Grade IV gliomas	Genetically modified hematopoietic stem cells	Introducing a gene in blood stem cells to confer protection from chemotherapy in glioblastoma patients
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

CLIN2-12595: Previous CIRM Funding to Applicant

Project Stage	Indication	Project Outcome	Project Duration	Award Amount	Milestones*
Clinical trial (Active)	Refractory B cell malignancies	Complete phase 1 trial	Jun 2018 – May 2022	$11,976,906	**M1-M5**: Enrollment and treatment (Achieved on time) **M6-M7**: Complete enrollment and study completion (On track)

CLIN2-12595: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Scientific Score	GWG Votes
1	14
2	0
3	0

DEI Score: 8

CIRM Team Recommendation: Fund (concur with GWG recommendation)

CIRM Award Amount: $ 11,998,310*

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

CLIN2-12735: Cell Therapy for Heart Failure

Therapy	hESC-derived cardiomyocytes
Indication	Chronic ischemic left ventricular dysfunction
Goal	Complete a phase 1 trial to assess safety and initial efficacy
Funds Requested	$6,987,507 (co-funding: $0)

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

CLIN2-12735: Background Information

Clinical Background: About 6.2 million adults in the United States have heart failure. Heart failure costs the nation an estimated $30.7 billion in 2012. This total includes the cost of health care services, medicines to treat heart failure, and missed days of work.

Value Proposition of Proposed Therapy: A major issue underlying heart failure is that a large number of heart muscle cells are killed or damaged by ischemic injury, and the adult heart has a negligible capacity to replace these cells. The proposed therapy has the potential to improve recovery of cardiac function following myocardial infarction.

Why a stem cell project: The therapeutic candidate is a human embryonic stem cell-derived cardiomyocyte product.

CLIN2-12735: Similar CIRM Portfolio Projects

No other currently active projects in the CIRM portfolio for heart failure.

CLIN2-12735: Previous CIRM Funding to Applicant

Project Stage	Indication	Project Outcome	Project Duration	Award Amount	Milestones*
IND-enabling (Closed)	Heart failure	Preclinical studies, IND filing	Apr 2013 – Oct 2019*	$19,060,330	**M1:** GMP compatible material released (achieved on time) **M2:** Draft GLP study reports to CIRM **(**achieved with minor delays) **M3:** File IND **(**achieved with minor delays)
Translational (Closed)	Cardiotoxicity prediction for screened drugs	A preclinical drug screening kit with beta test feedback	Jul 2017 – Aug 2019	$975,000	**M1:** Characterization of 20 iPSC patient lines (achieved on time) **M2:** Validate cardiotoxicity responses **(**achieved with minor delays) **M3:** Perform above activities on 20 additional lines an distribute kit for testing (not completed)

*NOA revised in 2016 to streamline milestones to CIRM 2.0 OM format.

CLIN2-12735: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Scientific Score	GWG Votes
1	10
2	0
3	2

DEI Score: 10

CIRM Team Recommendation: Fund (concur with GWG recommendation)

CIRM Award Amount: $ 6,987,507*

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