SOMETHING BETTER THAN HOPE

Right now.

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California Institute for Regenerative Medicine

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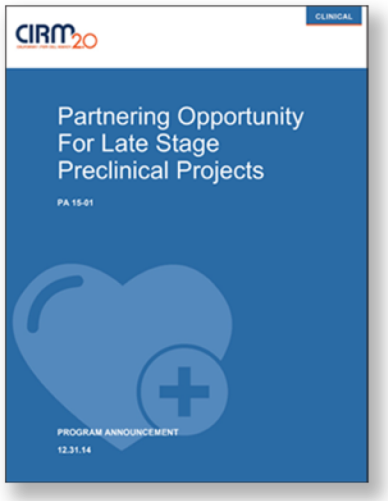
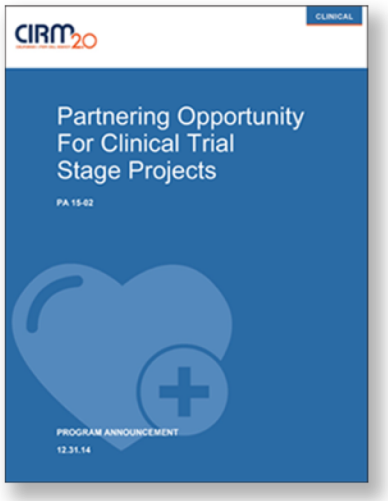
CIRM
CALIFORNIA'S STEM CELL AGENCY

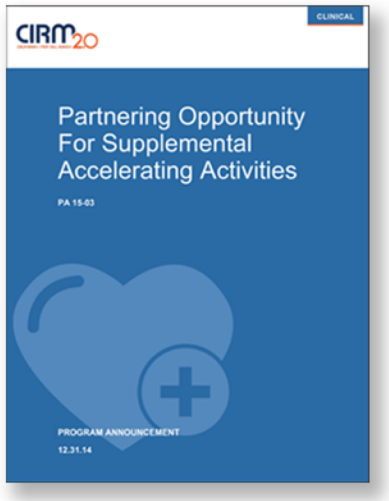
Every Moment Counts. **Don't Stop** Now.

Clinical Stage Programs

CLINICAL STAGE







CLIN 1 **CLIN 2** **CLIN 3**

Scoring System for Clinical Applications

- **Score of "1"**

  Exceptional merit and warrants funding.

- **Score of "2"**

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

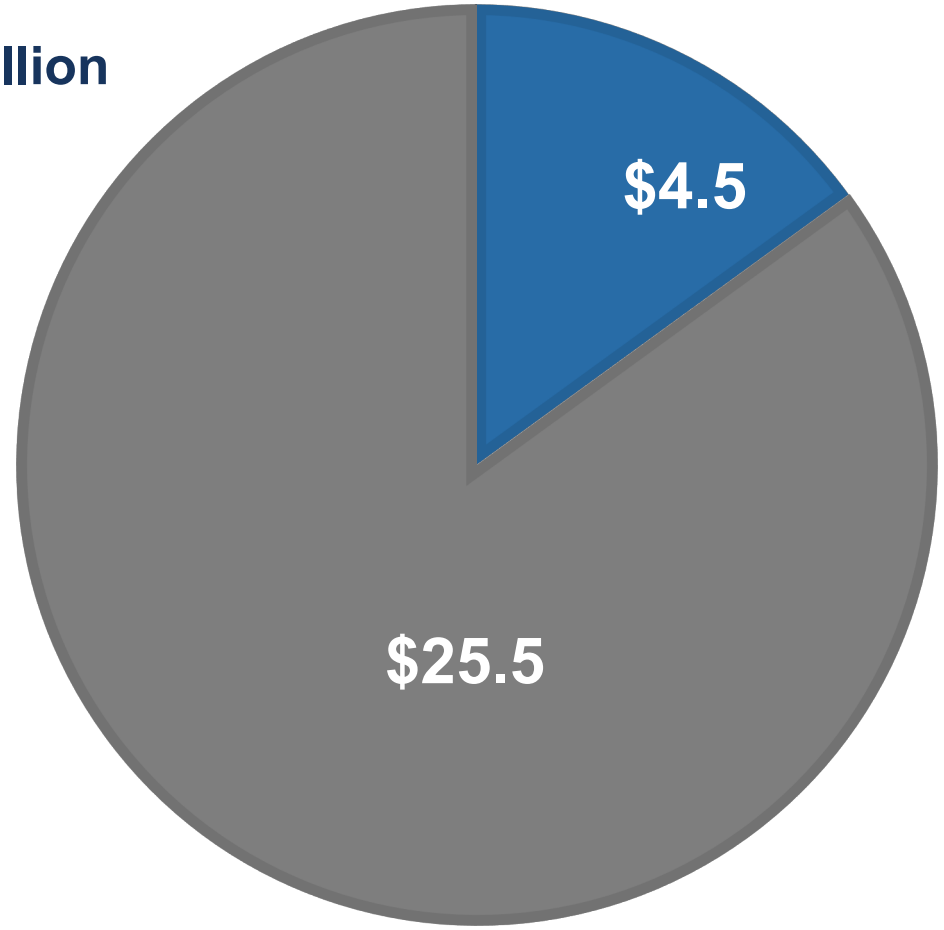
- **Score of "3"**

  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.

2019 Sickle Cell Disease Clinical Budget Status

Annual Allocation: $30 million

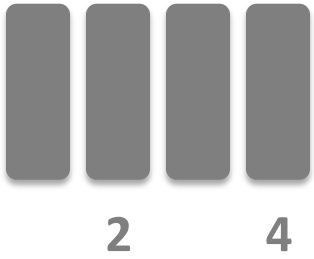


- Amount Requested Today
- Approved Awards
- Unused Balance

Amounts are shown in millions

2019 Sickle Cell Disease Award Targets

CLIN2
Clinical Trials



GOAL

CLIN1
Late Stage Preclinical

GOAL

Approved Award

Awaiting Today's Approval

CLIN1-11497: Project Summary

Therapy	Autologous CRISPR-edited hematopoietic stem cells (HSC)
Indication	Sickle Cell Disease (SCD)
Goal	Completion of IND-enabling studies and IND filing
Funds Requested	$4,490,777 ($0 Co-funding)

Maximum funds allowable for this category: $6,000,000

CLIN1-11497: Background Information

Clinical Background: SCD affects approximately 100,000 Americans. SCD is particularly common in those with sub-Saharan African ancestry affecting 1 in 365 African-American births. Globally, over 300,000 babies are born with SCD every year.

Value Proposition of Proposed Therapy: The only current cure is allogeneic HSC transplantation. The proposed therapy will restore expression of normal hemoglobin by correcting the mutation in the patient's own HSCs. Thus, it could be a curative treatment option for a much broader SCD patient population and may overcome the limitations of allogeneic transplantation.

Why a stem cell project: The therapy includes genetically-modified hematopoietic stem cells.

CLIN1-11497: Related CIRM Portfolio Projects

Application/ Award	Project Stage	Project End Date	Indication	Candidate	Mechanism of Action
Current Application	IND	N/A	Sickle Cell Disease	Autologous CRISPR-edited hematopoietic stem cells	Virus-free CRISPR editing to correct the pathogenic hemoglobin S allele mutation in HSC
CLIN1	IND	06/30/19	Sickle Cell Disease	Autologous CRISPR-edited hematopoietic stem cells	CRISPR editing to correct the pathogenic hemoglobin S allele mutation in HSC
CLIN2	Phase 1	12/31/21	Sickle Cell Disease	Autologous lentiviral gene-modified hematopoietic stem cells	Expression of lentiviral transferred anti-sickling hemoglobin gene
CLIN2	Phase 1	04/30/22	Sickle Cell Disease	CD4 T Cell depleted haploidentical HSC transplant	Achieving immune tolerance by inducing mixed chimerism

CLIN1-11497: Previous CIRM Funding

Applicant has received previous funding from CIRM for development of the proposed therapy.

Project Stage	Project Outcome	Project Duration	Award Amount	Milestones
Translational (TRAN1)	Pre-IND Meeting	02/01/17 - 08/31/19	$4,463,435	**OM1:** Gene correction process optimization (Achieved on time)
				OM2: Off-target assessments; Manufacturing process development (Achieved on time)
				OM3: Pre-IND Meeting (Achieved early) and GMP-compliant manufacturing (On track)

CLIN1-11497: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Score	GWG Votes
1	14
2	1
3	0

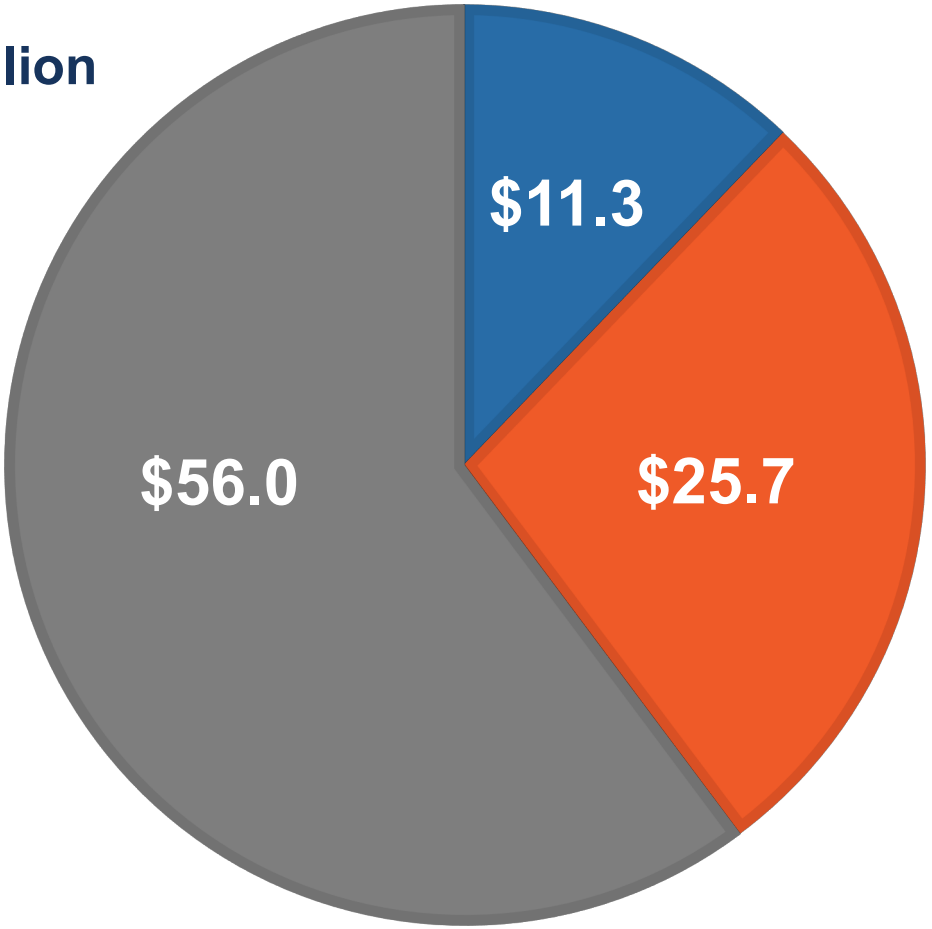
CIRM Team Recommendation: Fund (concur with GWG recommendation)

Award Amount: $4,490,777*

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

2019 Clinical Budget Status

Annual Allocation: $93 million



- Amount Requested Today
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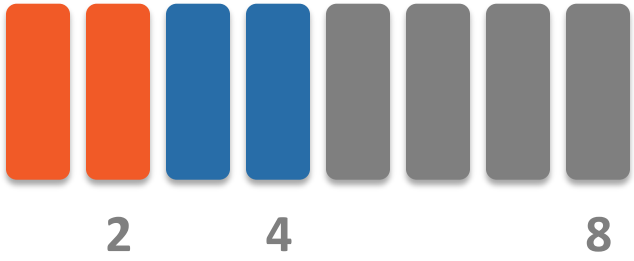
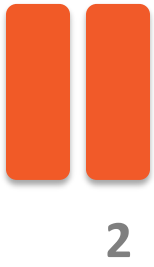
2019 Clinical Award Targets

CLIN2
Clinical Trials



GOAL

CLIN1
Late Stage Preclinical



GOAL

Approved Award

Awaiting Today's Approval

CLIN2-11480: Project Summary

Therapy	Autologous CD18 gene-modified hematopoietic stem cells
Indication	Leukocyte Adhesion Deficiency-1 (LAD-1)
Goal	Phase 2 trial completion
Funds Requested	$6,567,085 ($5,594,183 Co-funding)

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

CLIN2-11480: Background Information

Clinical Background: LAD-1 is a very rare autosomal recessive disorder estimated to occur in 1/1 million people worldwide. It results in immunodeficiency and most children with severe LAD-1 die from infections before age of 2.

Value Proposition of Proposed Therapy: The only current cure for LAD-1 is allogeneic HSC transplantation. The proposed curative gene therapy will restore immune function by lentiviral-mediated CD18 gene transfer into the patient's own HSCs. Thus, it has the potential to be a curative option for a wider LAD-1 patient population and to overcome the limitations of allogeneic transplantation.

Why a stem cell project: The therapy includes genetically-modified hematopoietic stem cells.

CLIN2-11480: Related CIRM Portfolio Projects

There are currently no CLIN stage projects targeting Leukocyte Adhesion Deficiency-1 in CIRM's active projects portfolio.

CLIN2-11480: Previous CIRM Funding

Applicant has not received previous funding from CIRM for development of the proposed therapy.

CLIN2-11480: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Score	GWG Votes
1	13
2	0
3	0

CIRM Team Recommendation: Fund (concur with GWG recommendation)

Award Amount: $6,567,085*

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

CLIN2-11380: Project Summary

Therapy	Autologous gene-modified hematopoietic stem and T cells expressing NY-ESO-1 T cell receptor
Indication	Advanced NY-ESO-1+ sarcomas
Goal	Phase 1 trial completion
Funds Requested	$4,693,839 ($0 Co-funding)

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

CLIN2-11380: Background Information

Clinical Background: Synovial sarcoma is rare and usually affects young adults. An estimated 800-900 young adults are diagnosed with the disease in the US each year. Patients with locally advanced or metastatic tumors have poor prognoses and low survival rates.

Value Proposition of Proposed Therapy: There is currently no treatment option for synovial sarcoma patients who've exhausted surgery and chemotherapy. The proposed dual cell therapy could improve patient survival by targeting NY-ESO-1 positive tumor cells with both an immediate and sustained antitumor response. The trial will also inform immunotherapy approaches in other cancers.

Why a stem cell project: The therapy includes genetically-modified hematopoietic stem cells.

CLIN2-11380: Related CIRM Portfolio Projects

Application/ Award	Project Stage	Project End Date	Indication	Candidate	Mechanism of Action
Current Application	Phase 1	N/A	NY-ESO-1 positive sarcoma	Autologous gene-modified HSC and T cells expressing NY-ESO-1 TCR	Immediate and sustained NY-ESO-1+ antitumor response
Disease Team	Phase 1	11/30/20	NY-ESO-1 positive multiple myeloma	Autologous gene-modified HSC and T cells expressing NY-ESO-1 TCR	Immediate and sustained NY-ESO-1+ antitumor response

CLIN2-11380: Previous CIRM Funding

Applicant has received previous funding from CIRM for development of the proposed therapy.

Project Stage	Project Outcome	Project Duration	Award Amount	Milestones*
Clinical (Disease Team)	Ongoing	04/01/14 - 11/30/20	$19,999,563 ($14.2M issued to date)	**OM1:** IND (Achieved on time)
				OM2: Treat first subject# (Achieved with delays)
				OM3: Treat first subject in Cohort 2 (Delayed with serious concerns)
				OM4: Complete Cohort 2 enrollment (Expected delay)
				OM5: Final CSR (Expected delay)

*CIRM 2.0 Milestones Displayed. Award converted to CIRM 2.0 on 10/03/16.
Sarcoma patient treated.

CLIN2-11380: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Score	GWG Votes
1	14
2	1
3	0

CIRM Team Recommendation: Fund (concur with GWG recommendation)

Award Amount: $4,693,839*

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