SOMETHING BETTER THAN HOPE

Right now.

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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"**

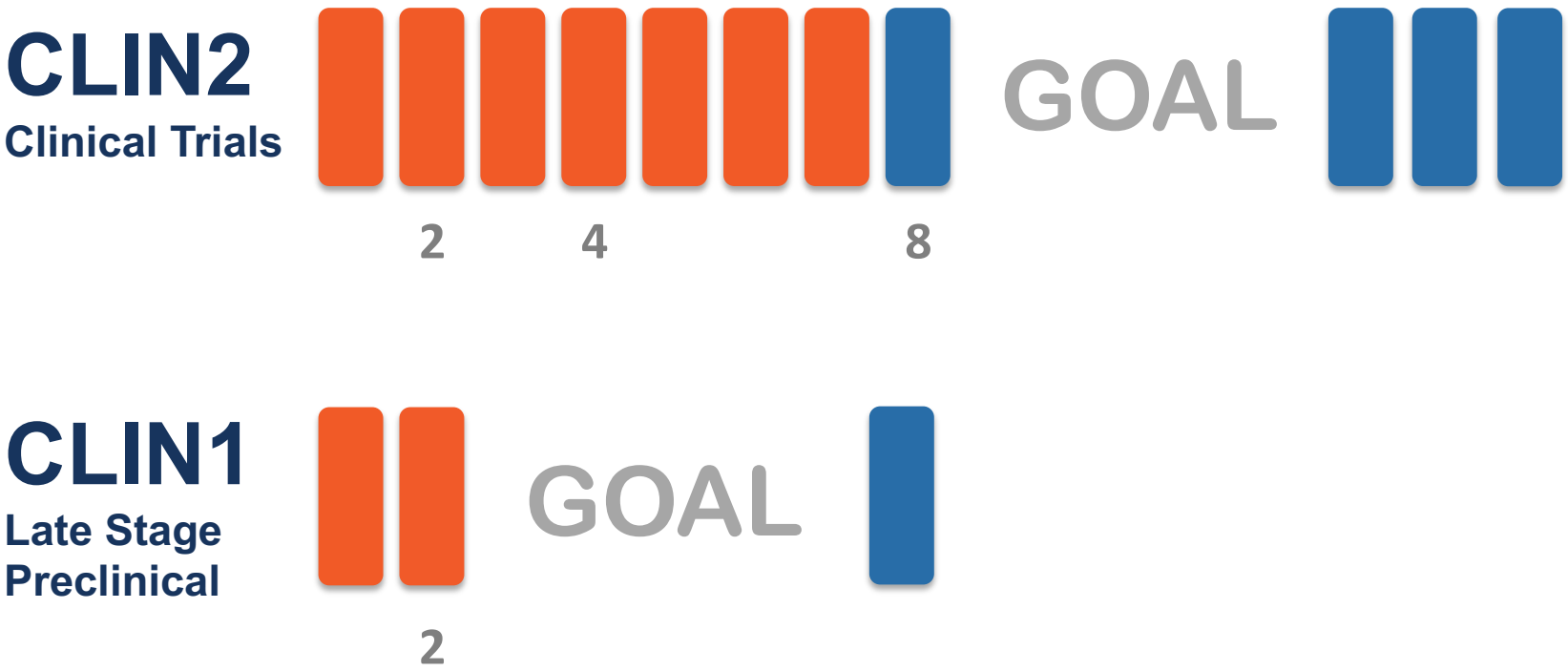
  Needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.

- **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 Clinical Award Targets



CLIN1-11591: Project Summary

Therapy	Autologous FOXP3 gene-modified CD4+ T cells
Indication	Immune dysregulation polyendocrinopathy enteropathy x-linked (IPEX) syndrome
Goal	IND filing
Funds Requested	$5,527,984 ($0 Co-funding)

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

CLIN1-11591: Background Information

Clinical Background: Immune Dysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) syndrome is a rare autoimmune disease. IPEX is an autoimmune inflammatory disease caused by a FOXP3 gene mutation that leads to a lack of regulatory T cells and is fatal if untreated.

Value Proposition of Proposed Therapy: The current standard of care options are either chronic immunosuppression or allogeneic hematopoietic stem cell transplant (HSCT). Immunosuppression is not curative and has significant side effects. HSCT is curative but there are insufficient matched donors. Other future curative autologous gene editing therapies are a longer-term goal, and the proposed therapy offers a bridging opportunity for IPEX treatment. In addition, it could impact other autoimmune diseases that do not have gene editing options.

Why a stem cell project: This is a gene therapy approach that is not stem cell-based and was submitted as a 'vital research opportunity' project.

Sources:

CLIN1-11591: Related CIRM Portfolio Projects

There are currently no clinical stage projects targeting IPEX in CIRM's active projects portfolio.

CLIN1-11591: Previous CIRM Funding

Applicant has received previous funding from CIRM for the same indication but not for earlier stages of this specific project.

CLIN1-11591: GWG Review

Vital Research Opportunity Vote:

	GWG Votes
Yes	22
No	0

GWG Recommendation: Exceptional merit and warrants funding

Score	GWG Votes
1	13
2	2
3	0

CIRM Team Recommendation: Fund (concur with GWG recommendation)

Award Amount: $5,527,984*

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

CLIN2-11650: Project Summary

Therapy	Autologous limbal stem cells
Indication	Corneal limbal stem cell deficiency
Goal	Phase 1 trial completion
Funds Requested	$10,301,486 ($650,000 Co-funding)

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

CLIN2-11650: Background Information

Clinical Background: Limbal Stem Cell Deficiency (LCSD) is a rare corneal disease where there is a loss of corneal stem/progenitor cells or their function is impaired. This leads to decreased vision, discomfort, and pain.

Value Proposition of Proposed Therapy: LCSD does not currently have any approved autologous treatments in the US. The proposed autologous, xeno-free therapy would likely be an improvement to an approved autologous treatment in the EU that uses xenogenic reagents. The current standard of care in the US is allogeneic transplantation, which requires immunosuppression.

Why a stem cell project: The proposed therapy is composed of limbal stem cells.

Sources: JDRF, NIDDK, CDC

CLIN2-11650: Related CIRM Portfolio Projects

CIRM is currently supporting applicant's IND stage activities for the same project (please see next slide).

There are currently no clinical stage projects targeting corneal limbal stem cell deficiency in CIRM's active projects portfolio.

CLIN2-11650: Previous CIRM Funding

Applicant has received previous CIRM funding for the same candidate.

Project Stage	Project Outcome	Project Duration	Award Amount	Milestones*
CLIN1 (Late stage preclinical)	Ongoing	8/31/2017-12/31/2019	$4,244,211	**OM1:** Manufacturing testing and qualification (Achieved on time)
				OM2: Tech transfer to GMP facility (Achieved with delay)
				OM3: File IND with FDA (Achieved with delay)
				OM4: Complete clinical trial start-up activities (Delayed with minor concerns)
TR2 (Early Translation)	Closed	3/1/2011-2/28/2014 (8/1/2014-4/30/2015 Bridging award)	$1,524,947 (+$697,507 Bridging award)	**5 milestones proposed, 5 achieved.** Received additional 6-month 'Bridging' award with two milestones proposed and achieved.

CLIN2-11650: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Score	GWG Votes
1	12
2	3
3	0

CIRM Team Recommendation: Fund (concur with GWG recommendation)

Award Amount: $10,301,486*

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

CLIN2-11661: Project Summary

Therapy	AAV2-GDNF gene therapy
Indication	Parkinson's Disease
Goal	Phase 1b trial completion
Funds Requested	$7,998,962 ($3,500,000 Co-funding)

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

CLIN2-11661: Background Information

Clinical Background: Parkinson's disease (PD) is a progressive neurological disorder affecting almost 1 million Americans and an additional 60,000 Americans are newly diagnosed each year. PD is caused by dopaminergic neuronal cell death in regions of the brain, especially the substantia nigra. Patients experience motor symptoms such as tremors, limb stiffness and impaired balance and non-motor symptoms affecting cognition and behavior.

Value Proposition of Proposed Therapy: There is no cure for PD. Levodopa medication controls motor symptoms but loses efficacy as the disease progresses. Deep brain stimulation surgery controls motor symptoms in patients non-responsive to medication. The proposed single-dose GDNF gene therapy acts by protecting neurons and regenerating dopaminergic terminals. It has the potential to provide sustained symptomatic relief as well as delay or reverse disease progression.

Why a stem cell project: This is a gene therapy approach that is not stem cell-based and was submitted as a 'vital research opportunity' project.

Sources: NIH

CLIN2-11661: Related CIRM Portfolio Projects

Application/ Award	Project Stage	Project End Date	Indication	Candidate	Mechanism of Action
Current Application	Phase 1b trial	N/A	Parkinson's Disease	AAV2-GDNF gene therapy	Protection and regeneration of dopaminergic neurons via sustained expression of GDNF in putamen
CLIN1-11059	IND	Jan 2020	Parkinson's Disease	Allogeneic neural progenitor cells (NPC) gene-modified to secrete GDNF	Protection and regeneration of dopaminergic neurons via NPC secreted GDNF

CLIN2-11661: Previous CIRM Funding

Applicant has received previous funding from CIRM for the same indication but not for earlier stages of this specific project.

CLIN2-11661: GWG Review

Vital Research Opportunity Vote:

	GWG Votes
Yes	21
No	0

GWG Recommendation: Exceptional merit and warrants funding

Score	GWG Votes
1	13
2	2
3	0

CIRM Team Recommendation: Fund (concur with GWG recommendation)

CLIN2-11661: GWG Review

Applicant Request: $7,998,962*

GWG Advice: CIRM should not fund proposed manufacturing activities that would support the eventual phase 2/3 clinical trial.

Award Amount without Manufacturing Activities: $5,510,462*

CIRM Team Recommendation: Concur with GWG advice to fund award amount of $5,510,462*

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

CLIN2-11620: Project Summary

Therapy	Allogeneic neural progenitor cells
Indication	Retinitis pigmentosa
Goal	Phase 1/2a trial completion
Funds Requested	$10,494,682 ($0 Co-funding)

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

CLIN2-11620: Background Information

Clinical Background: Retinitis Pigmentosa (RP) is a group of genetic disorders that causes photoreceptor cell death leading to progressive vision loss and resulting in tunnel vision. Symptoms become apparent in childhood and patients become legally blind by ages 40-50. RP is a rare disease that affects up to 109,000 Americans.

Value Proposition of Proposed Therapy: There is no cure for retinitis pigmentosa. Luxturna gene therapy is a treatment option for a small subset of patients with mutations in both copies of the RPE65 gene. The proposed cell therapy has the potential to stabilize or improve vision by protecting photoreceptors in a broad population of RP patients.

Why a stem cell project: The proposed therapy includes neural progenitor cells.

Sources: NIH, Spark Therapeutics

CLIN2-11620: Related CIRM Portfolio Projects

Application/ Award	Project Stage	Project End Date	Indication	Candidate	Mechanism of Action
Current Application	Phase 1/2a trial	N/A	Retinitis Pigmentosa	Allogeneic neural progenitor cells	Neurotrophic support of photoreceptors
CLIN2-09698	Phase 2	Jun 2021	Retinitis Pigmentosa	Allogeneic retinal progenitor cells	Neurotrophic support of photoreceptors

CLIN2-11620: Previous CIRM Funding

Applicant has received previous funding from CIRM for earlier stages of this project as described below. Applicant has also received previous funding from CIRM for projects with related candidates and indications (not shown).

Project Stage	Project Outcome	Project Duration	Award Amount	Milestones*
Late Stage Preclinical	Filed IND	Aug 2015 – Nov 2018	$4,954,514	**OM1:** Manufacture and release clinical lots (Achieved with minor delays)
				OM2: Complete IND-enabling studies (Achieved with minor delays)
				OM3: File IND (Achieved with minor delays)

CLIN2-11620: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Score	GWG Votes
1	15
2	0
3	0

CIRM Team Recommendation: Fund (concur with GWG recommendation)

Award Amount: $10,494,682*

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

CLIN2-11472: Project Summary

Therapy	Allogeneic retinal progenitor cells
Indication	Retinitis pigmentosa
Goal	Complete commercial manufacturing technology transfer & phase 2 trial
Funds Requested	$6,608,592 ($4,405,728 Co-funding)

Maximum funds allowable for this category: $15,000,000

CLIN2-11472: Background Information

Clinical Background: Retinitis Pigmentosa (RP) is a group of genetic disorders that causes photoreceptor cell death leading to progressive vision loss and resulting in tunnel vision. Symptoms become apparent in childhood and patients become legally blind by ages 40-50. RP is a rare disease that affects up to 109,000 Americans.

Value Proposition of Proposed Therapy: There is no cure for retinitis pigmentosa. Luxturna gene therapy is a treatment option for a small subset of patients with mutations in both copies of the RPE65 gene. The proposed cell therapy has the potential to stabilize or improve vision by protecting photoreceptors in a broad population of RP patients. The therapy is delivered by intravitreal injection, which is less invasive than subretinal delivery.

Why a stem cell project: The proposed therapy includes retinal progenitor cells.

Sources: NIH, Spark Therapeutics

CLIN2-11472: Related CIRM Portfolio Projects

CIRM is currently supporting applicant's phase 2 trial for the same candidate (please see next slide).

CLIN2-11472: Previous CIRM Funding

Project Stage	Project Outcome	Project Duration	Award Amount	Milestones*
CLIN2 (clinical trial)	Ongoing	Feb 2017-current	$8,295,750	**OM1-3:** Recruit and treat up to 85 patients (Achieved early)
				OM4: Primary endpoint analysis with 12-month follow-up (On track, expected Q4 2019)
				OM5: Final clinical study report and/or BLA filing (On track, expected Q3 2020)
DR2A (IND enabling, clinical trial)	Closed	Jan 2013-Dec 2017	$17,144,825	5 milestones for manufacturing, IND enabling studies, IND filing, completion of phase 1/2a trial; 5 milestones achieved (All on time)
TR2 (Preclinical development)	Closed	July 2011-Sept 2012	$1,803,768	Three milestones proposed; one achieved (OM1 on time, OM2-3 on track at transition to DR2A award)
DT1 (Disease team planning award)	Closed	Aug 2008-Jan 2009	$23,537	Awardee submitted successful disease team award

CLIN2-11472: GWG Review

GWG Recommendation: Exceptional merit and warrants funding

Score	GWG Votes
1	12
2	1
3	2

CIRM Team Recommendation: Fund (concur with GWG recommendation)

Award Amount: $6,608,592*

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