# GWG Recommendations: Clinical Program (CLIN1, CLIN2, CLIN4)

CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

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ICOC/ARS Meeting

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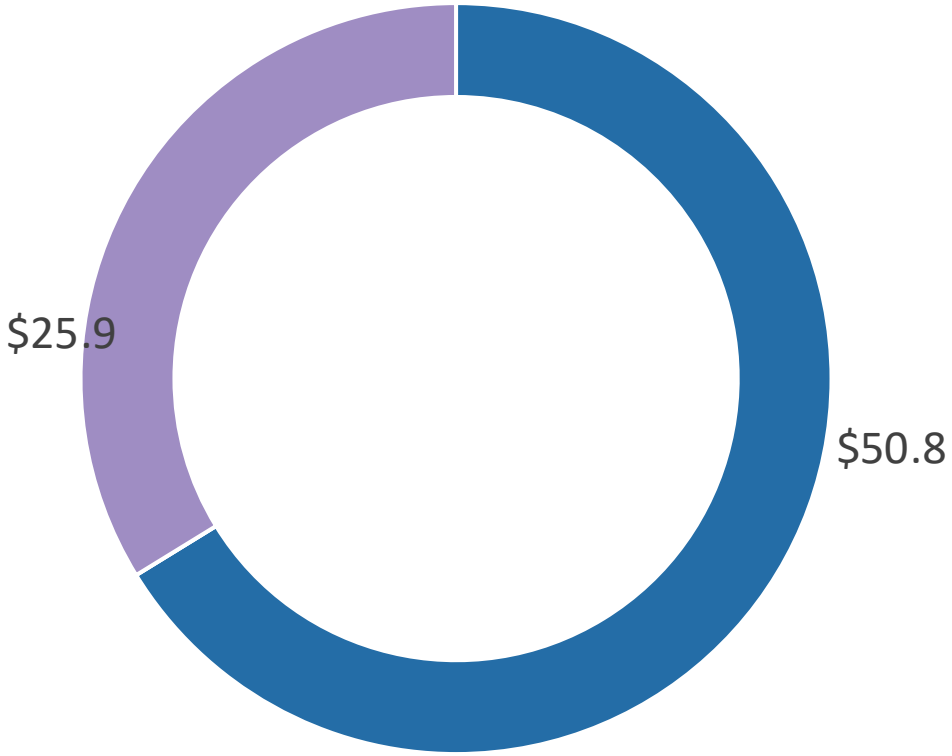
# Our Mission

Accelerating world class science to deliver transformative regenerative medicine treatments in an equitable manner to a diverse California and world.

# Clinical Budget Status

## Budget Allocation: $76.7 million (Jan to June 2025)

- Amount Requested Today
- Approved Awards
- Unused Balance



# Clinical 

## Scientific Scoring System

- **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.

# Clinical 

## Scientific Review Criteria

1. Does the project hold the necessary significance and potential for impact? *(what value does it offer; is it worth doing?)*
2. Is the rationale sound? *(does it make sense?)*
3. Is the project well planned and designed?
4. Is the project feasible? *(can they do it?)*
5. Does the project uphold principles of diversity, equity, and inclusion (DEI)? *(e.g., does it consider patient diversity?)*

# Clinical 

## Diversity, Equity and Inclusion Scoring System

- DEI Score of 9-10: *Outstanding Response*
- DEI Score of 6-8: *Responsive*
- DEI Score of 3-5: *Not Fully Responsive*
- DEI Score of 0-2: *Not Responsive*

Applications are scored for adherence to principles of DEI by all GWG Board Members with no conflict.

The criteria used to measure adherence fall under overarching categories of: Commitment to DEI, Project Plans and Cultural Sensitivity.

# Clinical

## Review Panel Roles

| | |
|---|---|
| Scientific GWG Members | Scientific evaluation (disease area expert, regulatory, CMC, product development)<br>Provides scientific score on all applications |
| GWG Board Member<br>(Patient Advocate/Nurse) | DEI evaluation, patient perspective on significance and potential impact, oversight on process<br>Provides DEI score on all applications<br>Provides a suggested scientific score |
| Scientific Specialist<br>(non-voting) | Scientific evaluation (specialized expertise as needed)<br>Provides initial but not final scientific score |

# CLIN1-16103

## Targeted DOK7 gene therapy for Congenital Myasthenic Syndromes

### FUNDS REQUESTED

$2,894,305

Co-funding: $723,577 (20% required)

California organization

### THERAPY

A gene therapy product for the treatment of DOK7 Congenital Myasthenic Syndrome

### INDICATION

DOK7 Congenital Myasthenic Syndrome

### GOAL

IND filing for the therapeutic candidate

# CLIN1-16103 Background Information

## Clinical background

Congenital Myasthenic Syndromes (CMS) are a group of rare genetic neuromuscular disorders that cause muscle weakness. Patients with DOK7 CMS have decreased quality of life. The severity of the disease ranges from using breathing aids to a complete inability to move with life-threatening complications.

## Value proposition of proposed therapy

The current standard of care treats symptoms only, requires chronic administration, and the effectiveness can decrease over time. The proposed gene therapy would potentially be a one-time curative treatment.

## Why a stem cell or gene therapy project

The therapy is a gene therapy product.

# CLIN1-16103 Similar CIRM Portfolio Projects

*CIRM does not currently have any active TRAN or CLIN awards addressing congenital myasthenic syndrome.*

# CLIN1-16103 Previous CIRM Funding to Applicant Team

*Applicant has not previously received a CIRM award*

# CLIN1-16103 GWG Review

## Targeted DOK7 gene therapy for Congenital Myasthenic Syndromes

**CIRM Award Amount:**
$2,894,305*

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

## GWG RECOMMENDATION

Exceptional merit and warrants funding

| Scientific Score | GWG Votes |
|---|---|
| 1 | 15 |
| 2 | 0 |
| 3 | 0 |

## DEI SCORE

8 (scale 1-10)

## CIRM TEAM RECOMMENDATION

Fund (concur with GWG recommendation)

# CLIN1-17165

## Advancing a novel antisense oligonucleotide for the treatment of SCA3, a devastating neurodegenerative disease

### FUNDS REQUESTED

$5,692,538

Co-funding: $0 (none required)

California organization

### THERAPY

An antisense oligonucleotide of the ATXN3 (Ataxin-3) gene

### INDICATION

Spinocerebellar Ataxia Type 3 (SCA3)

### GOAL

IND submission

# CLIN1-17165 Background Information

## Clinical background

Spinocerebellar Ataxia Type 3 (SCA3) is a neurodegenerative disease caused by a toxic mutation in the ataxin-3 gene. Disease symptoms appear around midlife and usually impacts patient gait, speech, balance/spatial awareness and eye movement. SCA3 progresses over time and is eventually fatal.

## Value proposition of proposed therapy

There are currently no effective treatments that target the underlying disease. Current standard of care is treatment for pain relief and anti-spasticity drugs. The proposed antisense oligonucleotide treatment skips the mutated part of the gene to produce a functional protein. Ideally, this reduces the accumulation of toxic protein, reduces symptoms, and slows progression of the disease.

## Why a stem cell or gene therapy project

The therapy is a genetic therapy.

# CLIN1-17165 Similar CIRM Portfolio Projects

*CIRM does not currently have any active TRAN or CLIN awards addressing SCA3.*

# CLIN1-17165 Previous CIRM Funding to Applicant Team

*Applicant has not previously received a CIRM award*

# CLIN1-17165 GWG Review

## Advancing a novel antisense oligonucleotide for the treatment of SCA3, a devastating neurodegenerative disease

**CIRM Award Amount:**
$5,692,538*

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

## GWG RECOMMENDATION

Exceptional merit and warrants funding

| Scientific Score | GWG Votes |
|---|---|
| 1 | 14 |
| 2 | 0 |
| 3 | 0 |

## DEI SCORE

7 (scale 1-10)

## CIRM TEAM RECOMMENDATION

Fund (concur with GWG recommendation)

# CLIN2-14796

## The [redacted] Delayed Immunological Tolerance after Kidney Transplantation Program

### FUNDS REQUESTED

$7,343,925

Co-funding: $0 (none required)

California organization

### THERAPY

CD34+ hematopoietic stem/progenitor cells (HSPC) and CD3+ cells

### INDICATION

Recipients with HLA-identical kidney transplant

### GOAL

Complete Phase 1 study

# CLIN2-14796 Background Information

## Clinical background

Kidney disease, where the organs cannot filter and clean the blood as they should, can ultimately lead to kidney failure and the need for dialysis or a kidney transplant. Current kidney transplant recipients need life long immunosuppressive drugs to prevent transplant rejection. Immunosuppressive drugs increase the risk of infection, cancer, diabetes, and heart disease.

## Value proposition of proposed therapy

The potential to withdraw these drugs from transplant recipients could extend the functionality of the transplanted kidney and positively impact patient quality of life. The ability to induce tolerance after the kidney transplant could benefit groups that are not able to undergo both procedures at the same time.

## Why a stem cell or gene therapy project

The therapy is made from stem/progenitor cells.

# CLIN2-14796 Similar CIRM Portfolio Projects

| Application/ Award | Project Stage | Project End Date | Indication | Candidate | Mechanism of Action |
|---|---|---|---|---|---|
| CLIN2 $11,217,155 | Phase 3 clinical trial | Q4 2024 | HLA matched kidney transplant recipients | Kidney transplant donor-derived CD34+HSCs and CD3+ T cells | Combine kidney transplant with donor stem cells to create immune tolerance to the donor kidney |
| CLIN2 $11,955,585 | Phase 1 clinical trial | Q4 2024 | HLA-mismatched kidney transplant recipients | Kidney transplant donor stem cells and expanded recipient Treg cells | Combine kidney transplant with donor stem cells and recipient Treg cells to create immune tolerance to the donor kidney |
| CLIN2 $6,653,266 | Phase 1 clinical trial | Q2 2025 | HLA-mismatched kidney transplant recipients | Kidney transplant donor stem cells and T cells | Combine kidney transplant with donor stem cells to create immune tolerance to the donor kidney |
| CLIN2 $11,998,188 | Phase 1b/2a clinical trial | Q1 2027 | HLA-mismatched pediatric kidney transplant recipients | Kidney transplant donor peripheral blood stem cells | Donor stem cell transplant followed by kidney transplant to create immune tolerance to the donor kidney |

# CLIN2-14796 Previous CIRM Funding to Applicant Team

*Applicant has not previously received a CIRM award*

# CLIN2-14796 GWG Review

## The [redacted] Delayed Immunological Tolerance after Kidney Transplantation Program

**CIRM Award Amount:**
$7,343,925*

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

## GWG RECOMMENDATION

Exceptional merit and warrants funding

| Scientific Score | GWG Votes |
|---|---|
| 1 | 15 |
| 2 | 0 |
| 3 | 0 |

## DEI SCORE

8 (scale 1-10)

## CIRM TEAM RECOMMENDATION

Fund (concur with GWG recommendation)

# CLIN2-17081

**Phase 1b/2a study of the safety and tolerability of human neural stem cells for Huntington's Disease**

## FUNDS REQUESTED

$11,955,874

Co-funding: $0 (none required)

California organization

## THERAPY

Human embryonic stem cell-derived neural stem cells

## INDICATION

Huntington's Disease

## GOAL

Complete Phase 1b/2a trial

# CLIN2-17081 Background Information

## Clinical background

Huntington's Disease (HD) is an inherited neurodegenerative disorder that is caused by mutations in the huntingtin gene. The disease is usually diagnosed in midlife, followed by 10-20 years of progressively worsening movement, cognition, and psychiatric symptoms. The disease is ultimately fatal and has a high burden on patient families because of the length of disease and severity of symptoms.

## Value proposition of proposed therapy

There are currently no FDA approved treatments for Huntington's that slow or prevent progression of the disease. The proposed therapy aims to provide neural stem cells that could support the survival and connectivity of existing neurons and potentially reduce the accumulation of the Huntingtin protein aggregates.

## Why a stem cell or gene therapy project

The therapy is a neural stem cell product.

# CLIN2-17081 Similar CIRM Portfolio Projects

| Application/ Award | Project Stage | Project End Date | Indication | Candidate | Mechanism of Action |
|---|---|---|---|---|---|
| CLIN1 $5,635,393 | IND enabling | Q2 2025 | Huntington's Disease | Human embryonic stem cell-derived neural stem cells | The new neural stem cells support, maintain, or restore existing neurons and connectivity; reduce pathogenic protein accumulation. |

# CLIN2-17081 Previous CIRM Funding to Applicant Team

| Application/ Award | Project Stage | Project End Date | Indication | Candidate | Mechanism of Action |
|---|---|---|---|---|---|
| CLIN1 $5,635,393 | IND enabling | July 2025 | Huntington's Disease | Human embryonic stem cell-derived neural stem cells | The transplanted neural stem cells support, maintain, or restore existing neurons and connectivity; reduce pathogenic protein accumulation. |
| PC1 $4,951,623 | Translational | Dec 2018 | Huntington's Disease | Human embryonic stem cell-derived neural stem cells | The transplanted neural stem cells support, maintain, or restore existing neurons and connectivity; reduce pathogenic protein accumulation. |
| TR2 $3,955,038 | Early Translational | Aug 2015 | Huntington's Disease | Human embryonic stem cell-derived neural stem cells | The transplanted neural stem cells support, maintain, or restore existing neurons and connectivity; reduce pathogenic protein accumulation. |
| DISC2 $1,650,263 | Candidate Discovery | Nov 2019 | Huntington's Disease | Gene modified human embryonic stem cell-derived neural stem cells to express protein ApiCCT1 | The modified neural stem cells support, maintain, or restore existing neurons and connectivity; reduce pathogenic protein accumulation. |

# CLIN2-17081 GWG Review

**Phase 1b/2a study of the safety and tolerability of human neural stem cells for Huntington's Disease**

## CIRM Award Amount:

$11,955,874*

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

## GWG RECOMMENDATION

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

| Scientific Score | GWG Votes |
|---|---|
| 1 | 1 |
| 2 | 6 |
| 3 | 8 |

## DEI SCORE

9 (scale 1-10)

## CIRM TEAM RECOMMENDATION

Do not fund (concur with GWG recommendation)

# CLIN2-17083

## Phase 1b Study of [redacted] in Adults with PKP2 Mutation-associated Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

### FUNDS REQUESTED

$8,000,000

Co-funding: $15,936,236 (40% required)

California organization

### THERAPY

AAV gene therapy to deliver a functional PKP2 gene

### INDICATION

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

### GOAL

Phase 1b study completed

# CLIN2-17083 Background Information

## Clinical background

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart condition that causes progressive heart muscle loss and typically manifests in young adults. This condition results in a high risk of life-threatening ventricular arrhythmias, sudden cardiac death, and progression to heart failure.

## Value proposition of proposed therapy

The current standard of care does not address the underlying disease. The proposed product would deliver a functional version of the Plakophilin-2 (PKP2) gene, restoring lost function in heart cells, which can potentially slow or reverse disease progression.

## Why a stem cell or gene therapy project

The therapy is a gene therapy product.

# CLIN2-17083 Similar CIRM Portfolio Projects

| Application/ Award | Project Stage | Project End Date | Indication | Candidate | Mechanism of Action |
|---|---|---|---|---|---|
| CLIN1 $4,000,000 | IND enabling | Q2 2026 | Desmoplakin-Associated Arrhythmogenic Cardiomyopathy | Adeno-associated virus vector-based gene therapy that drives over expression of FGF21 | Targets liver specific expression of FGF21 to restore heart cell function in patients at high risk of life-threatening arrhythmias and sudden cardiac death. |

# CLIN2-17083 Previous CIRM Funding to Applicant Team

| Application/ Award | Project Stage | Project End Date | Indication | Candidate | Mechanism of Action |
|---|---|---|---|---|---|
| DISC2 $1,017,000 | Candidate discovery | Aug 2024 | Heart Failure | A gene therapy to deliver cardiac reprogramming factors | Deliver reprogramming factors to convert resident cardiac fibroblasts into functioning cardiac muscle |

# CLIN2-17083 GWG Review

## Phase 1b Study of [redacted] in Adults with PKP2 Mutation-associated Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

**CIRM Award Amount:**
$8,000,000*

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

## GWG RECOMMENDATION

Exceptional merit and warrants funding

| Scientific Score | GWG Votes |
|---|---|
| 1 | 15 |
| 2 | 0 |
| 3 | 0 |

## DEI SCORE

8 (scale 1-10)

## CIRM TEAM RECOMMENDATION

Fund (concur with GWG recommendation)

# CLIN2-17091

## Phase 3 (Pivotal) Clinical Trial for SPG50

### FUNDS REQUESTED

$14,908,859

Co-funding: $9,939,239 (40% required)

California organization

### THERAPY

AAV9 gene therapy encoding human AP4M1 transgene

### INDICATION

Spastic Paraplegia Type 50 caused by the AP4M1 gene

### GOAL

Complete Phase 3 trial with BLA approval

# CLIN2-17091 Background Information

## Clinical background

Spastic paraplegia type 50 (SPG50) is a rare genetic neurodegenerative disease caused by a mutation in the adapter protein complex 4 (AP-4). The disease is characterized by the gradual onset of spastic paraplegia during the initial decade of life, which escalates to quadriplegia during adolescence or early adulthood. About 16 individuals in North America are affected by this specific disorder.

## Value proposition of proposed therapy

The proposed therapy offers the potential to correct the gene mutation in SPG50 patients and to develop a framework for applying this approach to other ultra-rare monogenic diseases.

## Why a stem cell or gene therapy project

The therapy is a gene therapy product.

# CLIN2-17091 Similar CIRM Portfolio Projects

*CIRM does not currently have any active TRAN or CLIN awards addressing SPG50.*

# CLIN2-17091 Previous CIRM Funding to Applicant Team

| Application/ Award | Project Stage | Project End Date | Indication | Candidate | Mechanism of Action |
|---|---|---|---|---|---|
| CLIN1 $3,930,964 | IND enabling | Dec 2025 | Charcot-Marie-Tooth disease type 4J (CMT4J) | AAV9-mediated gene therapy for CMT4J, a rare neurodevelopmental disease | Targets affected neurons to provide a functional version of the FIG4 gene to slow or halt disease progression |

# CLIN2-17091 GWG Review

## Phase 3 (Pivotal) Clinical Trial for SPG50

**CIRM Award Amount:**
$14,908,859*

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

## GWG RECOMMENDATION

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

| Scientific Score | GWG Votes |
|---|---|
| 1 | 0 |
| 2 | 0 |
| 3 | 14 |

## DEI SCORE

8 (scale 1-10)

## CIRM TEAM RECOMMENDATION

Do not fund (concur with GWG recommendation)

CIRM

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

# Thank You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