CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Memorandum

To: The Application Review Subcommittee of the ICOC
From: CIRM Leadership Team
Re: CIRM Team Recommendations: CLIN2
Date: September 24th, 2026

Executive Summary

This memo summarizes the CIRM Team funding recommendations for applications submitted to the CLIN2 program for consideration by the Application Review Subcommittee (ARS) on September 24, 2026.

This is the first CLIN2 cycle of the 2027 fiscal year. Of the 8 applications that underwent full scientific review by the GWG, 6 were recommended for funding and 2 were not recommended for funding by the GWG.

The CIRM Team concurs with the GWG recommendation to not fund 2 applications, concurs with the GWG and recommends funding 5 of the 6 GWG-recommended applications and does not concur with the GWG's recommendation to fund 1 application.

The Team assessment considered the GWG recommendation together with CIRM's programmatic priorities. In addition to the scientific merit, the Team considered the potential for transformative patient benefit, barriers to patient access, the balance of CIRM's clinical portfolio, the external therapeutic landscape, prior CIRM investment, and whether the proposed activities are positioned to efficiently advance clinical development to late-stage trials.

This distinction is relevant as CIRM evaluates its clinical portfolio and its own role in funding within the clinical development pathway. A scientifically compelling clinical trial is not necessarily, on its own, a sufficient programmatic rationale for CIRM investment. As CIRM evaluates its clinical portfolio, the Team is placing a greater emphasis on investments that will resolve enough development uncertainty to support a clear next decision point and position successful programs to continue beyond CIRM funding.

The Appendix contains detailed application assessments, including portfolio and programmatic considerations where relevant, and the basis for the CIRM funding.

I. Background

Introduction

The GWG recommendation reflects the scientific review of each application. The ARS has the separate responsibility to consider that recommendation together with CIRM's programmatic priorities, portfolio, available resources, and experience from prior investments. In doing so, the ARS may place different weight on considerations identified during scientific review when evaluating whether a proposed award represents an appropriate CIRM investment.

The role of the CIRM Team during the ARS meetings is to assist the ARS in making well-informed funding decisions by providing programmatic context alongside the outcomes of the Grants Working Group (GWG) recommendations. In developing these recommendations to the ARS, the CIRM Team evaluated all applications consistent with the following CIRM funding recommendation framework presented to the ICOC (March 2026):

1. Available program budget
2. GWG score & comments
3. Programmatic factors
4. Prior awardee performance
5. New information available to CIRM after GWG review

Summary of Program Budget Considerations

Available Program Budget (Annual)	$160M
Budget Utilization – GWG Recommended	$56.2M
Budget Utilization – CIRM Recommended	$44.2M
Remaining Program Budget	$115.8M

II. Proposal

After a review of all applications, the CIRM Team recommends:

1. To fund the following 5 applications:
    - CLIN2-20416
    - CLIN2-20392
    - CLIN2-20291
    - CLIN2-20409

- CLIN2-20350

2. To *not* fund the following 3 applications:
   - CLIN2-20316
   - CLIN2-20839
   - CLIN2-20454

Summary of Funding Recommendations

Application	Median Score	Scores to fund	Scores not to fund	GWG recommendation	CIRM Recommendation
CLIN2-20316	90	15	0	Fund	Do not Fund
CLIN2-20416	90	14	0	Fund	Fund
CLIN2-20392	87	14	1	Fund	Fund
CLIN2-20291	86	10	4	Fund	Fund
CLIN2-20409	85	15	0	Fund	Fund
CLIN2-20350	85	13	0	Fund	Fund
CLIN2-20389	84	3	11	Do not fund	Do not fund
CLIN2-20454	80	1	14	Do not fund	Do not fund

For the ARS, the CIRM Team provides assessments for any applications with a GWG score above or tied with the lowest scoring application where the CIRM recommendation differs from the GWG recommendation or for which there is a minority report.

Appendix: Application Assessments

1. Application number: CLIN2-20316

Title: In Utero Stem Cell Transplantation to Prevent Bone Marrow Failure and Cancer in Fanconi Anemia

GWG Outcome: Fund

Median	Mean	High	Low	Scores to fund	Scores not to fund
90	90	92	85	15	0

CIRM Team Recommendation: Do not Fund

CLIN2-20316 proposes an in utero stem cell transplantation approach for Fanconi anemia. The CIRM Team recognizes the strong scientific rationale, unanimous GWG support, and potentially transformative benefit of the proposed treatment. However, the Team recommends that the ARS **Not Fund based on programmatic considerations**.

The key consideration is whether the proposed investment is sufficiently positioned to move the program to a meaningful next development point during the term of the award. The proposed study represents an important early clinical step, but substantial development would remain beyond the 4-year award period before the program is positioned for later-stage development. Moreover, enrollment feasibility remains uncertain because the proposed approach depends on timely prenatal diagnosis, a concern also identified by the GWG.

Given the limited reachable population, enrollment and timeline risk, and lessons learned from CIRM's prior investment in FA and in utero transplantation, the Team does not believe this award is sufficiently positioned to de-risk the program to the point needed to support continued development beyond the CIRM-funded stage. Key activities and data from the trial would not be completed until 2 years later. As a result, the award is unlikely to produce, within the CIRM funded period, the evidence needed to determine whether the program should advance and what subsequent development would require.

Summary:

GP #1: Offer transformative impact for patients, meaning therapies that provide significant benefits over existing therapies and those in clinical trials	• The proposed approach could be transformative by avoiding genotoxic conditioning and immunosuppression, using the mother as the donor, and potentially applying across FA genotypes. • The proposed study would advance the program through Phase 1 and Phase 2 clinical testing and generate important early clinical information regarding the approach, but substantial development would remain beyond the 4-year award period before the program is positioned for later stage development. • As a result, the CIRM Team is not confident that the proposed award would move the program to a meaningful next development point, sufficiently derisked in 4 years and positioned for credible

	continuation into later stage development by another capable party.
GP #2: Advance strategies to improve patient access to stem cell-based and genetic therapies	• Use of maternal cells eliminates the need to identify a matched donor and is mutation agnostic, which could address an important access barrier. • Enrollment feasibility is an additional concern. The GWG identified recruitment as a risk, and delays further reduce confidence that the award reaches a meaningful development decision point within the CIRM-supported period. Even assuming timely enrollment, however, the CIRM Team remains concerned that substantial development would still be required beyond the 4-year award before the program is sufficiently de-risked and positioned for credible continuation into later stage development. Key activities and data from the trial would not be completed until 2 years after the award ends. • These considerations do not argue against investment in an ultra-rare disease. They do raise uncertainty about whether the proposed enrollment and treatment timeline is achievable and therefore whether the award will reach its intended development milestone by the end of the funding period.
GP #3: Broadly address both prevalent and rare diseases affecting Californians	• FA is an ultra-rare disease, with an estimated 4 affected births annually in California. The population eligible for this intervention would be smaller because treatment depends on prenatal diagnosis, timing and maternal and fetal eligibility. • CIRM has previously invested in the broader FA and in utero transplantation space. Those investments have generated useful scientific and clinical information, but they also demonstrate the difficulty of moving promising early results into sustained clinical development, regulatory approval and broader delivery. Those investments do not argue against additional investment in FA. They do, however, make it particularly important to understand what new development milestone this award would achieve by the end of 4 years and who would carry the program forward afterward. • Given the enrollment and timeline risk, the very small reachable population, the substantial development likely to remain after the study, and the conditional path for continued financing and development, the CIRM Team does not believe the

	proposed award is sufficiently positioned to move the program to a meaningful next development inflection point.

2. Application number: CLIN2-20416

Title: A Phase 1 study of an engineered Treg cell therapy, [Redacted], in adults with recently diagnosed Type 1 Diabetes

GWG Outcome: Fund

Median	Mean	High	Low	Scores to fund	Scores not to fund
90	90	95	85	14	0

CIRM Team Recommendation: Fund

CLIN2-20416 proposes an autologous engineered Treg treatment for newly diagnosed Type 1 diabetics. The CIRM Team recommendation is based on GWG scoring, GP#1 (transformative impact), GP#2 (improved patient access), GP#3 (significant CA patient population) and a unique therapeutic approach in CIRM's portfolio addressing a disease for which CIRM currently has no active clinical programs. Of note, however is that the HLA restriction is a significant access and equity limitation because the current product is applicable to only about 30% of recent-onset T1D patients and is expected to disproportionately serve white patients. The CIRM Team nevertheless recommends funding the Phase 1 because it provides a relatively contained opportunity to establish human proof of concept for an engineered immune-tolerance strategy. Any subsequent CIRM investment should require evidence not only of clinical activity, but also a credible strategy to broaden the approach beyond the current HLA-restricted population.

Summary:

GP #1: Offer transformative impact for patients, meaning therapies that provide significant benefits over existing therapies and those in clinical trials	• Current treatment for newly diagnosed Type 1 diabetics is exogeneous insulin and glucose monitoring but does not stop autoimmune destruction of beta cells. There is one FDA-approved allogeneic islet product (Lantidra) for a limited population, but it requires donor islets and immunosuppression. • Current CGTs in development are primarily cell therapies (allogeneic islets, allogeneic and autologous stem cell-derived islets).

	• There are two competing tolerizing cell therapies under development: an autologous Treg therapy (Ph2) and an autologous dendritic cell therapy (Ph1/2). • Unlike allogeneic islet transplantation, this one-time treatment requires neither islet sourcing nor immunosuppression and could potentially prevent the long-term issues associated with insulin administration. • CIRM has no active CLIN2s addressing T1D. An active TRAN1 award,14609, is evaluating autologous re-aggregated islets, which may improve function of surviving islets but would not prevent the autoimmune process triggering islet death. • Regarding closed awards, CLIN2-09730 was a Ph2 trial of autologous Tregs for the same indication; no efficacy was seen. The two approaches differ in that CLIN2-09370 used unmodified cells, while CLIN2-10416 uses cells genetically engineered to express an islet-specific T-cell receptor that targets the IGRP peptide presented on HLA-DRB1*04:01, a major histocompatibility complex allele highly associated with T1D. In addition, the cells are modified to express stable FOXP3, which is essential for regulatory function, and a chemically inducible signaling complex (CISC) that selectively induces an IL-2 signal, activated by low dose rapamycin.
GP #2: Advance strategies to improve patient access to stem cell-based and genetic therapies	• A single autologous treatment could preserve endogenous islet function without donor cells or chronic immunosuppression, potentially reducing lifelong treatment burden. However, the therapy still requires leukapheresis, individualized manufacturing and specialized cell therapy infrastructure, creating scalability and cost challenges. • Importantly, the approach is limited to patients expressing HLA-DRB1*04:01, representing roughly 30% of the recent-onset population. Based on genetics, 85% of the patients would be expected to be white. This is a significant access and equity limitation for a therapy intended to address a prevalent disease affecting CA highly diverse population.
GP #3: Broadly address both prevalent and rare diseases affecting Californians	• California has the highest Type 1 prevalence in the US, with >150,000 patients.

3.Application number: CLIN2-20392

Title: First-in-human trial for [Redacted], a novel epigenetic therapy for FSHD targeting D4Z4 epigenome

GWG Outcome: Fund

Median	Mean	High	Low	Scores to fund	Scores not to fund
87	87	90	84	14	1

CIRM Team Recommendation: Fund

CLIN2-20392 proposes in vivo epigenetic editing to treat facioscapulohumeral muscular dystrophy (FSHD). The CIRM Team recommendation is based on GWG scoring, GP#1 (transformative impact), GP#2 (improved patient access), and a unique therapeutic approach in CIRM's portfolio and in the external landscape, directed towards a disease not represented in CIRM's active clinical portfolio.

Summary:

GP #1: Offer transformative impact for patients, meaning therapies that provide significant benefits over existing therapies and those in clinical trials	• There are no approved disease modifying therapies for FSHD. • Epigenetic modification is a new field with transformative potential impact. One single treatment could provide durable benefit. • The competing cell therapy under development (Ph2) is an allogeneic umbilical cord-derived MSC-like cell. • The external FSHD landscape includes a substantially more advanced DUX4-targeted competitor. Novartis/Avidity's del-brax (AOC 1020), which reduces DUX4 through targeted siRNA delivery, is currently in an enrolling Phase 3 trial and has demonstrated DUX4 biomarker target engagement in Phase 1/2. • The proposed phase 1 / 2 trial can provide the clinical evidence needed to determine whether the program remains competitive and warrants further investment. • CIRM has no active awards addressing FSHD.
GP #2: Advance strategies to improve patient access to stem cell-based and genetic therapies	• A one-time treatment removes the need for repeated dosing of a palliative MSC-like treatment. • This product could offer an important access and treatment burden advantage over the leading competitor delbrax, which requires IV administration every 6 weeks.

	A durable one-time treatment could eliminate repeated infusions and ongoing treatment center visits.
GP #3: Broadly address both prevalent and rare diseases affecting Californians	• There are 2,000-5,000 FSHD patients in California.

4.Application number: CLIN2-20291

Title: Phase 2 Open-Label Single-Arm Trial of [Redacted] in Participants with Refractory Moderate-to-Severe SLE with Lupus Nephritis

GWG Outcome: Fund

Median	Mean	High	Low	Scores to fund	Scores not to fund
86	86	93	80	10	4

CIRM Team Recommendation: Fund

CLIN2-20291 proposes an iPSC-derived, allogeneic anti-CD19 CAR-T treatment for systemic lupus with lupus nephritis. The CIRM Team recommendation is based on GWG scoring, GP#1 (transformative impact), GP#2 (improved patient access), GP#3 (significant CA patient population). This program builds on CIRM supported Phase 1 development and is designed to test whether an off the shelf product can achieve the clinical benefit that is emerging from autologous CAR-T while also reducing patient specific manufacturing and treatment barriers. The field is advancing rapidly, and a positive Phase 2 could meaningfully advance this program toward later stage development.

Summary:

GP #1: Offer transformative impact for patients, meaning therapies that provide significant benefits over existing therapies and those in clinical trials	• There are no approved therapies for refractory lupus nephritis. • Cell therapies under development include autologous anti-B cell-directed CAR-Ts (both engineered ex-vivo and in-vivo), allogeneic donor-derived CAR-Ts, gamma/delta T cells, and CAR-NK cells. None of the cell therapies have moved beyond Phase 2 currently. • Autologous CAR-Ts against CD19 have shown early efficacy and safety in early-stage trials, validating B-cell depletion as a therapeutic strategy.

	• The approach has already shown early clinical activity in systemic sclerosis, providing initial human evidence that this product can achieve meaningful B-cell depletion and disease improvement in severe autoimmune disease. • The proposed product's key differentiation is that it is an allogeneic iPSC-derived platform, which could provide a standardized, readily available alternative to autologous CAR-T. • CIRM has an active CLIN2 from the same PI to complete a Ph1 trial. This award should represent the next clinical decision point. • A previous CLIN2 from a different applicant using an autologous bi-specific CAR for the same target was terminated when the company was acquired
GP #2: Advance strategies to improve patient access to stem cell-based and genetic therapies	• The off-the-shelf nature of the one-time treatment obviates the risk of manufacturing failures and the logistical difficulties of collecting patient samples, thereby decreasing travel and lodging concerns.
GP #3: Broadly address both prevalent and rare diseases affecting Californians	• 80,000-100,000 California patients with lupus nephritis. The relevant population is the refractory lupus nephritis subset, substantially smaller than the overall lupus nephritis population.

5. Application number: CLIN2-20409

Title: [Redacted], an RNA Splicing and Base Editing Inhibitor to Target Cancer Stem Cells in Refractory Myeloid Malignancies

GWG Outcome: Fund

Median	Mean	High	Low	Scores to fund	Scores not to fund
85	87	92	85	15	0

CIRM Team Recommendation: Fund

CLIN2-20409 proposes a small molecule to inhibit splicing of the cancer-driving gene ADAR1 in cancer stem cells in secondary AML and myelofibrosis. The CIRM Team recommendation is based on GWG scoring, GP#1 (transformative impact), GP#2 (improved patient access), GP#3 (significant CA patient population) and a unique therapeutic approach in CIRM's portfolio for a disease otherwise addressed only by autologous CAR-T cells.

Summary:

GP #1: Offer transformative impact for patients, meaning therapies that provide significant benefits over existing therapies and those in clinical trials	• Current treatment for the targeted diseases involves hematopoietic stem cell transplants (HSCTs), however, these diseases typically afflict older patients who, due to co-morbidities, are often precluded from this approach. • Of the 98 experimental CGTs under development for these diseases, 94 are cell therapies (typically autologous gene-modified), with the remainder either oligonucleotides or viruses. • [Redacted] has a differentiated mechanism targeting ADAR1-associated cancer stem-cell persistence and treatment resistance. • CIRM currently has 1 active CLIN2 that uses autologous CAR-T cells to treat AML.
GP #2: Advance strategies to improve patient access to stem cell-based and genetic therapies	• As a small molecule therapy, [redacted] avoids the need for a matched donor (typically harder to identify in underserved populations) as well as the requirement for life-long immunosuppression. • The current IV formulation still requires oncology-center treatment but relies on conventional infrastructure and could be more scalable than individualized cell therapies.
GP #3: Broadly address both prevalent and rare diseases affecting Californians	• AML: Roughly 500 new diagnoses annually in California • MF: 1,600-2,400 cases statewide • The relevant population is narrower than overall AML or MF because the trial targets refractory secondary AML and high-risk MF

6. Application number: CLIN2-20350

Title: Optogenetic Therapy for Treatment of Stargardt Disease

GWG Outcome: Fund

Median	Mean	High	Low	Scores to fund	Scores not to fund
85	87	95	85	13	0

CIRM Team Recommendation: Fund

CLIN2-20350 proposes an in vivo gene therapy using a novel transgene delivered to the retina by AAV for Stargardt's disease. The proposed study addresses a significant unmet need and would provide a meaningful early clinical de-risking step by establishing initial

safety, dose, and preliminary clinical activity. These data would help determine whether the program warrants further development.

A more advanced optogenetic program from Nanoscope targets the same retinal cell population, but the applicant's product differs in capsid and channelrhodopsin design, with preclinical data suggesting potential advantages. Whether those differences translate into clinical benefit remains unknown and is appropriately tested through early clinical development. CIRM's existing support of the applicant's related RP program reduces some platform and manufacturing risk but does not answer whether the product is safe and active in Stargardt disease.

The applicant's successful financing also provides a credible path to continue development if the program is successfully de-risked. Taken together, the proposed award would move the program to a meaningful evidence-based decision point without positioning CIRM as the primary funder of later-stage development.

Summary:

GP #1: Offer transformative impact for patients, meaning therapies that provide significant benefits over existing therapies and those in clinical trials	• There are no current approved treatments for Stargardt's disease. • This approach is a one-time treatment that is designed to transduce surviving neurons to restore vision rather than slow down loss and is agnostic as to the mutation causing the disease. • A related CIRM-funded optogenetic program from the same applicant in retinitis pigmentosa has generated encouraging early clinical findings, providing supporting evidence for the broader platform while leaving the Stargardt indication to be tested independently. • Nanoscope Biotechnology is developing a more advanced optogenetic therapy for Stargardt disease. Both approaches use AAV to express engineered channelrhodopsins in ON-bipolar cells, but they differ in capsid and transgene design. The applicant has presented preclinical evidence suggesting greater retinal transduction and light sensitivity, although whether these differences result in clinically meaningful advantages remains unknown. • Nanoscope is further advanced clinically. Its Stargardt program has completed a Phase 2 study and is planning a 60-patient pivotal trial. Nanoscope's same product has also shown positive clinical results in retinitis pigmentosa, and FDA accepted its RP BLA on September 9, 2026. • Nanoscope therefore provides an important clinical and regulatory benchmark for the applicant's product, but its advancement does not eliminate the value of evaluating a potentially differentiated approach. The

	applicant's proposed study would determine whether its product demonstrates sufficient safety and clinical activity in Stargardt disease to warrant further development. • The external CGT landscape for retinal degeneration is already active and includes multiple cell-based approaches, including hESC- and iPSC-derived retinal progenitors delivered by patch or subretinal injection, as well as four AAV programs, one of which is in Phase 3 • CIRM has other active investments in retinal disease, including cell-based approaches using hESC-, iPSC-, and allogeneic retinal progenitors. These programs represent different therapeutic strategies and do not, by themselves, argue against investment in a differentiated optogenetic approach • The proposed early clinical study represents a defined de-risking step. It is expected to establish initial safety, support dose selection, and determine whether there is sufficient evidence of activity to justify further clinical development. It is not expected at this stage to establish superiority over competing therapies • The applicant's successful financing provides greater confidence that, if the program is successfully de-risked, the applicant has the resources and development capacity to continue advancing it beyond the CIRM-supported stage
GP #2: Advance strategies to improve patient access to stem cell-based and genetic therapies	• Intravitreal administration is less complex than subretinal surgery and, if successful, could support broader delivery of the therapy • The mutation-agnostic approach could make the therapy applicable across the genetically diverse Stargardt patient population rather than limiting treatment to patients with a specific mutation • A one-time treatment and relatively straightforward route of administration could offer practical advantages for future patient access if clinical benefit is demonstrated
GP #3: Broadly address both prevalent and rare diseases affecting Californians	• Approximately 3,500 patients in California are estimated to have Stargardt disease, with advanced disease representing a subset of this population. • There is no approved therapy for these patients, and advanced disease is associated with substantial and irreversible loss of central vision.

	• The proposed study addresses a defined patient population while testing an approach that, if successful, may also have broader application across retinal degenerative diseases.