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CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Grants Working Group Recommendations

CLIN2 Clinical Trial Awards

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Agenda

1. CLIN2 Program Overview
2. Review Process
3. Recommendations

CLIN2
Program Objective

To support the completion of an interventional phase 1, 2, or 3 trial for an innovative stem cell-based or genetic therapy addressing a serious unmet need and with the potential for transformative benefits to patients, families and the health care system.

CLIN2 Program Contributes to These Impact Goals

Goal 3: Advance 4-7 rare disease projects to Biologics License Application (BLA)

Goal 4: Propel 15-20 therapies targeting diseases affecting Californians to late-stage trials

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CLIN2 Program Structure

	CLIN2		
	First-in-Human	Phase 2 or subsequent*	Phase 3 or pivotal
Recurrence	*4x per year*		
Max Duration	4 years		
Applicant	California or non-California organizations		
Co-funding**	30% (for-profit) None (non-profit)	50% (for-profit) None (non-profit)	50%
Max Award (Total Cost)	$8M (for-profit) $12M (non-profit)	$15M	$15M
Awards/Year	11-20 awards***		
Allocation 2026/27	$160M		

* Subsequent trials are Ph1 trials following a First-in-Human trial with the same candidate, disease indication and route of administration
** Co-funding is a percentage of total Allowable Project Costs
*** Number of awards is dependent on how many at each stage and organization status.

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Review Process

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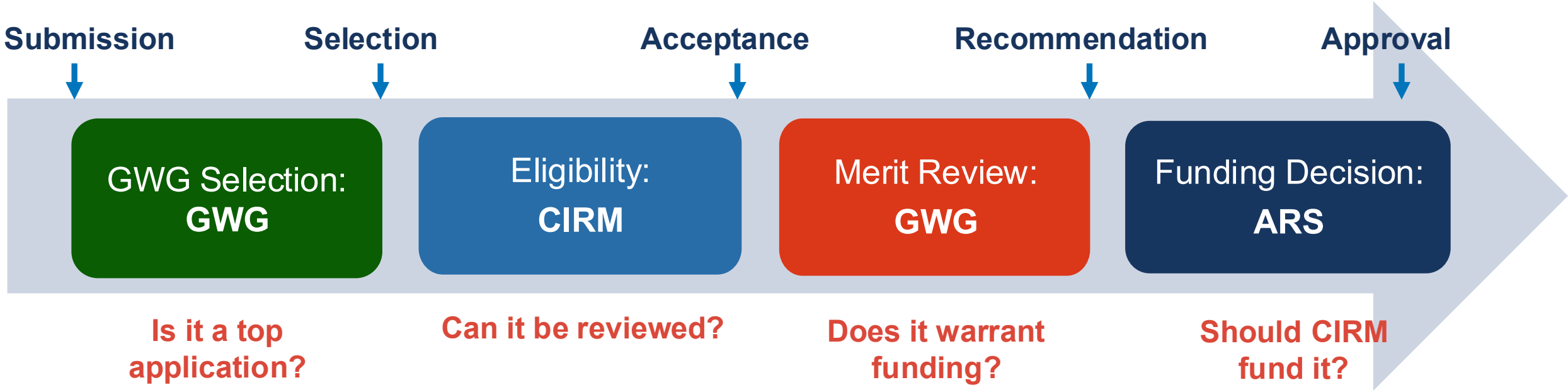
CLIN2 Application and Review Process



4 cycles per year (quarterly)

GWG – Grants Working Group; ARS – Application Review Subcommittee of the Independent Citizens' Oversight Committee

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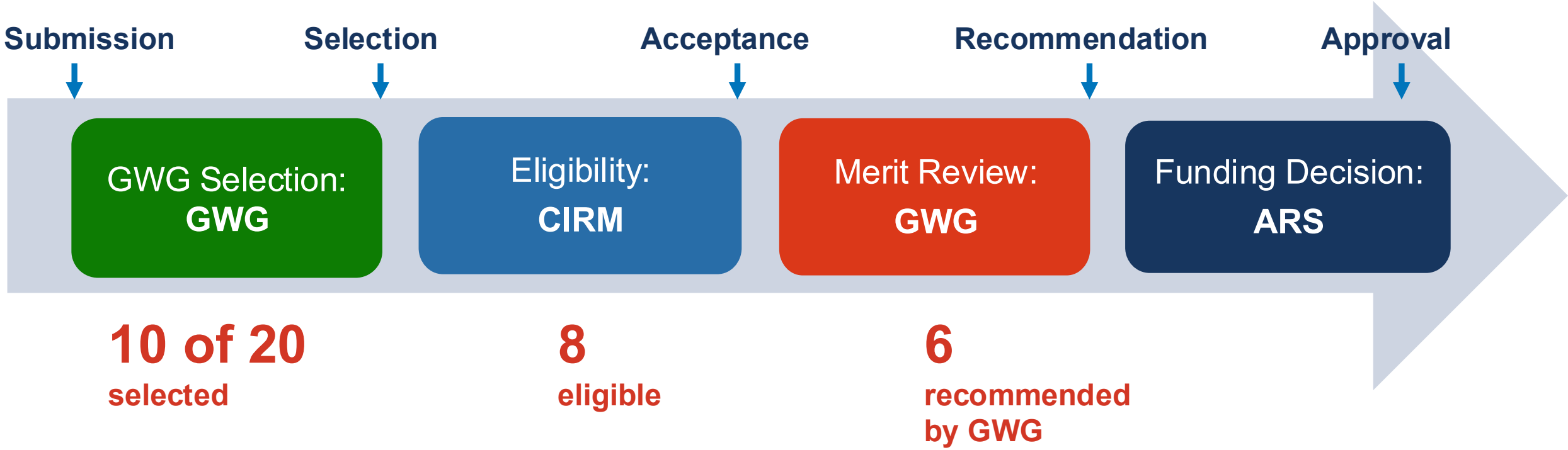
CLIN2 Application and Review Process



GWG – Grants Working Group; ARS – Application Review Subcommittee of the Independent Citizens' Oversight Committee

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CLIN2 GWG Panel Composition and Roles

Who participates and how they contribute

Scientific GWG Members	Scientific evaluation (disease area expert, regulatory, CMC, clin-ops, product development)
GWG Board Members	Patient perspective on significance and potential impact, oversight on process
Scientific Specialists	Scientific evaluation based on specialized expertise including access

Scientific Scoring System

Using the 1 to 100 scale

- **Median score of 85-100:** Exceptional merit and warrants funding, if funds are available.
- **Median score of 1-84:** Not recommended for funding.
- Scoring is holistic and based upon all facets of the expert review.
- GWG are encouraged to make full use of the scoring range to signal their enthusiasm for each project.

CLIN2 Scientific Review Criteria

- **Value Proposition** - Evaluate the extent to which the therapy offers a compelling value proposition
- **Rationale** - Evaluate the scientific rationale for the proposed therapy and the strength of the supporting data
- **Project Plan and Design** - Evaluate the project's plan and design
- **Project Team and Resources** - Evaluate the expertise and resources that will be deployed to achieve the project deliverables
- **Population Impact** – Evaluate the extent to which the project considers the potential impact of the proposed therapy across affected populations

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Recommendations

GWG Recommendations

Recommendation	Number of Apps	Total Applicant Request	Funds Available
Recommended for funding	6	$56,247,796	$160,000,000
Not recommended for funding	2		

For each award, the final award amount shall not exceed the amount approved by the ICOC Application Review Subcommittee and may be reduced contingent on CIRM's assessment of allowable costs and activities.

CIRM Team Recommendations

App #	Budget Request	GWG Score	Lo	Hi	Y	N	CIRM Recommendation
CLIN2-20316	**$11,999,999**	**90**	85	92	15	0	**DO NOT FUND**
CLIN2-20416	**$7,766,382**	**90**	85	95	14	0	**FUND**
CLIN2-20392	**$8,000,000**	**87**	84	90	14	1	**FUND**
CLIN2-20291	**$15,000,000**	**86**	80	93	10	4	**FUND**
CLIN2-20409	**$5,546,253**	**85**	85	92	15	0	**FUND**
CLIN2-20350	**$7,935,162**	**85**	85	95	13	0	**FUND**

Total Applicant Request	Funds Available
$44,247,797	$160,000,000

For each award, the final award amount shall not exceed the amount approved by the ICOC Application Review Subcommittee and may be reduced contingent on CIRM's assessment of allowable costs and activities.

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CLIN2-20316

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

Therapy	Trial Phase	Prior Funding to Team
CD34 selected maternal HSC	Phase 1	Yes

CIRM Team Recommendation: Do not fund

Rationale: Concerns that an award will not move the program to a meaningful next stage development point because critical data would not be available within the award period and enrollment feasibility is uncertain. CIRM's experience with related investments reinforces these concerns.

Summary:

	Assessment
Transformative Clinical Impact	The proposed approach could be transformative by avoiding genotoxic conditioning and immunosuppression required for allogeneic bone marrow transplant in these DNA damage prone patients.
Patient Access	The treatment model obviates the need to identify allogeneic donors but requires identifying maternal/fetal pairs at a specific gestational window, constraining access.
Disease Representation	Approximately 4 births/year in California.

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CLIN2-20416

A Phase 1 study of an engineered Treg cell therapy in adults with recently diagnosed Type 1 Diabetes

Therapy	Trial Phase	Prior Funding to Team
MHC specific, genetically modified autologous CD4+ T cells	Phase 1	No

CIRM Team Recommendation: **Fund**
Rationale: GWG score, novel to CIRM portfolio and external landscape, CA prevalence

Summary:

	Assessment
Transformative Clinical Impact	Potential to preserve T1D islet function sans exogenous insulin or immunosuppression (allo islet replacements).
Patient Access	Single treatment requiring apheresis and individualized manufacturing is HLA type specific and thereby restricted to a largely White population.
Disease Representation	California has the highest T1D prevalence in the US, 150,000 patients.

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CLIN2-20392

First-in-human trial for a novel epigenetic therapy for FSHD targeting D4Z4 epigenome

Therapy	Trial Phase	Prior Funding to Team
AAV-delivered epigenetic D4Z4 repeat editor	Phase 1/2	No

CIRM Team Recommendation: **Fund**
Rationale: GWG score, novel therapeutic platform to portfolio and externally, indication novel to portfolio

Summary:

	Assessment
Transformative Clinical Impact	No disease modifying therapies are approved for FSHD. Epigenetic modification approach holds potential for transformative impact.
Patient Access	This single dose regimen could offer an access and treatment burden advantage over a competing later stage candidate (dosed every 6 weeks).
Disease Representation	There are approximately 2,000-5,000 FSHD patients in California

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CLIN2-20291

Phase 2 Open-Label Single-Arm Trial in Participants With Refractory Moderate-to-Severe SLE With Lupus Nephritis

Therapy	Trial Phase	Prior Funding to Team
hiPSC-derived anti CD19 CAR T	Phase 1	Yes

CIRM Team Recommendation: **Fund**
Rationale: GWG score, potential to improve patient access, potential to advance prior CIRM funded asset to late-stage development, significant CA population

Summary:

	Assessment
Transformative Clinical Impact	No approved therapies approved for refractory LN; this allogeneic approach has shown early clinical activity in systemic sclerosis autoimmune disease.
Patient Access	Off the shelf, allogeneic approach obviates patient apheresis, autologous manufacturing and the resultant patient logistical and travel burdens as well as increased manufacturing failure risk.
Disease Representation	The refractory LN population is a yet to be quantified subset of the 80,000-100,000 Californians living with LN

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CLIN2-20350

Optogenetic Therapy for Treatment of Stargardt Disease

Therapy	Trial Phase	Prior Funding to Team
AAV-delivered, genetically modified channel-rhodopsin	Phase 1	Yes

CIRM Team Recommendation: **Fund**
Rationale: GWG score, enables evidence-based decision to proceed to late-stage development

Summary:

	Assessment
Transformative Clinical Impact	No approved therapies for Stargardt's disease. One time treatment gene modifies surviving neurons into light sensing cells to restore vision in late-stage disease.
Patient Access	Intravitreal delivery is possible in office; the therapy is mutation agnostic.
Disease Representation	Approximately 3,500 California patients with Stargardt's of which advanced disease is a subset.

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CLIN2-20409

An RNA Splicing and Base Editing Inhibitor to Target Cancer Stem Cells in Refractory Myeloid Malignancies

Therapy	Trial Phase	Prior Funding to Team
Small molecule ADAR-1 inhibitor	Phase 1	Yes

CIRM Team Recommendation: **Fund**
Rationale: GWG score, patient access, novel therapeutic approach in CIRM's portfolio,

Summary:

	Assessment
Transformative Clinical Impact	Provides an option for older and medically complex patients for whom a bone marrow transplant is not feasible.
Patient Access	This small molecule obviates the need for a matched bone marrow donor and immunosuppression. The IV route relies upon existing oncology center infrastructure.
Disease Representation	The relevant refractory/secondary population is narrower than the overall AML or MF population.

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CLIN2-20389

Phase I Clinical Trial of a Trispecific CAR T-Cell Therapy for Multi-Antigen Targeting in CNS and B-Cell Lymphomas

Therapy	Trial Phase	Prior Funding to Team
Triple B cell antigen targeting CAR T	Phase 1	Yes

CIRM Team Recommendation: Do not fund
Rationale: CIRM concurs with the GWG recommendation

Summary:

	Assessment
Transformative Clinical Impact	Bispecific and trispecific CAR T intend to address antigen escape, but it has yet to be demonstrated that antigen escape is more significant than T cell exhaustion in post CAR T relapse.
Patient Access	Autologous manufacturing may limit patient access.
Disease Representation	Approximately 3,000 patients per year in CA.

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CLIN2-20454

An Oral Therapy to Inhibit Cancer Stem Cells

Therapy	Trial Phase	Prior Funding to Team
Small molecule SUMOylation inhibitor	Phase 1	Yes

CIRM Team Recommendation: Do not fund
Rationale: CIRM concurs with the GWG recommendation

Summary:

	Assessment
Transformative Clinical Impact	Takeda's drug against the same target proved ineffective and was discontinued. Highly populated landscape with over 40 approaches in development.
Patient Access	An oral treatment would simplify access.
Disease Representation	Approximately 14,000 Californians are impacted per year.