APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Area of Impact
DISC2-14130	A Treatment for Artemis-deficient Severe Combined Immunodeficiency using Non-Viral CRISPR-driven Safe Harbor Transgenesis in Hematopoietic Stem Cells	**$1,809,372**	**Y**	**90**	90	4	85	95	14	0	Y	N	Development of a non-viral gene editing technology to improve efficacy, safety, and scalability of gene therapies
DISC2-14190	Reprogramming Somatic Cells into iPSCs Engineered with an Anti-PSCA CAR to Develop Allogeneic Off-the-Shelf Cell Therapy to Treat Pancreatic Cancer	**$2,263,500**	**Y**	**90**	90	0	90	90	12	0	Y	N	Development of an iPSC based CAR NK allogenic cell product to treat pancreatic cancer
DISC2-14049	Microgel encapsulated iPSC-derived notochordal cells to treat intervertebral disc degeneration and low back pain	**$2,020,166**	**Y**	**90**	89	3	85	95	14	0	Y	Y	Development of an injectable iPSC-derived notochordal cell product to treat chronic back pain
DISC2-14180	Excitatory spinal interneurons from human pluripotent stem cells to treat spinal cord injury	**$2,942,198**	**Y**	**90**	89	2	85	90	14	0	Y	Y	Development of an interneuron cell therapy from pluripotent stem cells to treat spinal cord injury
DISC2-14045	Novel Lipid Nanoparticles for Enhancing eNOS Synthesis for Cardioprotection Post Myocardial Infarction	**$2,060,248**	**Y**	**90**	88	4	75	90	12	1	N	Y	Development of a lipid nanoparticle that delivers a therapeutic mRNA to heart cells to improve function
DISC2-14090	Gene Therapy for SLC6A8 Creatine Transporter Disorder	**$2,296,920**	**Y**	**88**	89	1	87	90	15	0	N	N	Development of a gene therapy to treat creatine transporter deficiency that causes neural/brain dysfunction
DISC2-14133	Drug Discovery for Duchenne Muscular Dystrophy Using Patient-Derived Human iPSCs	**$675,000**	**Y**	**88**	87	1	86	90	13	0	Y	N	Development of an iPSC based platform for screening drugs to treat DMD cardiomyopathy
DISC2-14187	Expanded Capacity AAV Retinal Gene Therapy Enabled by Efficient RNA-Joining Technology	**$1,446,000**	**Y**	**87**	87	2	85	92	14	0	N	N	Development and optimization of a gene therapy vector with enhanced cargo capacity to treat Stargardt disease
DISC2-14053	Pluripotent Stem Cells for Tendon Tissue Engineering	**$2,734,163**	**Y**	**86**	86	0	85	86	14	0	N	Y	Development of a bio-tendon engineered from pluripotent stem cells to repair tendon injury and degeneration
DISC2-14041	Autologous stem cell-derived interneuron cell therapy for spinal cord injury (SCI)	**$2,025,000**	**Y**	**86**	86	1	85	90	13	0	N	N	Development of an interneuron cell therapy from pluripotent stem cells to treat spinal cord injury
DISC2-14169	Vax-T to promote formation of cancer-specific T memory stem cell for personalized cancer immunotherapy	**$2,267,714**	**Y**	**85**	86	3	85	95	14	0	N	Y	Development of a cancer vaccine booster to induce T memory stem cells and long-term immunity vs cancer
DISC2-14083	Development of novel small molecules against cancer stem cells in solid cancers	**$2,340,000**	**Y**	**85**	85	0	85	85	14	0	Y	N	Development of a drug candidate that targets glioma cancer stem cells
DISC2-14096	Pharmacological regenerative treatment of idiopathic pulmonary fibrosis targeting the senescent niche of lung progenitor cells.	**$1,450,876**	**Y**	**85**	85	3	80	90	12	3	N	N	Identification of a drug candidate that targets senescent lung stem/progenitor cells to treat IPF
DISC2-14166	Reversal of dysregulated myelopoiesis in breast cancers and cancer stem cells to boost antitumor immunotherapy	**$2,327,680**	**Y**	**85**	85	4	75	90	12	1	Y	N	Development of a drug candidate that can reverse dysregulated myelopoiesis of HSC in breast cancer
DISC2-14047	A Novel Therapy for Sanfilippo B	**$2,297,884**	**N**	**84**	84	3	80	90	6*	8	Y	N	
DISC2-14097	In Utero Treatment of Duchenne Muscular Dystrophy with Non-viral Gene Editing	**$2,035,544**	**N**	**83**	83	3	80	87	6*	8	Y	N	
DISC2-14089	Chemically engineered photoreceptors for vision restoration in retinal degeneration associated blindness	**$1,845,093**	**N**	**83**	80	7	65	90	7*	7	N	N	
DISC2-14033	Development of next-generation human cerebellar organoids to model hereditary cerebellar ataxias	**$834,000**	**N**	**82**	81	3	75	86	2	13	Y	N	

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Area of Impact
DISC2-14126	Functional chemical and genomic screens in human iPSC-derived cardiomyocytes to identify new cardioprotective drugs for heart transplantation	**$813,000**	**N**	**80**	80	5	69	85	4	9	N	N	
DISC2-14167	Engineered Human Stem Cell-Derived Pancreatic Islets Encapsulated in a Thin Film Device for Patients with Type 1 Diabetes	**$2,759,817**	**N**	**80**	79	3	70	82	0	14	Y	Y	
DISC2-14175	A Novel, Injectable, and Biodegradable Thermoresponsive Hydrogel for Improved Engraftment and Efficacy of Cell Therapy for Parkinson's Disease	**$1,470,000**	**N**	**80**	78	4	70	80	0	12	Y	Y	
DISC2-14043	Neuroprotective secretome of retinal progenitor cells for ameliorating vision loss	**$1,912,691**	**N**	**75**	76	2	75	80	0	15	N	Y	
DISC2-14192	Targeted Mesoporous Silica Nanoparticle delivery of Therapeutics to Cancer Stem Cells in Recurrent/Refractory Ovarian Cancer Models	**$1,882,963**	**N**	**75**	75	0	75	75	0	14	Y	Y	
DISC2-14032	CAR-Treg Therapy for Atherosclerosis	**$2,430,293**	**N**	**75**	74	2	70	75	0	14	N	N	
DISC2-14152	Developing stem cell-based cancer immunotherapy using human pluripotent stem cell-derived NK cells	**$2,263,500**	**N**	**75**	74	5	65	80	0	13	N	Y	
DISC2-14172	Development of CRISPR/Cas9 gene-edited stem cells to improve transplanted cell survival for cardiac regenerative therapy in end-stage heart failure	**$2,705,301**	**N**	**70**	70	1	70	72	0	13	Y	N	
DISC2-14183	Generation of T cell-specific synthetic promoters expressing Chimeric Antigen Receptors within Self-Inactivating Gammaretroviral Vectors	**$675,000**	**N**	**69**	68	3	65	75	0	14	N	N	
DISC2-14168	Human Corneal Stromal Stem Cell Extracellular Vesicles for Glaucoma Therapy	**$1,850,275**	**N**	**65**	68	5	60	80	0	15	Y	N	
DISC2-14174	Conditioning-free CAR-HSC (hematopoietic stem cell) therapy for solid tumors	**$788,558**	**N**	**60**	61	6	50	70	0	14	N	Y	
DISC2-14199	Multiorgan tool for the development of therapeutic agents using IPSC derived AD brain cells	**$675,000**	**N**	**60**	60	6	40	65	0	15	Y	N	
DISC2-14117	IPS derived progenitor cells to deliver BDNF as neuroprotection for the treatment of Huntington's Disease	**$2,366,401**	**N**	-	-	-	-	-	0	14	N	N	
DISC2-14061	HIV gene therapy for direct in vivo CAR-T Cells engineering as a single treatment for HIV definitive cure	**$1,429,839**	**N**	-	-	-	-	-	0	14	N	Y	
DISC2-14071	Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells by small molecule induction	**$2,723,000**	**N**	-	-	-	-	-	0	15	N	N	

*** Minority Report**

Application #	DISC2-14130
Title (as written by the applicant)	A Treatment for Artemis-deficient Severe Combined Immunodeficiency using Non-Viral CRISPR-driven Safe Harbor Transgenesis in Hematopoietic Stem Cells
Research Objective (as written by the applicant)	A Treatment for Artemis-deficient Severe Combined Immunodeficiency using Non-Viral CRISPR-driven Safe Harbor Transgenesis in Hematopoietic Stem Cells
Impact (as written by the applicant)	We aim to develop a novel genome editing based therapy for Artemis-deficient severe combined immunodeficiency that would improve upon prior gene therapies in efficacy, safety, and scalability.
Major Proposed Activities (as written by the applicant)	• Discover optimal approach for nonviral targeted integration of a functional DCLRE1C transgene into AAVS1 genomic safe harbor in hematopoietic stem and progenitor cells (HSPCs) • Discover optimal approach for generating Artemis-deficient HSPCs and characterize resulting cells • Demonstrate ex vivo restoration of Artemis function using Artemis-deficient HSPCs • Demonstrate in vivo restoration of Artemis function using Artemis-deficient HSPCs
Statement of Benefit to California (as written by the applicant)	Our target disease indication, ART-SCID, carries significant risk of death and long-term comorbidities and disproportionately affects descendants of Navajo and Apache Native Americans, although it can affect individuals of any genetic background. We aim to develop a genome editing therapy in blood stem cells using genome editing that will improve upon prior gene therapies with better efficacy, safety, and scalability, which will improve patient access.
Funds Requested	$1,809,372
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	90
Median	90
Standard Deviation	4
Highest	95
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Artemis-SCID (ART-SCID) is a heritable immunodeficiency disorder prevalent in some Native American populations as well as others. The standard treatment is allogenic bone marrow graft, but many patients have poor donor matches due to ethnicity. • An autologous bone marrow gene therapy approach would benefit Navajo/Apache population and improve treatments for all with ART-SCID • Development of an autologous source of corrected cells would alleviate graft-versus-host disease (which is common with allogenic transplants). • The approach is to use a non-viral gene editing method to supply a functional DCLRE1C gene to bone marrow cells (ex vivo). Only partial (5%) correction may be needed to supply enough DCLRE1C expression to have a therapeutic effect. • Strong impact in a disease with few options. • Artemis-deficient SCID is a rare condition affecting a specific population of individuals and replacement of Artemis function in HSCs is a significant and impactful treatment modality.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The idea is to use a non-viral (but CRISPR/Cas9 enabled) approach for ex vivo gene therapy to deliver the DCLRE1C gene (mutated in ART-SCID) into bone marrow cells by integrating into a safe harbor locus, AAVS1. This is a reasonable idea. • The preliminary data show that targeting into the AAVS1 safe harbor site occurs with reasonable efficiency and fidelity. (These data are also a part of a journal article not yet peer-reviewed, presented in BioRVX). • The expression of Artemis is only assessed at the level of RNA and enzymatic activity assays, but not at the level of Artemis protein - this is somewhat concerning. • Phase I clinical trial with virally-transduced HSCs demonstrates the efficacy of Artemis replacement. Replacement of lentiviral transduction with site-specific non-viral KI may maintain efficacy but reduces concerns of clonality and transformation.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The milestones are clear and logical: 1. DCLRE1C targeting optimization in normal HSPCs, 2. Make ART-SCID knockout HSPCs from normal HSPCs (as a research resource), 3. Correct the cells made in milestone 2 (this does make aim 3 dependent upon aim 2). 4. See if the corrected cells exhibit multi lineage engraftment into immunodeficient mice. • There is still some concern that off-target edits could be carcinogenic, and there is no "kill-switch" strategy proposed. • If the "knockout" of ART in milestone 2 is not very efficient (near complete), then this may constitute a roadblock that would prevent the use of these cells as a model system (which is needed to complete milestone 3). This is a concern, since unless nearly 100% of cells exhibit knockdown, the background of normal cells might render this critical reagent unworkable. • One concern is the generation of a model cell line with KO and then for KI. Reviewers would have preferred usage of patient cells as the model line.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• This is an ambitious grant but is now improved as compared to the original grant. • The PI has a good research record of work with ex vivo gene therapy approaches in HSPCs (bone marrow). • The feasibility is demonstrated with the phase I clinical trial and preliminary data. Others have recently demonstrated non-viral KI strategies in patient T cells.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**

Yes: 14	• ART-SCID is most common in Apache and Navajo individuals, and thus, this grant is especially geared toward a specific ethnicity. • Since well-matched allogenic donors are hard to find for many ethnicities and races, this approach which may lead to an autologous therapy could be very helpful. • Treats an underserved patient population. • Strong.
No: 0	*none*

Application #	DISC2-14190
Title (as written by the applicant)	Reprogramming Somatic Cells into iPSCs Engineered with an Anti-PSCA CAR to Develop Allogeneic Off-the-Shelf Cell Therapy to Treat Pancreatic Cancer
Research Objective (as written by the applicant)	Develop and characterize our candidate pancreatic cancer therapy, iPSC-derived PSCA-CAR NK.
Impact (as written by the applicant)	Product Functionality and Quality
Major Proposed Activities (as written by the applicant)	• Development and characterization of induced pluripotent stem cells (iPSCs) via somatic cell reprogramming of various human blood cells - umbilical cord blood (UCB) cells, CD34+ cells, natural killer (NK) cells, and T cells • Selection of optimal iPSC candidate line(s) by testing of NK cell differentiation potential • Engineering the selected iPSC candidate line(s) with depletion of B2M, replacement of CIITA with HLA-E, and expression of cancer-targeting PSCA-CAR_sIL-15 • Hematopoietic differentiation of engineered iPSC cells to NK cells • In vitro cytotoxicity studies, expansion and freezing studies to evaluate iPSC-derived PSCA-CAR_s15 NK cells as an "off-the-shelf" cell therapy for pancreatic cancer • In vivo studies of iPSC-derived PSCA-CAR_s15 cells
Statement of Benefit to California (as written by the applicant)	Our goal is to develop an "off-the-shelf," ready-to-use cell therapy that is appropriate and easily accessible for any patient regardless of race, ethnicity, sex, gender, age, or socioeconomic status. By leveraging an effective, innovative, safe, and standardized off-the-shelf cell therapy to kill tumor cells and energize latent immune responses, we expect our results to have a positive impact by ultimately reducing mortality for patients suffering from devastating and deadly cancers.
Funds Requested	$2,263,500
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	90
Median	90
Standard Deviation	0
Highest	90
Lowest	90
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 11	• The applicant's proprietary induced pluripotent stem cells (iPSCs) provide an opportunity to make chimeric antigen receptor (CAR) natural killer (NK) cell products with a significant reduction in cost per patient compared to CAR T cell therapy, enabling more patients to afford the therapy and reducing cancer healthcare disparities. • Pancreatic cancer is deadly, current therapies and approaches are limited, and new products are welcomed. • Yes; the proposed product could improve patient care if, as the applicant hopes, human iPSCs provide a universal source of CAR NK cells that can be engineered specifically for each pancreatic cancer patient. This remains to be determined. • The project addresses an unmet need. Potentially, there is wide applicability to treat other cancers that highly express PSCA (e.g., prostate cancer, urinary bladder cancer, gastric cancer, esophageal cancer). • It's an excellent idea to use iPSC to generate CAR cells. • The proposed project uniquely enabled by reprogrammed cells.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• Yes. The applicant has proof of principle that PSCA CAR NK cells have anti-cancer efficacy in a mouse model. They now hope to show similar or superior efficacy with iPSC-derived PSCA CAR NK cells. • The generation of this product from iPSCs is essential for the proposed engineering steps. • The proposed NK cell product has the following features that are potentially superior to a standard CAR T - reduced inflammatory activation, potentially universal use, and a safety switch. • The applicant's CAR NK expresses hIL-15 to provoke the endogenous immune system (e.g., hIL-15 activates CD8+ T and NK cells) and carries a tEGFR as a safety switch. • The applicants have generated iPSCs from NKs, expanded these cells, differentiated these cells back to NK cells, and shown anti-cancer cytotoxicity in vitro. They also show that these iPSC-derived NK cells have higher levels of anti-cancer cytotoxicity and IFN-γ production versus umbilical cord blood (UCB)-derived NK cells (Fig 5). This is strong initial data. • New data indicate this approach may be superior to UCB or other derivations of NKs. The biology underlying this superiority would be interesting to pursue, especially if there are pitfalls ahead that could be understood or circumvented by knowledge. • The description of plans for future translation is generic to all CAR approaches, e.g., dose determination, duration of treatment determination, etc., but the animal model for pre-clinical optimization testing is strong and will provide answers to likely questions from FDA. • Importantly, the application addresses previous critiques. Specifically, the resubmission addresses concerns regarding gene editing adverse effects, off-targeting effects, genome integrity, and homogeneity of product. • I suggest performing genomic analyses, and comparing UCB- vs. iPSC-derived cells, after each step of engineering. • The number of lines to be evaluated at each step, and how subclones will be selected, is still unclear. • The rationale to proceed is high.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**

Yes: 11	• Standard for this type of cellular product, but well detailed. • Overall, yes, but the biology and rationale for the number of lines, and for testing the lines against the engineered steps, remains unclear in this revision. • High-quality proposal from an experienced group who are experts in NK biology and their applied use. • The applicant addresses the two major issues that prior GWG reviewers raised: a) the need for comparison between iPSC and CB-derived NK cells and b) safety. • The applicant specifically discusses additional pitfalls and alternatives, as requested in the prior critiques. • The project plan is suitable, but ambitious. • The applicant's responses to the previous reviews are a strength. • Excellent revision!
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 11	• Milestones and expected project outcome are logical and likely to be achieved within the proposed timeline. • Excellent team with decades of experience in this area. • All resources are in place, and budget suitable. • Translatability is evidenced by clinical-grade master and working cell banks in their GMP facility.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 11	• The applicant discusses pancreatic cancer disparities, costs of treatment, and the benefits of an off-the-shelf cell therapy product to underserved groups. • Yes - the project outcomes will be universally beneficial. • The project upholds principles of diversity, equity and inclusion (DEI). • The applicant institution has established a Community Alliance for Research & Education, an initiative to reduce and eliminate health disparities. • The applicant incorporates perspectives and experience from the population that will benefit from the proposed product in the implementation of the research project.
No: 0	*none*

Application #	DISC2-14049
Title (as written by the applicant)	Microgel encapsulated iPSC-derived notochordal cells to treat intervertebral disc degeneration and low back pain
Research Objective (as written by the applicant)	We aim to discover an injectable, rejuvenating treatment for painful intervertebral disc degeneration using microtissue-encapsulated iPSC-derived notochordal cells (iNCs) using large animal model
Impact (as written by the applicant)	Our treatment candidate may allow for a non-invasive stem cell therapy, targeting the underlying pathogenesis of intervertebral disc degeneration, the leading cause of chronic back pain in adults.
Major Proposed Activities (as written by the applicant)	• Optimization, characterization and deliverability testing of iNC-loaded microgels, microtissues or bulk hydrogel as therapeutic candidates for injectable treatment of intervertebral disc degeneration. • To demonstrate the safety and efficacy of iNC-loaded microgel/microtissue and iNCs injected in bulk hydrogel in inhibiting disc degeneration in a large animal model.
Statement of Benefit to California (as written by the applicant)	Intervertebral disc (IVD) degeneration associated low back pain is a leading cause of disability. While it affects all adults, many people belong to underserved communities that more often carry government-sponsored health insurance. Despite decades of research, there are no robust therapies targeting the underlying causes of IVD degeneration. Spinal disc injections with the proposed treatment candidate may provide an IVD rejuvenating, inexhaustible off-the-shelf treatment accessible to all.
Funds Requested	$2,020,166
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	89
Median	90
Standard Deviation	3
Highest	95
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Currently there are few options for lower back pain and this would provide another option. If an off-the shelf therapy can be developed it would provide good value. • This is a revised submission that is premised on the team's prior CIRM funded study that demonstrated the intradiscal injection of iPSC- derived notochordal cells (iNCs) delivered in bulk-hydrogel can survive in the degenerated IVD and have the potential to rejuvenate IVDs. Successful completion of this current project will lead to the identification of a novel injectable therapeutic candidate for back pain and IVD degeneration. • Development of an allogenic stem cell therapy will allow for an off-the-shelf treatment accessible to different population groups suffering from painful IVD degeneration. However, the proposed therapy could also become autologous and patient-specific. • The use of iPSC-derived notochordal-like cells could advance efforts to regenerate the intravertebral disc. This addresses the unmet medical need of improving chronic back pain resulting from disc degeneration. • The encapsulation and delivery technologies developed here could improve engraftment and regenerative potency of the iPSC-NCs. This is a critical bottleneck of the application. • The progression to translation is very clear. The proposed project will advance the project to a relevant pre-clinical large animal. These data will be needed for eventual translation to humans.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• Notochordal cells have repair capacity in the intervertebral disc but are few in number in adults. During development, notochordal cells (NCs) give rise to mature nucleus pulposus (NP) cells; in humans, the NC population vanishes at the age of 10. Since humans develop age-dependent IVD degeneration, it has been suggested that NCs are essential for maintaining a healthy IVD and would be the ideal cell type to regenerate IVDs. • The premise for use of iPSC-NCs in IVD regeneration is strong given the roles of these cells in development and injury repair in juveniles. • The team presents strong preliminary data from a prior CIRM grant in generating iPSC-derived cells that express notochord cell markers, and in vitro characterization of the cells. • Yes. Their recent publication describes a novel method for deriving NCs from human iPSCs. They demonstrated no sign of teratoma formation iNCs in mice. In a larg animal model, the team showed prevention of IVD degeneration using iNCs delivered in hydrogel over 8 weeks. They now provide rationale for and preliminary data using their a different hydrogel, as well as functional data (pain) using iNC in microgels in the rat IVD. • They have a novel method of deriving notochord cells from human iPSCs. Appear to be safe as no sign of teratoma formation in Nog/SCID mice. In a swine model, the test article prevented intervertebral disc degeneration. • The proposal utilizes human iPSC-derived NCs using a methodology that the applicant has described in a publication related to a previous CIRM grant. • New in vivo data demonstrate feasibility of performing the proposed study and suggest possible regenerative benefits of the iPSC-NCs. • These experiments will help to determine efficacy, the need for immunosuppression, shipping parameters, dose range and potentially some understanding of mechanisms. Potency assays, safety, toxicity and manufacturing will be done in the next phase.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The team will test the hypothesis that micro-encapsulated iNC can attenuate IVD degeneration and reduce low back pain. • The project is founded on extensive preliminary data, most supported by recent publications, demonstrating the team's ability to successfully complete the milestones. The proposal has detailed schematics/tables of the experimental design and each aim with a corresponding rationale. The therapeutic candidate's regenerative potential and reproducibility of results will be evaluated using several methods.

	• Overall, no problems are anticipated as all aspects of the proposal has been demonstrated in principle in the preliminary data and in their publications. • The project is clearly focused on translational advancement through complementary use of in vitro and clinically relevant in vivo large animal models. • Evaluation of multiple delivery modalities raises the likelihood of success. • Experiments are very well-designed with clear experimental groups, controls, and comprehensive analysis of outcomes to test the project hypotheses. • Characterization of the cells and the regenerative capacity is strong. • Very responsive to the previous critique. A previous concern was use of the proprietary hydrogel and they have added an additional test matrix. A second concern is that they did not show complete regeneration or new matrix formation which was not addressed and adds risk to the proposal. • Consideration of quality attributes based on marker expression is appropriate, but functional assessment would improve potency testing. • While the proposed hydrogels are mechanically tunable, there is not a clear plan to do so other than as an alternative approach. This is likely an important parameter to optimize. • Consideration of delivery from a manufacturing site to the clinic is important for translation and a strength of the proposal. It isn't clear why cryopreservation of the product isn't considered.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The time line is appropriate for the proposed studies. In parallel with translational studies, there are also mechanism of action studies that will explore the transplanted cell fate and sequencing of the treated IVDs. • Milestones and success criteria are clear and quantitative. There is a good likelihood of this project being successful. • All experiments have been previously done, so they should have no problem completing the work. This is a well qualified staff and equipment and facilities along with the needed resources are in place. • The multidisciplinary team (including expertise in bioengineering, imaging, clinical (spine) orthopedics) is well suited to carry out the proposed studies. • The facilities and resources are well suited to support the proposed activities,
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12	• Lower back pain and disc degeneration affect the general population. Female animals are studied as there is a higher prevalence of disc degeneration. • Underserved individuals may have higher incidence of back pain and disc degeneration due to their occupation. • Experimental design focuses on females. They plan to address sex in a future study. • All communities suffer from chronic back pain, with underserved communities having higher incidence. A regenerative therapy would benefit all of California.
No: 2	• These preliminary experiments are not powered to account for race, ethnicity and gender, but at this stage, it is likely not important. • While it is early to give a definitive response, it does not appear that much effort was used to address this DEI directive.

Application #	DISC2-14180
Title (as written by the applicant)	Excitatory spinal interneurons from human pluripotent stem cells to treat spinal cord injury (SCI)
Research Objective (as written by the applicant)	The primary objective of this research is to test whether excitatory human V2a spinal interneurons engineered from pluripotent stem cells (PSCs) can repair the damaged spinal cord and restore motor function.
Impact (as written by the applicant)	Currently no existing therapies are capable of repairing the injured spinal cord. Our therapeutic cell candidate - human V2a spinal interneurons - could address this significant unmet medical need.
Major Proposed Activities (as written by the applicant)	• Determine GMP-compliant pluripotent stem cell (PSC) line(s) that yield optimal V2a donor populations. • Define the optimal dose of transplanted GMP-V2a neurons that can be safely administered to the injured spinal cord. • Determine the timeline for donor cells to anatomically integrate with damaged spinal cord and repair motor networks. • Determine the timeline for transplanted V2a neurons to functionally connect to injured motor networks and contribute to recovery. • Determine the therapeutic efficacy of transplanted V2a neurons derived from GMP-compliant PSCs to functionally repair motor circuits following spinal cord injury.
Statement of Benefit to California (as written by the applicant)	Spinal cord injury (SCI) is a permanently debilitating condition that renders individuals partially or fully paralyzed. The associated life-time health care costs are exorbitant (millions of dollars) and the ongoing need for assisted care impacts family members and friends. A reparative cell therapy for SCI that could restore motor function would benefit the autonomy of the individual and enable an effective return to society and improved quality of life.
Funds Requested	$2,942,198
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	89
Median	90
Standard Deviation	2
Highest	90
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Transplantation of excitatory V2a spinal neurons in a cervical spinal cord injury (SCI) is a very promising potential cell therapy and would overcome a current bottleneck in bringing cell therapies to clinical fruition. • Treatment to restore function in the injured spinal cord is very much needed, and the novel approach in this application could provide important benefits to people with these injuries. • Should this candidate be successful, it would be a promising new way to restore function in the injured spinal cord that would be entirely dependent upon the use of stem cell-based therapies. • There is potential for significant impact.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The scientific rationale is straightforward. The goal is to replace damaged neurons in a particular location where long-distance axonal growth is not required in order to restore important functions, in this case function of the phrenic nerve that is critical in breathing. • The applicants have successfully developed differentiation protocols to generate human V2a interneurons with a high (50%) rate of success. They also have generated a GMP-compliant stem cell line. • The applicant has successfully addressed a number of previously raised issues: (i) the concern of scaling was addressed, (ii) the PI's role and expertise has been addressed, (iii) more information has been added as to the selection of the lines, and importantly, (iv) functional outcomes have been included. • A number of additional concerns remain unresolved. In the prior review, testing of more clinically relevant immunosuppressive regimens and establishment of a cGMP compliant manufacturing protocol was deemed as being beyond the scope of the current proposal. • The rationale for studying a large number of donor cells (embryonic and induced PSCs of both sexes (WA01, XY and WA09, XX; WiCell) and induced PSCs of several ancestral backgrounds (African American, Asian, Caucasian and Hispanic/Latinx) is not clear. • What does the applicant mean by "best performing" lines? For example, if a line from a female donor has the highest efficiency would the applicant use such a line only in female patients? • Plans for progression from the laboratory to the clinic are very well thought out. • Sound scientific rationale.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The project is very well thought out and designed to achieve the expected outcomes. • Effort is dedicated to confirming robustness of a number of GMP-compliant human PSC lines, showing restored motor function in a rat model, testing for aberrant sensory effects, and establishing a treatment timeline and doses. • Revised proposal addresses previous GWG concerns. • Well planned and designed proposal. • There is good discussion of possible pitfalls and alternatives.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The primary data on differentiation are all excellent, as is the in vitro characterization. • The preliminary experiments demonstrate generation of synapses from cells transplanted into cervical contusion SCI one week post injury. The transplanted cells extend neurites rostral and caudal to the injury and are still present at 2 months post-transplantation. • Transplanted cells enhance motor network recovery as demonstrated by diaphragm electromyography. These experiments tested functioning transplants in eupneic breathing in and respiratory challenge and showed that the amplitude of diaphragm muscle contraction was enhanced in animals that received a transplant.

	• Optogenetics experiments also revealed the donor neurons enhanced motor output of the hemi-diaphragm on the side of the injury. • Excellent preliminary data: the applicant tested the freeze-thaw protocol and dosing of graft cells and showed feasibility of the approach. • New preliminary data showing diaphragm function in transplant recipients during normal and stress breathing are promising. • Milestone 1 lacks a clear rationale. The desired/optimal outcome of the proposed single cell RNA-Seq analysis of each line is not clear. • Is differentiation efficiency more important than purity? • Should the studies in Milestone 3 prioritize the already established 1 million cell dose? It seems that the timing associated with functional repair is more critical than the limited dose escalation. • Pilot experiments (using 1 million previously generated graft cells) assessing motor recovery at 6 months should start immediately. The current timeline will not get to this critical data before year 2. • Strong preliminary data. • Expertise in place.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• This is appropriately addressed. • Availability of a treatment for spinal cord injury will benefit diverse populations. • There appears to be good integration with a spinal cord injury community. • What is the basis for the hypothesis that sex or ethnicity (rather than the culturing protocol) are the critical factors in generating an optimized graft product? • Additional funds are requested for ten cell lines, but the rationale for testing these in detail is lacking. It is also not clear what the selection criteria will apply to the extensive (and expensive) testing of many lines.
No: 0	*none*

Application #	DISC2-14045
Title (as written by the applicant)	Novel Lipid Nanoparticles for Enhancing eNOS Synthesis for Cardioprotection Post Myocardial Infarction
Research Objective (as written by the applicant)	Our therapeutic candidate is a lipid nanoparticle that delivers a therapeutic dose of mRNA to the human heart, which transiently transfects of cells within the heart to improve function after myocardial infarction (MI).
Impact (as written by the applicant)	There is evidence for eNOS therapy as a cardioprotectant post MI; however, the progression of to the clinic has stalled due to inadequate delivery systems. Our therapeutic addresses this bottleneck.
Major Proposed Activities (as written by the applicant)	• Optimize PEGylated LNPs that edit heart muscle derived from XR1-iCMs. To achieve this goal, we will synthesize new lipids that increase diffusivity in the heart micromuscle derived from hiPSC. • Assess endogenous NO synthesis via eNOS mRNA delivered to heart micromuscles constructed from various patient lines. Deliverable is at least 5 LNPs to be evaluated in Milestone 3. • PEGylated LNP-induced expression in infarcted Ai6 mice. Deliverable is at least one LNP for optimal mRNA delivery into an infarcted heart with minimal toxicity that we will test in Milestone 5. • Develop LNPs that target coronary artery endothelial cells (aECs). Deliverable is at least one EC targeted LNP for evaluation in Milestone 5. • Efficacy of eNOS mRNA LNPs on improving cardiac function in mice with acute MI. Deliverable is a eNOS mRNA LNP therapeutic for the cardioprotection of mice after acute myocardial infarction.
Statement of Benefit to California (as written by the applicant)	Heart failure (HF) is a common human disease; after 40 years of age, the lifetime risk of developing heart failure is 20% for both women and men. The disparity of HF amongst various racial and ethnic US populations is also well documented. Our therapeutic candidate is a lipid nanoparticle that delivers a therapeutic dose of mRNA to the human heart to improve function after a heart attack. If successful, then our therapeutic would provide needed therapy for millions of Californians.
Funds Requested	$2,060,248
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 90

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	88
Median	90
Standard Deviation	4
Highest	90
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• The project is significant, and if successful, will generate a valuable therapy to prevent or minimize heart failure resulting from myocardial infarction (MI); this is an unmet clinical need. The applicants are proposing to test a hypothesis that lipid nanoparticle (LNP)-mediated transfection of cardiomyocytes (CMs) or endothelial cells (ECs) with endothelial nitric oxide synthase (eNOS) mRNA will result in cardioprotective nitric oxide (NO) production. • There is an urgency for myocardial infarction disease. There is evidence for eNOS therapy as a cardioprotectant post MI. • The project develops LNPs that can be used as vectors to deliver eNOS mRNA for cardioprotection. This technology is likely to result in a candidate product for cardioprotection. • The applicant tested their mRNA+LNPs in both human cardiac tissues and in vivo mouse heart. Thus, the applicant presented thoughtful options for translation. • Could positively impact a common disease.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The project is based on a sound scientific rationale of a cardioprotective role of eNOS/NO signaling and is empowered by the recent successes in LNP-mediated mRNA delivery in COVID vaccine development. • There is no preliminary data showing that eNOS mRNA expression reduced MI progression. • Yes, ample experimental evidence for eNOS therapy as a cardioprotectant post MI. • Overexpression of human eNOS in transgenic mice attenuates both HF and myocardial reperfusion injury • NO production from eNOS protects CMs from apoptosis. • The system allows for transient transfection of cells within the human heart with eNOS mRNA, which prevents overdosing the patient. This is a completely different approach compared to gene therapy where the cell is permanently altered and therefore continually expresses the therapeutic. • This is a genetic therapy project, focusing on eNOS mRNA.
No: 1	• The stop flow method to inject the LNP has significant safety issues in diseased heart. • Most of the studies cited are not altering eNOS post MI but prior where it is likely to have an effect on MI size and severity. I don't believe altering eNOS post MI will have any effect.
GWG Votes	**Is the project well planned and designed?**
Yes: 11	• The project is well-planned and designed. The preliminary results address different technical steps and provide a proof-of-concept for the project thereby favorably positioning the investigative team to successfully achieve the milestones and transition into large animal translational studies. • Risks and mitigation strategies were proposed. • This project focused on discussion of optimization of LNPs for delivery. While LNP optimization is important, development of robust eNOS mRNA plays a critical role for therapeutic effects of this project. The applicant should also discuss what strategy they will use to prevent potential immune rejection of eNOS expressing mRNA. • Application supported by sound scientific rationale but unclear how big the gap is for current approaches.
No: 1	• I would like to see them testing efficacy earlier in the proposal.

GWG Votes	Is the project feasible?
Yes: 12	• The proposed milestones are logical and are likely to be achieved within the proposed timeline. Given that the evidence of a cardioprotective effect of NO is currently available only in small animal models, and not in humans, this is a high-risk project. But the project also has high potential reward, which adds enthusiasm for the application. • Yes, the proposed milestones are logical and can be achieved within three years. • Yes, a good team and they can do all the work. • The institution has ample resources and facilities for this project. • RNA has translational potential. • The proposed team is acceptable. The PI is a tissue engineer who can produce good quality cardiac tissues, necessary for this project. Co-I is a researcher in the field of drug delivery. Another collaborator is a leading cardiac disease expert. • This team should include an expert in the field of modified mRNA technology.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12	• The project considers the influence of race, ethnicity and gender by employing a panel of hiPSC lines derived from healthy control subjects from diverse backgrounds to generate the cardiac microtissues. Additionally, the project's design that targets ECs would allow delivery of the LNPs via standard drug delivery angioplasty catheters, available in most hospitals throughout the U.S., which will greatly expand the access of this technology to the underserved communities. • The applicant plans to use a diverse panel of hiPSC lines. • It will benefit the diverse California population. • The project upholds the principles of diversity, equity and inclusion (DEI).
No: 0	*none*

Application #	DISC2-14090
Title (as written by the applicant)	Gene Therapy for SLC6A8 Creatine Transporter Disorder
Research Objective (as written by the applicant)	The objective is to define a final therapeutic candidate for an effective gene therapy for mutations of the creatine transporter SLC6A8, a major cause of X-linked intellectual disability (ID).
Impact (as written by the applicant)	This disorder results in severe ID, autistic-like behavior, seizures, & lack or delay of speech with no treatment. Improving brain transduction is essential and widely applicable to other conditions.
Major Proposed Activities (as written by the applicant)	• Develop multiple adeno-associated viral (AAV) vectors expressing human SLC6A8, package, determine titers and expression in human induced pluripotent stem cell (hiPSC)-derived neurons in vitro. • Assess resolution of any deficits and improvement in creatine transport in SLC6A8-mutated hiPSC-derived neurons by vector-mediated expression. • Assess transduction efficiency of AAV-SLC6A8 in vivo with brain cell expression and distribution of vector copies and tissue creatine levels in non-brain organs and tissues in Slc6a8-mutated mice. • Assess disease modifying activity of AAV-SLC6A8 in the a murine Slc6a8-mutated model. • Determine final therapeutic candidate, complete draft target product profile, and develop assays of purity, activity and identity. • Request INTERACT meeting.
Statement of Benefit to California (as written by the applicant)	Genetic-based intellectual disability of all causes is a more common occurrence than is appreciated. Effective therapies for these intellectual disabilities, where often there are none, could improve the lives of thousands of afflicted Californians & their families along with many hundreds of thousands of afflicted people worldwide. Brain gene therapy may result in novel, effective treatments for these disorders & improvement in their quality of life, with applicability to other conditions.
Funds Requested	$2,296,920
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 88

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	89
Median	88
Standard Deviation	1
Highest	90
Lowest	87
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• There is currently no treatment for the orphan disease caused by mutations in SLC6A8 and this candidate proposes to use gene therapy to address the loss of function of the creatine transporter gene, using an AAV-based therapy for SLC6A8 deficiency. • Focus is on developing a gene therapy for disorders of the creatine transporter SLC6A8 which have early onset of disease, intellectual disability and seizures. Applicant proposes that restoration of creatine transport by AAV-mediated transduction into the brain will lead to improvement in the phenotype of mice and will be a disease modifying therapeutic approach by correcting neuronal levels. • Second most common class of disorders of X-linked intellectual disability (after Fragile X syndrome). • No effective treatments: high dose creatine monohydrate does not increase cerebral creatine and does not significantly improve their condition.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• Yes, since creatine is not bioavailable to cells, the gene therapy aims to restore function to the creatine transporter SLC6A8. • SLC6A8 patients have one of over 80 identified mutations in the creatine transporter. Thus, direct correction of specific mutations is not feasible. • Exogenous creatine monohydrate is thought to fail due to creatine being unable to enter neurons due to the defective transporter. Gene therapy is a valid approach to restore transporter. Low efficiency in CRISPR/Cas9-mediated correction is a limitation as many neurons need to be transduced. • Previous work on a gene therapy for a metabolic disorder caused by a single gene mutation did not meet preclinical in vivo proof of concept. The applicant states "scientific and technical challenges" but does not further explain hurdles. Could the current applicant face similar challenges? This should have been addressed by the applicant.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• Yes, combination of in vitro and in vivo experiments are planned. Experiments include functional/behavioral studies, as well as other imaging and neural activity tests. • AAV vectors and animal model are in hand. Human iPSC induced neurons can be produced. The applicant has also generated human creatine transporter mutated cortical neurons and isogenic corrected controls for testing vector constructs.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• Yes, given extensive prior work in related fields and the presented preliminary data. • Feasibility of patch clamping demonstrated. • Indication that gene therapy in mice normalized weight and RNA expression after expression in brain. • IV injection results in transduced cells and myocardium and brain (not neurons) indicate that proof of concept using AAV9 to target neurons is not clear. • Animal studies on glucose uptake are not clear. Figure 6 compared wild type female to mutant male with no statistics. What is the rationale and significance of this? • iPSC neurons will represent cortical neurons, however preliminary animal studies (Fig. 7) use cerebellar Purkinje neurons making it difficult to compare in vitro human iPSC experiments to the mouse model. The rationale for these two different tissues is not clear.

	• Many in vitro experiments are performed before efficacy in vivo experiments (Milestone 4). Not clear whether mutant neurons grown in vitro will have a phenotype that can be rescued (Milestone 1). • Optimizing the vector seems challenging as it is not clear how much creatine will be optimal for different neurons. • Oligodendrocytes also express the transporter - are they affected by the mutation? Are myelination defects drivers of progression? This is not discussed. • Significance of myocardial expression after transduction is not addressed.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• Yes, given all races seem to be affected and communities will be invited to inform the research. • Why are female mice not included? Abnormalities in SLC6A8 are X-linked but female carriers can also have pathology.
No: 0	*none*

Application #	DISC2-14133
Title (as written by the applicant)	Drug Discovery for Duchenne Muscular Dystrophy Using Patient-Derived Human iPSCs
Research Objective (as written by the applicant)	We will utilize human induced pluripotent stem cells derived from Duchenne muscular dystrophy (DMD) patients for drug testing and drug discovery for this rare genetic disease.
Impact (as written by the applicant)	Diverse iPSC-derived lines that recapitulate patient phenotypes will supplement preclinical studies to de-risk clinical trials while identifying a therapeutic target for DMD-associated cardiomyopathy.
Major Proposed Activities (as written by the applicant)	• Clinical evaluation of DMD patients recruited for the generation of iPSCs. • Generation of DMD induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs). • Cellular and molecular characterization of DMD iPSC-CMs. • Drug testing of our candidate for safety and efficacy in DMD iPSC-CMs. • Drug screen of ~8,000 small molecules in DMD iPSC-CMs. • Validation of drug candidates in 3D cell models and in DMD mouse model.
Statement of Benefit to California (as written by the applicant)	Duchenne muscular dystrophy (DMD) is a genetic disorder affecting 1 in 3,500 male births. Thousands are estimated to be affected in California. In DMD, cardiomyopathies are highly prevalent and the leading cause of death in the disease. By discovering a safe and effective drug for these heart problems, we can help meet an urgent need for DMD patients and establish a proof of concept in applying induced pluripotent stem cell technology for the discovery of drugs for rare orphan diseases.
Funds Requested	$675,000
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 88

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	87
Median	88
Standard Deviation	1
Highest	90
Lowest	86
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• The goal of this revised application is to test the efficacy of a previously identified small molecule compound - an antagonist of the adenosine receptor (A2BAR) - and identify several new compounds that may decrease or prevent progressive cardiomyopathy, fibrosis and heart failure in patients affected by Duchenne muscular dystrophy (DMD). Given that heart failure is a leading cause of death in DMD patients, this is a highly significant clinical goal addressing an unmet clinical need. • The goals of this revised proposal are to characterize an ethnically diverse set of 10 iPSC-CMs, test an adenosine receptor antagonist on iPSC-CFs, and conduct a screen of FDA approved and active compounds on the iPSC-CMs that show the greatest response in decreased viability due to adrenergic stress and validate the candidates on the other 9 iPSC-CM lines, in cultures and in vivo. • These goals will provide a great resource of diverse iPSC-CMs and iPSC-CFs to the DMD community, and possibly identify new therapeutic approaches for dystrophic cardiomyocyte dysfunction. • Identifying a novel compound that prevents fibroblast activity may provide therapeutic avenues for an even wider variety of cardiomyopathies and acute cardiac conditions. • This resubmission application is much improved and now extends the studies into safety and efficacy in a DMD mouse model and discusses a potential pathway to translation. • The proposed technology could lead to the development of a new treatment for DMD cardiomyopathy • There are few and limited treatments for DMD, a devastating disease.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The idea that DMD iPSC-derived cardiomyocytes can be used as a screening tool for a drug discovery for DMD-associated cardiac dysfunction has a strong scientific rationale. • Defining the variability in numerous iPSC-CM outcomes across an ethnically diverse set of samples has strong rationale for developing potential therapies for DMD cardiomyopathy that are useful for all patients or to be able to screen for non-responders prior to treatment. • The rationale has been improved by removing the previous rationale of using these cells to improve exon skipping drugs. • The use of iPSC-CFs for testing novel anti-fibrotic therapies may have value, although only one drug will be tested, its relevance in DMD cardiomyopathy is unknown. The activation of alpha-smooth muscle actin and collagen I by conditioned media from DMD iPSC-CMs on primary cardiac fibroblasts strongly supports the rationale for this assay. • A major strength is that all cell lines have been collected from ethnically diverse DMD patients and controls. • A major strength is the data from DMD iPSC-CM conditioned media inducing fibrotic genes on primary cardiac fibroblasts. • A major strength is the cardiac fibrosis reporter lines. • A major strength is the development of an iPSC-CM assay where beta-adrenergic stress induced reductions in viability that can be prevented by a beta-blocker. • A moderate strength is the ability of the adenosine receptor antagonist to reduce TGF-b induced fibrotic genes in control iPSC-CFs, although it's relevance to dystrophic fibroblasts stimulated with DMD iPSC-CM conditioned media is not yet known or the data shown. • A minor weakness is that in Fig. 16 utrophin is only present in the starting material lane of only one of the two DMD-iPSC-CMs. That result doesn't make sense, since if anything, utrophin should be increased in the absence of dystrophin, not reduced. • The revised project provides a sound scientific rationale.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The revised proposal addressed previous concerns, and it is now well planned and designed (in vitro and in vivo, with proper controls). • In general, the project is well-designed. However, relevance of in vitro efficacy assays of the proposed therapy using CM conditioned medium to DMD cardiac fibrosis is

	speculative, because of a key role of DMD-mediated inflammation to cardiac fibrosis in vivo. From this perspective, the incorporation of the D2-mdx DMD mouse model into the revised application is a valuable addition. Demonstration of antifibrotic effect of the product in this model would significantly strengthen the application. ● The applicant has addressed critiques from prior review, including control drugs. ● The goals of the project have been improved to more likely achieve one or more candidates ready to advance to translation. ● Major strengths include the measurement capabilities for iPSC-CMs, and the wide array of outcome measures proposed to characterize the cells in Aim 1. ● A major strength is the generation of iPSC-CFs and the use of conditioned media to induce a response for drug testing. ● A major strength added to the resubmission is that newly identified molecules will be compared to cardiac therapies currently used in DMD, including ACE inhibitors, mineralocorticoid receptor antagonists (MRAs) and sGLT2 inhibitors. ● A major strength is that now three of the drugs identified in the hiPSC-CMs, and the applicant's current candidate, will be tested in cultures and in vivo.
No: **0**	*none*
GWG Votes	**Is the project feasible?**
Yes: **13**	● Significant body of preliminary data. The team has plenty of expertise on the type of experiments proposed. ● The milestones are logical and achievable within the proposed timeline. ● The team is outstanding, and it is appropriately staffed to achieve the goals of the project. ● The team has access to all the necessary resources. ● Yes, strong approach, team, and resources. ● Milestones are achievable but given the important inclusion of further in vitro and in vivo testing, the timeline is tight. ● The team assembled has all of the expertise to quickly embark on the aims and it is clear they have been gathering additional data on the iPSCs. At the least, they will likely have echocardiography data on treated mice, if not all of the downstream ex vivo analysis, completed.
No: **0**	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	● A panel of 10 DMD iPS cell lines with diverse ethnic background will be generated. ● The project plan and design adequately account for the influence of race and ethnicity on the outcomes of the study. To this end, the investigators will utilize 10 DMD iPSC lines generated from the individuals of diverse racial and ethnic backgrounds: three Caucasian, three African American, two Asian, and two Hispanic/Latino. ● Ethnic diversity is a major goal of the study and is well addressed. ● Ultimately, the project would inform development of a product that serves the ethnic diversity of DMD patients throughout CA and the world. ● Ethnically diverse samples.
No: 0	*none*

Application #	DISC2-14187
Title (as written by the applicant)	Expanded Capacity AAV Retinal Gene Therapy Enabled by Efficient RNA-Joining Technology
Research Objective (as written by the applicant)	A novel AAV-based gene therapy candidate for use in treatment of inherited ocular disease.
Impact (as written by the applicant)	AAV vectors have a limited cargo capacity (<5kb), preventing their use in the treatment of many untreatable genetic diseases caused by large genes.
Major Proposed Activities (as written by the applicant)	• In vitro optimization and selection of gene therapy candidates • In vivo testing to establish efficacy of gene therapy candidates • Demonstration of disease-modifying activity in mouse genetic model of ocular disease • Evaluation of safety for a dual vector AAV approach • Testing activity in human photoreceptors
Statement of Benefit to California (as written by the applicant)	Of the 280 genetic mutations that cause inherited retinal disease (IRD), there is an approved treatment for just one. Our innovative technology provides a solution for challenges encountered by conventional AAV-based gene therapy approaches. Because our technology is agnostic to gene, the advancement of this therapy will be an important step forward for developing treatment for a wide variety of genetic diseases, including those that impact the diverse California population.
Funds Requested	$1,446,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 87

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	87
Median	87
Standard Deviation	2
Highest	92
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• Yes. This is a well-designed project offering a candidate that potentially may help target several diseases, for which current treatments are limited or not available. • The proposed project offers a new gene therapy approach by addressing a bottleneck related to the capabilities of viral vector deliveries. • Increasing the packing limit of AAV could open up new areas in gene therapy.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The application of this technology for rare retinal disorders is appropriate and will have a high impact. • Yes. The scientific rationale is very sound. • The preliminary data are very compelling and supportive of the proposed project.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The proof of concept data are very convincing, and the study is generally very well designed. • Preclinical and safety testing projects arms are well designed and appropriate. • Yes. The potential pitfalls are identified and well thought through, and the contingency plans are put in place and well described. • My only concern is related to the human iPSC arm of the project, in which photoreceptor cells will be differentiated from iPSCs from a healthy African American individual. One individual is not enough for a scientifically sound conclusion - particularly when it comes to iPSCs. • Overall, yes, but the use of just one cell line limits rigor. • The project is very well constructed - but requires more than one human iPSC line. • Yes, no concerns.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• Yes - the proposed milestones are well thought through and the experimental set up is appropriate. This makes this project achievable within the proposed timelines. • The team is well qualified, but a project of this scope (even with the proposed collaborations) is likely to require more experienced staff than are currently proposed. • Well-budgeted project. • Yes, no concerns.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 11	• Yes, but the applicant should be aware that underrepresented minorities are not necessarily more affected by a disease indication; they may simply have less access to care. Care should be taken to critically analyze data. • The project plan would benefit from adding iPSC lines from donors with different racial/ethnic backgrounds. • Perhaps, but more action should be taken to uphold these principles.
No: 2	• Study of an iPSC line from an African American donor may seem like a good step, but is actually not sufficient. • If successful, this project offers a one-time treatment which is particularly suited for underserved communities. • The applicant will incorporate perspectives and experience from the population that will benefit from the proposed product in the implementation of the research project.

Application #	DISC2-14053
Title (as written by the applicant)	Pluripotent Stem Cells for Tendon Tissue Engineering
Research Objective (as written by the applicant)	We propose to develop a bio-tendon engineered from differentiated pluripotent stem cells for the repair of tendon injuries and degeneration.
Impact (as written by the applicant)	Rotator cuff tears are the most common causes of shoulder pain that require surgery. However, failure rates range from 20% to 90%. A successful tendon repair will have a major impact on outcomes.
Major Proposed Activities (as written by the applicant)	• We will develop assays for activity, purity, and identity of the cells. • We will generate proof of concept of tendon repair after implantation in animal models of tendon injury. • We will prepare an INTERACT application to submit to the FDA for approval for the preclinical phase.
Statement of Benefit to California (as written by the applicant)	Annually, over 100,000 Californians sustain tendon injuries, the majority of which require surgical repair. Failure rates for shoulder rotator cuff tendon repairs vary between 20% and 90%. Failed rotator cuff tendons lead to early development of osteoarthritis, for which the only effective treatment is total joint replacement. There are significant socioeconomic benefits in preventing disability. The reductions in healthcare costs are also likely to be significant.
Funds Requested	$2,734,163
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 86

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	86
Median	86
Standard Deviation	0
Highest	86
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• The proposed project aims to develop a new off-the-shelf therapeutic tissue engineered product – bio-tendon – to be used for repair of rotating cuff injuries. Effective tendon repair is an unmet clinical need and if the project is successful, the product will have a significant impact of treatment of tendon injuries. • Tendon tears are among the most common musculoskeletal conditions. Current approaches are not successful and many clinical trials failed. Tendon tears impact the ability to work, making it a costly social disease. • Development of an engineered bio-tendon that can potentially replace lost tissues in large/massive tears is novel and there is to date no adequate approach. • This bio-tendon, envisioned to be an off the shelf product, will augment traditional surgical repair of rotator cuffs and prevent or significantly reduce failures after surgery. The bio-tendon can also be used as a graft for filling of large tendon defects that present the greatest challenge for surgical repair. • Despite major advances in surgical techniques and repair materials, the repair fails to heal in 20% to 90% of patients, depending on age, size of tear, time after injury, and muscle function. Untreated tears do not heal and become chronic resulting in significant loss of tendon tissue, fatty degeneration of muscle, and progression to end-stage osteoarthritis requiring total shoulder replacement. Clinical augmentation repair is inconsistent.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The proposed tissue engineered bio-tendon uses an allogeneic cell line with low risk for immunorejection and is designed to heal tendon tears that are due to injuries and degeneration. • Applicant proposes to generate an off-the-shelf tissue for rotator cuff repairs. • A biomimetic bio-tendon will replace torn and diseased tissue and accelerate the stages of repair by limiting the phase of inflammation, circumventing the need for host biosynthesis, encouraging cell migration into the bio-tendon, and accelerating the phase of tissue remodeling. • The project is based on a solid scientific rationale and on several recent publications resulting from the labs of the PI and collaborators. • Generally speaking, the different components of the experimental design (rotator cuff repair) have been demonstrated for applications of the meniscus. The team has several publications related to the scaffolds, including a review paper on using such scaffolds for rotator cuff repair. • They have reported that a key transcription factor initiates differentiation of tenogenic cells and promotes maturation of tendon tissue. This transcription factor is also mechanoresponsive and induces formation of neotissue with collagen fibrils aligned in the direction of tensile stretch. • They have also shown proof of concept of generating fibrocartilage and calcified cartilage in vitro to represent the enthesis. Because rotator cuff tendons typically tear at their bony attachment, the regeneration of an adequate enthesis is critical for adequate tendon-to-bone healing. • The applicants show upregulation of tenogenic gene expression in their manipulated iPSC lines but it remain unclear how these levels compare to cells that have already been tested and failed to show regeneration (i.e., MSC, tendon progenitors). Thus, it is not clear whether and how levels of expression translate to clinical efficacy. • The applicant states that the success of graft materials in current use is limited and proposes that mechanical properties of the bio-tendon are critical to combat current limitations. However, this seems to be speculative (except for suture pull-out complications) as no data are discussed that would connect current limitations to mechanical properties of the bio-tendons.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The project is well-planned and designed for achieving its goal and for transitioning into translational phase. Proof-of-concept data is provided.

	• Their approach is to deliver an off-the-shelf tissue that can be used directly to augment conventional tendon repairs with a special focus on the unmet needs of rotator cuff repair. Aim 3 will include working with a consulting company to help with regulatory, QC and QA and help with an INTERACT meeting as a precedent to a pre-IND meeting for a combination product. • The proposal spans in vitro optimization and an array of in vivo studies toward clinical translation. • The proposal is clearly laid out and provides rationale for each aim. The figures and schematics of the research plan help to convey the experimental design. • Two pluripotent cell lines will be evaluated. Both cell lines are compliant with the following FDA requirements for donor eligibility. • They will explore potential benefits of conjugating various factors in the enthesis portion of the construct to promote calcified cartilage tissue formation in order to mimic the transition zone of native tendons. This specifically addresses major failure point of rotator cuff repair. • A graft used for augmentation of repair will serve as a clinically-relevant control graft for the animal studies. The FDA has approved grafts to augment rotator cuff repair, but has yet to approve an interpositional graft. The final embodiment will depend on input from the FDA. • Previous grant did not meet all milestones, and its relationship to the current proposed project is not discussed.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The project's milestones are logical. The proposed timeline appears to be reasonable and achievable. • The timeline is aggressive but doable as supported by progress of a previous CIRM grant where all milestones were met and a pre-IND approved for pluripotent stem cell treatment for cartilage repair. • Applicant already reported proof of concept efficacy in a mouse tendon repair model. • Proposed cell lines are compliant with FDA requirements for donor eligibility. • Informal discussions with the FDA in preparation for the INTERACT submission have been initiated. • The PI is a MD/PhD orthopedic surgeon with extensive research experience and a current clinical trial looking at iPSCs for cartilage repair. The proposed project is a pivot for the PI, but all the expertise necessary to shift meniscus work to rotator cuff, including sports/shoulder surgeons, are in place. The rest of the team includes shoulder orthopedic surgeons, a Nobel laureate, and musculoskeletal developmental biologist. • The institution is well equipped with resources to successfully carry out the proposed research. • A discussion of how animals models are suitable in predicting human outcomes is lacking - in other words, did previous approaches that failed in patients show efficacy in animals? If yes, how is the approach different from previous approaches that failed?
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• Tendon injuries and degeneration are more common in patients with diabetes and metabolic disorders and are more prevalent in minorities and underserved communities. • Therapeutic would have the potential to combat pain, and restores function to a degree that patients could resume work. As ethnic minorities and disadvantaged segments of the population are disproportionately affected the positive impact would be very high. • Preclinical in vivo studies include male and female animals to assess the effect of sex on tissue regeneration. • The project is appropriately designed to account for the influence of race, ethnicity, sex, and gender diversity, because the bio-tendon will be an off-the-shelf acellular product expected to exert no or minimal allogeneic response. Therefore, the therapeutic application of the product will not be constrained by racial, ethnic, sex and gender boundaries.
No: 0	*none*

Application #	DISC2-14041
Title (as written by the applicant)	Autologous stem cell-derived interneuron cell therapy for spinal cord injury (SCI)
Research Objective (as written by the applicant)	Functional restoration following spinal cord injury using defined excitatory and inhibitory spinal interneuron progenitor cell transplantation
Impact (as written by the applicant)	The development of a stem cell derived progenitor cell therapy with disease modifying potential for spinal cord injury
Major Proposed Activities (as written by the applicant)	• Define and characterize DI4 GABA and V3 Glut spinal interneuron progenitor cells derived from pluripotent stem cells • Evaluate and compare the effects of transplantation of DI4 GABA vs. V3 Glut spinal interneuron progenitors subacutely and chronically after a non-clinical spinal cord injury model • Evaluate the effects of combined transplantation of DI4 GABA and V3 Glut spinal interneuron progenitors subacutely and chronically after a non-clinical spinal cord injury model • Evaluate the effects of chemogentic activation and inactivation through DREADD receptors expressed on transplanted dI4 GABA vs. V3 Glut spinal interneuron progenitors on behavioral outcomes after SCI • Establish initial Target Product Profile for potential future progenitor cell therapy application • Develop the basis for the submission of a CIRM TRAN1 grant application
Statement of Benefit to California (as written by the applicant)	In the United States, currently there are more than 17,900 new spinal cord injury (SCI) patients annually. Of particular concern in the California population are that SCI affects all races, with a higher incidence in Asians (28%), 24% in non-Hispanic blacks, 13.3% in Hispanics, and lower incidence in Caucasians and Native Americans. Our research aims to delineate the effectiveness of stem cell derived spinal interneurons to correct SCI deficits in order to develop better therapies.
Funds Requested	$2,025,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 86

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	86
Median	86
Standard Deviation	1
Highest	90
Lowest	85
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• Spinal cord injury is a leading cause of disability worldwide - for which there are no treatments. In this respect, any new candidate, even if offering only a stepwise improvement, provides hope for many SCI patients. • SCI is a major cause of disability and pain, including in younger age groups. • This project proposes to identify spinal interneuron progenitor cell candidates derived from human pluripotent stem cells to attenuate functional deficits commonly exhibited after injury, including locomotor function, spasticity and chronic pain.after subacute and chronic SCI. If successful, this would have a significant impact. • If the project is successful then the transplantation of the interneuron progenitor cells would offer a stem cell technology that improves patient care in respect to an important unmet medical need. • Advances important cell therapy candidate for SCI.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The scientific rationale for this project is very clear and sound; and backed up by good and convincing preliminary data. • The rationale is built on strong preliminary data. • Replacing the proposed interneurons is scientifically reasonable. • Grafted cells promote some recovery of function beginning seven weeks after transplantation. Although recovery is often limited, the prospect of any recovery after a chronic SCI injury is something of great interest. • Preliminary studies indicate the transplantation of the GABA interneurons mitigates spasticity in pain and improves locomotion. The goal is to build on the studies by transplanting both GABA and Glut interneurons during the sub acute to chronic phase after mid thoracic contusion injury to try and bridge the corticospinal tract and remodel the local spinal circuit.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The product is well designed and thought out, and looks like it will provide proof of concept data. • Potential pitfalls and alternative plans are provided. • This is a well-planned project and designed with the end goal in mind which increases the confidence that the project will be successfully executed. The applicants put a lot of attention to sensory recovery following SCI, however only the Von Frey test is proposed to be used. Additional tests, e.g. hot plate, would be highly beneficial as the sensory loss after SCI is multifaceted and as such should also be tested after potential treatments. • The same is true for locomotion - addition of additional (more sensitive) assays to test locomotor recovery would be beneficial. Kinematic analysis of locomotion is also recommended. • There are minor concerns regarding the choice of metrics for functional rescue and on the immunogenicity of the cell product.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The preliminary data suggest that the project is feasible. • Yes, no concerns. • The proposed project is doable within the proposed timelines.

	• The team is well suited for this project. However, the time allocation (100%) and description of project related duties assigned to the PI is not realistic - e.g., planning and executing all daily activities, etc...
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• Interactions have begun with the spinal cord injury community in California. • Spinal cord injury affects all races and genders. The use of allogenic cells eliminates the need for immune suppression, which will increase accessibility for all communities. • Well addressed. • The project plan and design adequately address DEI.
No: 0	*none*

Application #	DISC2-14169
Title (as written by the applicant)	Vax-T to promote formation of cancer-specific T memory stem cell for personalized cancer immunotherapy
Research Objective (as written by the applicant)	A vaccine booster to induce antigen-specific T memory stem cells (TMSCs) that will help enhance the long-term immunity against cancer recurrence
Impact (as written by the applicant)	Cancer recurrence represents an unmet medical need. Cancer vaccines are promising, but often lack long-term protection. We will induce T memory stem cells (TMSCs) to boost long-term immunity to cancer.
Major Proposed Activities (as written by the applicant)	• To develop micro-/nanoparticles with a sustained release of small molecule and T cell activation signals to promote the formation of T memory stem cells (TMSCs) and tumor-antigen-specific dendritic cells (DCs) in vitro. • To investigate the induction of TMSCs by injectable cancer vaccine booster in young and aged mice. • To investigate the prevention of cancer recurrence in murine models.
Statement of Benefit to California (as written by the applicant)	Cancer recurrence presents an unmet medical need. Chemotherapy and radiation therapy have side effects. Cancer vaccines are promising, but may not achieve long-term protection, especially in the elderly. Our approach may boost the therapeutic efficacy of the cancer vaccines and help protect patients with a more effective and less painful therapy. This will greatly reduce burden of healthcare and benefit society.
Funds Requested	$2,267,714
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	86
Median	85
Standard Deviation	3
Highest	95
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• Vax-T is a system utilized for the delivery of a therapeutic vaccine with traditional vaccine components plus a small molecule to induce the formation of T memory stem cells (TMSCs). The overall goal is to achieve a long-term immunity memory against specific antigens (e.g., cancer antigens, virus antigens). • This technology is related to cancer vaccine development. If successful, it will have a huge impact for many cancer patients. • This proposal will utilize Vax-T to deliver a therapeutic vaccine composed of tumor lysate, TWS119-PLGA particles and adjuvant to induce TMSCs to create a long-term immunity against melanomas. The proposed therapeutic candidate is likely to address an unmet need of cancer patients, especially elderly patients. • Although the proposed therapeutic strategy does not involve the direct use of stem cells as therapeutic agents, the proposed cancer vaccine could potentially activate antitumor immune responses induced by TMSCs. • The proposed cancer vaccine has been developed and its antitumor efficacy has been shown in pilot studies. The proposed project will further optimize and evaluate the optimum dosage as well as safety of Vax-T in a mouse tumor model. • The investigators have presented a detailed plan and demonstrated capability for translating the proposed therapeutic. • This project focuses on using drug delivery to induce immune response and T memory stem cells. • The applicant will investigate the prevention of cancer recurrence in murine models using their vaccine approach. • This may improve outcomes for melanoma as well as other cancers. • Overall, yes, but the sole focus on (highly immunogenic) melanoma limits impact.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• Yes, the long-term immunity is important to prevent tumor recurrence which is often devastating and deadly. Therefore, it is important to activate long-lived TMSCs which can provide anti-cancer protection that lasts. • The potential of the proposed cancer vaccine to activate TMSCs and facilitate long-term cancer immunity is undoubtedly an advancement in the field. • The proposed therapeutic candidate has the potential to help a wide range of cancer patients. • Using tumor cell lysate in a vaccine for treating cancer is reasonable. • The preliminary data obtained by investigators suggests that the proposed cancer vaccine is able to activate TMSCs in vitro and inhibit tumor growth in vivo. • The applicant provided strong preliminary data for all three of their aims. • These data are compelling. • However, no data are presented showing the proposed therapeutic to be superior to currently used therapies. • The investigators have demonstrated combined expertise in developing and optimizing the proposed therapeutic.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The lead candidate is likely to advance to translation as the materials and methods are mainly FDA-approved, and the facility is FDA-compliant. • The investigators anticipate that the proposed therapeutic has the potential to replace radiation and chemotherapy. However, none of the experiments were planned or designed to compare therapeutic efficacy to current standard of care. • The B16F10 melanoma model will be used in this project. B16F10 cells are highly immunogenic and the likelihood that the mice in the study (treated and not) will immunologically reject the re-challenge is high. The use of additional tumor cell lines or models would better characterize the robustness of the proposed therapeutic. • The proposed assays to evaluate the cancer vaccine in vitro and in vivo are relevant, yet a direct experimental comparison between the proposed therapy and currently used therapies is still necessary.

	• B16F10 cells are very immunogenic. In Aim 3a, 95-99% of the tumor will be removed in one of the experimental subgroups. It will not be surprising to see a long-lasting memory induced in the mice with ~100% of the tumor being removed and rescued. An additional tumor model is required to further confirm the therapeutic efficacy. • A challenge with a more difficult mouse model of cancer would enhance the proposal. • The applicant should test less immunogenic tumor models. • The project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission. • Yes, the project is well planned. • Yes, this is a very good project. • The project plan is logically laid out. • Each of the aims discussed potential pitfalls and alternative approaches.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• Yes, but it could be achieved in a shorter timeline given the experience of the team and the proposed experiments. • The publication record of the team and the presented preliminary data support the feasibility of this research proposal. • The PI has extensive experience in performing the proposed research activities. • The budget is appropriate. • Based on the applicant's preliminary data, this project is feasible. • This is a strong team, including bioengineers, immunology professors, and bioinformatics scientist. • Yes, the institution has all the necessary resources and facilities for the proposed research. • The budget is too high. Also, I note that the applicant has one NIH pending award with a similar cancer vaccine concept to this one. • Yes, based on the available data.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• The investigators will address the needs of diverse and underserved communities by investigating the induction of TMSCs from donors with different race, ethnicity, sex, gender, and age. These cells will be highly representative of the diverse California (and USA) population. • Outcomes would inform the development of a product or tool that serves the unmet medical needs of the diverse California population, especially elderly Californians. • Yes, the applicant addresses the influence of race, ethnicity, sex and gender diversity. • Cancer will affect everyone, including the diverse California population.
No: 0	*none*

Application #	DISC2-14083
Title (as written by the applicant)	Development of novel small molecules against cancer stem cells in solid cancers
Research Objective (as written by the applicant)	To study and optimize lead compounds with multi-kinase activity against existing glioma stem cells and radiation-induced phenotype conversion of non-stem glioma cells into induced glioma stem cells.
Impact (as written by the applicant)	Glioblastoma (GBM) is a universally deadly disease. While radiotherapy prolongs survival in glioblastoma it has hit a critical barrier. The proposed study aims to improve the efficacy of radiotherapy in GBM.
Major Proposed Activities (as written by the applicant)	• Define and validate the molecular targets of two small molecules in vitro and in vivo • Optimize the small molecules to increase their activity against existing glioma stem cells and to prevent radiation-induced conversion of non-stem glioma cells into induced glioma stem cells • Perform pharmacokinetics studies in tumor-bearing mice • To demonstrate efficacy of the lead small molecule and/or a second small molecule against glioblastoma alone and in combination with radiation in patient-derived orthotopic models of glioblastoma
Statement of Benefit to California (as written by the applicant)	Glioblastoma is a universally deadly disease and treatment outcome has not been improved for two decades. The standard-of-care for patients with glioblastoma is surgery, followed by radiotherapy and chemotherapy and the median survival is only 15-18 months. The proposed studies aim to develop novel compounds against glioblastoma that will enhance the efficacy of radiotherapy to improve survival for patients with GBM, thereby improving value-based care and the life of Californians.
Funds Requested	$2,340,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	85
Median	85
Standard Deviation	0
Highest	85
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• The project aims to address the critical unmet need of enhancing the current standard of care for the deadly malignant brain tumor glioblastoma and improving the outcome of patients. • The proposed small molecular drug development will likely to result in a candidate that could improve therapeutic efficacy of radiation therapy in GBM patients, a major unmet medical need. • Inhibiting the generation of glioblastoma stem cells after radiation could be medically very useful in regards to this important medical need. • Candidates selected in the preliminary screen show a promising activity profiles against GBM both in vitro and in vivo without significant toxicity. • Further pre-clinical testing and mechanism-based enhancement of antitumor activity is well-justified and will likely generate new therapeutic candidates for GBM with enhanced activity without added toxicity. • The revised application is responsive to prior critiques. • The project has a potential to develop novel small molecule compounds that can be used in combination with radiation therapy to inhibit the generation of glioblastoma cancer stem cells and increase the effects of radiation for patients with glioblastoma. This proposal is not focused on developing a stem cell technology or use stem cell based therapies for cancer. • The revised application is now presenting detailed options for the progression of a successful candidate into clinical settings. Specifically, the project proposes to optimize key drug properties such as blood brain barrier penetration, safety to normal tissues, along with efficacy data in clinically relevant animal models, which will pave the way to clinical translation. • The proposal would benefit from adding a transgenic GBM model in which both antitumor activity and toxicity could be tested in a syngeneic system, overcoming a major limitation of the proposed models. In particular, such a model would allow evaluation of the potential toxicity of new compounds on the immune system which plays a major role in controlling GBM progression.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The need for a product with the proposed characteristics is clear and the drug screen to identify candidates appears to have been successful. • The PI's group has a strong track record of publication on research directly relevant to this proposal, and this proposal is a rational extension of the line of ongoing research. • The PI's group has identified the lead compounds and present a set of strong preliminary data showing their capacity to inhibit GBM cell plasticity post radiation, penetrate the blood brain barrier and not cause major toxicity to normal cells. • There is a sound scientific rationale to targeting GBM with the lead compound, a novel inhibitor of radiation-induced phenotype conversion of non-stem GBM cells to induced glioma-initiating cells. • The small molecule candidate looks like it has the properties needed to be used in proof of product analysis. • Strong preliminary data providing a rationale for the lead candidate based on results from in vitro and in vivo GBM models. • Specifying efficacy based on improved median survival is an important part of the rationale for this proposal. • The proposal is not necessarily enabled by the use of stem cells, but it takes advantage of novel compounds to inhibit radiation-induced cancer stem cells to improve therapeutic effects. • The proposed project is uniquely enabling for the advancement of a cancer stem cell-targeting therapy. • The PI's team has already demonstrated and published the efficacy of dopamine receptor antagonists using analogous concepts and approaches. However it is still not clear if the new compounds are superior to dopamine receptor antagonists.

No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The plan for further progression of the research is well described. • The project is very well planned using appropriate models, controls, and endpoints. • There is well-developed proof-of-concept data in support of the small molecule as the lead candidate. • The project has two aims: 1) optimizing the compounds and 2) characterizing their efficacy and mechanisms when combined with radiation therapy in humanized mouse models, which are designed to produce key basic data towards initiating clinical trials. The investigators have clarified that IC50 values for the targeted kinases leave room for further improvements, and their medicinal chemistry expertise will allow them to achieve even higher efficacy at lower doses. • The availability of a large panel of glioblastoma models enables testing in heterogenous tumor models and gives strength and clinical relevance to this proposal. • Specific aims are well designed and will likely produce informative results. • Applicants addressed many relevant pitfalls and described alternative approaches. • The project plan and timeline are feasible. • The investigators showed that the lead compound is a multi-kinase inhibitor, and assumed that the compounds function via inhibiting kinase pathways. However, it is possible that they, particularly the other compound (whether it's structurally similar to the lead compound is unknown), might have other actions than kinase inhibition. This aspect is not appropriately considered or discussed. • There's insufficient attention to potential immune-related toxicity of the lead candidate and derivatives. Such toxicity is quite possible considering multi-kinase inhibitory activity of the drugs and dependence of immune effector cells on kinase activation. • The pharmacokinetics and maximum tolerated dose studies will provide key data to help translate the agents to human studies. However, the PI did not propose to study potential delayed adverse effects of the compounds. Studies with immunodeficient mice will not allow assessment of potential adverse effects on the immune system, which is still not properly considered. • Project plan and timeline does not fully demonstrate an urgency that is commensurate with CIRM's mission.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The fact that this is a drug development project, and the proof of concept data provided, suggest this project is suitable for advancement to translational studies. • In the prior submission, there were concerns with regards to the ambitious nature of the proposal which involves creating and testing new compounds and testing many humanized mouse models and cutting-edge molecular analysis, casting some doubt if this can be completed during the 2-year time frame. The investigators have now extended the proposal into a 3-year proposal with a specific focus on one molecule as the lead candidate and another as a backup. • The proposed milestones and expected project outcome are logical and likely to be achieved within the proposed timeline. • The publication record of the PI's team and presented preliminary data support the feasibility of this research proposal. • The team is exceptionally qualified and staffed. • The team has access to all the necessary resources to conduct the proposed activities. • The budget is appropriate. • There is still a lack of transplantation data regarding whether or not glioblastoma stem cells have been truly eliminated, although the in vitro data are promising. However, they show data indicating in vivo efficacy and lack of in vivo toxicity.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• Demographic information of the humanized mouse models is available and the PI plans to cover models derived from patients of diverse racial backgrounds.

	• Any drug that enables better treatment of glioblastoma will impact multiple communities. • The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity. • The project outcomes inform the development of a drug that serves the unmet medical needs of the diverse California population, including underserved racial/ethnic communities. • The applicant incorporates perspectives and experience from the population that will benefit from the proposed product in the implementation of the research project. • This part of the plan is minimally described. • Minimally addressed.
No: 0	*none*

Application #	DISC2-14096
Title (as written by the applicant)	Pharmacological regenerative treatment of idiopathic pulmonary fibrosis targeting the senescent niche of lung progenitor cells.
Research Objective (as written by the applicant)	Novel selective pharmacological strategy targeting senescent lung stem cells
Impact (as written by the applicant)	Idiopathic pulmonary fibrosis (IPF) along with other interstitial and age-related lung diseases
Major Proposed Activities (as written by the applicant)	• Characterize senescence cells, including senescent stem and progenitor cells in the lung of patients affected by idiopathic pulmonary fibrosis • Screening of a library of senolytic small molecules prodrug on Idiopathic pulmonary fibrosis primary cells • Development and charcterization of a humanized mouse model based on the primary IPF senescent cells characterized in Activity 1 • Pharmacological characterization of the lead senolytic compound • Efficacy studies of the lead senolytic compound on the humanized IPF model
Statement of Benefit to California (as written by the applicant)	Progressive pulmonary fibrosis is an age-related degenerative interstitial lung disease that affects an increasing number of population in California and worldwide. The reasons of this increase include a growing aging population, decreased air quality due to increased air pollution, partially driven by climate change, and more recently by the impact of the virus SARS-CoV-2 on COVID-19 survivors. The proposed therapy will benefit less privileged aging populations affected by environmental hazards.
Funds Requested	$1,450,876
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	85
Median	85
Standard Deviation	3
Highest	90
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• The lack of therapies to treat patients with idiopathic pulmonary fibrosis makes this a significant medical need. • IPF is a serious disease and there is no cure at present - If successful, this project could result in the identification of an impactful drug candidate for IPF. • Developing treatments for idiopathic pulmonary fibrosis (IPF) is an urgent and unmet medical need. • Senescence of stem or progenitor cells, such as the lung epithelial stem cells, is thought to be critical in understanding IPF pathogenesis. Thus, the targeting of such cells by the drugs developed in this proposal meets the criteria of being a stem cell technology. • Accumulation of senescent cells has been associated with IPF, and studies in animal models have demonstrated that using therapies that decrease the number of senescent cells can reduce fibrosis. The proposal takes advantage of the concept that in senescent cells, there is an increase in lysosomal activity to activate pro-drugs inside the cell. • The team is outstanding and well-qualified to complete the proposed experiments.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The need for targeted elimination of senescent cells in a manner that has low toxicity for normal cells is very clear. Existing approaches do not demonstrate the level of selectivity that would be preferred, and thus their translational value is limited due to systemic toxicity. This project offers a potentially exciting alternative. • The use of pro-drugs to specifically target senescent cells is novel. There is mild concern about the specificity of the proposed therapy for stem cells. • The project starts strong with an exciting idea but unfortunately the experimental design does not follow. The progression of studies do not show any urgency to obtain results.
No: 2	• The stem/progenitor aspects of the proposal are not well supported by preliminary data. • It is unclear whether there is actually regeneration in this proposal.
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• Proposed experiments to address the specific aims are logical and well designed. • The path to translation is well thought out, and the medical need is such that there is a very high possibility of rapid movement to the clinic. • The preliminary data are very exciting. The prodrugs show selective senolytic activity in senescent lung cell lines in vitro. They also show enhanced activity in targeting IPF lung-derived senescent fibroblasts from a few IPF patients and a healthy donor. • The pharmacokinetic studies show favorable profiles for lung delivery, and the drug appears to be well tolerated. • What is missing is in vivo proof of principle in a murine model of IPF that shows repair (i.e., demonstration of pro-reparative effects). Does this treatment slow the rate of progression or does it actually allow recovery? These are very important experiments to include.
No: 2	• The regenerative response is not directly examined by the proposed studies. • The project is open-ended since there are too many variables that need to work for the project to be successful. • The application proposes several milestones that require optimization. • The set up of in vitro systems and new mouse models are not necessarily trivial. The rationale for the need to perform these is not well articulated (and it will take most of year 1). • Dependent aims - Why not focus on relevant in vivo studies?
GWG Votes	**Is the project feasible?**
Yes: 13	• Preliminary data demonstrated expertise in vitro and in vivo models and also in the development of pro-drugs to be used in the different models. • All of the key necessary components exist, and the team is outstanding. • This is an excellent team.
No: 1	• I have serious doubts about the establishment of an in vitro system for senescent cells (in particular of primary samples). This is Milestone 1. What happens next if this does not work?

	• Preliminary data on prodrug is provided (and probably compelling) but images are small and low quality. For example, it is hard to understand what is the message behind the heatmaps shown in Figure 2. • Application needs focus.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• This is appropriately addressed. • IPF has no strong demographic profile, but is higher in smokers. There are 50,000 new cases/year in the US. • Although there is no text that directly addresses DEI concerns, successful treatments would be helpful to people from all communities.
No: 0	• There is no discussion in the proposal about how the team will promote or support diversity and inclusion.

Application #	DISC2-14166
Title (as written by the applicant)	Reversal of dysregulated myelopoiesis in breast cancers and cancer stem cells to boost antitumor immunotherapy
Research Objective (as written by the applicant)	A new antiestrogen drug will be developed to stop breast cancer (BC) by direct effects on BC cells including stem cells and indirect action on specific procancer immune cells that surround the cancer.
Impact (as written by the applicant)	Substantial numbers of patients with localized breast cancer (BC) and essentially all patients with advanced BC become resistant to current endocrine therapies. New therapeutic strategies are needed.
Major Proposed Activities (as written by the applicant)	• Synthesize sufficient amounts of a purified antiestrogen drug candidate in the chemistry laboratory for use in preclinical work to assess antitumor efficacy and safety in the oncology laboratory. • Validate antiestrogen properties of a lead SERD candidate, including specific estrogen receptor (ER) binding, elimination of tumor ER and blockade of breast cancer progression in preclinical models. • Assess effect of estrogens on hematopoietic stem/progenitor cells and expansion of myeloid-derived suppressor cells in bone marrow samples from breast cancer patients and antagonist actions of SERDs. • Assess antitumor action of SERDs alone and with immunotherapy in diverse breast cancers in preclinical models, with transcriptome sequencing of tumors and assays of the immune tumor microenvironment. • Characterize myeloid-derived suppressor cell markers and estrogen receptor expression in retrospectively collected, de-identified breast cancer specimens including ER-positive breast cancer and TNBCs.
Statement of Benefit to California (as written by the applicant)	This project aims to assess biologic factors that impact racial/ethnic disparities in breast cancer (BC) mortality and address unmet medical needs of diverse California populations, including underserved communities. African American women are almost twice as likely to die from BC as compared to European Americans and are often diagnosed with aggressive TNBCs. The proposed work may allow better understanding of racial/ethnic differences in BCs and lead to more effective therapies to benefit Californians.
Funds Requested	$2,327,680
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	85
Median	85
Standard Deviation	4
Highest	90
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• Yes - this research may move JD128 (the proposed product) forward. The product is an estrogen analog drug that has an MOA of being a selective estrogen receptor down regulator (SERD) for breast cancer (BC). This drug may suppress the action of estrogen-responsive myeloid-derived suppressor cells (SERDS) that existing in the tumor microenvironment (TE) and drive drug resistance and metastasis. • JD128 may be useful in combination with immunotherapy. • JD128 might allow for treatment of BC patients with drug resistant and malignant tumors. In addition, ER-minus tumors might respond as MDSCs still express estrogen receptor and are targeted by JD128. • While this is not technically a stem cell technology nor a gene therapy approach, JD128 may affect hematopoiesis that leads to tumor promoting MDSCs. Therefore, the connection to stem cells is the potential effect of this drug on hematopoietic (myeloid lineage especially) stem cells. • Few drugs work toward macro or microenvironmental effects in TNBCs for humans. The candidate lead, JD128 provides an excellent starting point, and could replace poorly bioavailable Fulvestrant. • The candidate profile does not clearly indicate the HSC or B-CSC based targeting of JD128 candidate. • Proposed pre-IND work would provide evolved JD128 analogs for refined delivery and clinical testing e.g., AMDE, SAR workup etc. to progress to ER resistant patients or in combined immunotherapy. • Preliminary data suggests that JD128 has increased potency compared to Fulvestrant, which lacks sustained bioavailability. • MDSC activation and expansion within the tumor microenvironment may be related to estrogen signaling (preliminary data supports this). • Novel mechanism of estrogen-driven tumor progression.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The idea is that MDSCs exist in the TME that drive cancer progression and metastasis. Further, these MDSCs retain estrogen receptor expression, even if the bulk tumor has become ER negative or estrogen independent. Targeting MDSCs with this drug may lead to therapeutic outcomes, and this drug may pair well with immunotherapy approaches. • The connection to CIRM's mission here is that myelopoeisis can be targeted in vivo. So, the connection to stem cell research is a drug that impacts the behavior (differentiation) of adult stem cells, which can affect the TME. • Initial work with PDX models using primary BCSCs or ER resistant cells would have enhanced the candidate role in future therapies, along with comparison to Fulvestrant. Scientific basis to use 3GF NSG mice is unclear vs. other NOD/SCID immune deficient mice given human B-CSCs have been defined in NOD/SCID and NSGs. • Unclear how this endocrine therapy would be combined with immunotherapy in a pre-clinical testing setting, with or without use of ER resistant BC cells. • The need for scRNA-seq and use of BC- CSCs in unclear. Organoid implants are not CSC assays. • Fig 2 provides interesting data that JD128 has a strong effect at targeting sorted MDSCs based on phenotypic screening and STAT phosphorylation. A cellular control for non-MDSCs is required to show specificity as well as ER expression. • Fig4F provide the only ER data for MDSCs in the mouse by mean signal intensity. A relevant comparison to other receptors, commonly and standardly know would provide context. Down regulation or conformation change in response to SERD is not shown here using CyTOF.

	• Fig4E indicates significant differences, assumed to be from control, of the percentage of CD45+ cells assumed to be MDSCs. Differences shown seem to be statistically relevant but raises concerns of biological significance e.g., what reduction in MDSC or whatever these are, translates to differences in tumors growth or cellular status of BCSCs? • Use of JD128 is independent of stem cell biology from either HSCs or if targeting occurs on B-CSCs. • MDSCs (and lymphocytes) express estrogen receptor transcripts and presumably protein and inhibition of estrogen signaling within MDSCs may reduce immune suppression within the tumor microenvironment. This approach may enhance the activity of CD8 TILs through reduced suppression from MDSCs.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• At the completion of this grant, JD128 would be ready for translation and possibly clinical trials. • The addition of research to assess effects on myeloid hematopoiesis using samples from deidentified BC patients is a good addition to this grant, and now more effectively assesses the action of JD128 on human hematopoiesis. • Detailed but the use of organoids, vs. cell lines vs ultimate use of PDX models is unclear. The advancement of each and how one informs the others has not been delineated or utilized. The need or use of ex vivo work or scRNA-seq analysis is unclear as it relates to application or biology • Collection of collaborators, and expertise has been gathered. • The HSC and CSC assays are limited to phenotype and non-quantitative function, without addressing the property of CSCs or HSCs that makes them unique, e.g., self-renewal. • Unclear in presentation of pitfalls/alternative approaches. • Suitable project plan but unfocussed given the movement toward clinical application. A clearer set of experiments that enforce and streamline requirements for IND development would benefit the proposal. • Inclusion of PDX models in humanized mice (NSG-SGM3) and plans to evaluate MDSCs and CD8 TILs through cyTOF. • Examination of biomarkers of ER and MDSCs in BC TMAs is a bit distant from the rest of the proposal.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 12	• The organization and logic of the milestones is excellent as is the research team. • Yes, this is feasible, though unlikely within proposed timeline given the broader set of experiments in this revision. • This is a well-suited team. Collaborating with a group well-versed in IND submission would streamline the project. • Resources are in place given the scope and breadth of experiments proposed. The budget is suitable. • Feasibility is strongly displayed within the preliminary data.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12	• This grant seeks to study JD128 (a selective estrogen receptor inhibitor) for use in breast cancer therapy. Since ethnic minorities of several classifications have poor outcomes, this approach should be helpful for these groups. • This group proposes to utilize a patient advocate that will communicate findings to lay public and members of diverse groups. • The proposed product may have activity in TNBC despite lack of estrogen receptor expression by tumor cells since MDSCs continue to express receptor. Clinical efficacy from this approach would benefit African American patients highly impacted by TNBC and an underserved population.
No: 0	*none*

Application #	DISC2-14047
Title (as written by the applicant)	A Novel Therapy for Sanfilippo B
Research Objective (as written by the applicant)	To develop a stem cell therapy for Sanfilippo B syndrome.
Impact (as written by the applicant)	There is no treatment for Sanfilippo syndrome, and other therapeutic approaches have failed in clinics. This proposal will develop a stem cell based therapy for Sanfilippo syndrome.
Major Proposed Activities (as written by the applicant)	• Generation of universal donor Embryonic Stem Cells (ESC H1) using state of the art genome editing technique. • Increase the level of the missing enzyme in universal donor ESC (H1) using state of the art genome editing technique. • Differentiate ESC into brain stem cells in vitro capable of secreting NAGLU (NAGLU-NPC). • Transplantation of NAGLU-NPC to evaluate if the cells can survive in the mouse brain and can repair brain tissue provide NAGLU enzyme. • Transplantation of NAGLU-NPC to evaluate if cells differentiate into functional neuron and integrate in the neuronal networks. • Transplantation of NAGLU-NPC to evaluate if cells can repair brain tissue and correct abnormal mouse behavior associated with Sanfilippo syndrome.
Statement of Benefit to California (as written by the applicant)	This application will help develop a stem cell therapy for Sanfilippo B disorder, a pediatric genetic disorder that currently has no treatment. If successful, this approach could be extended to several other lysosomal storage diseases, bringing a therapy for these catastrophic disorders.
Funds Requested	$2,297,884
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 84

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	84
Median	84
Standard Deviation	3
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	8

* See Minority Report below

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to

indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Important but rare disease to target. • If successful, this project may lead to the development of a novel treatment for Sanfilippo B, and potentially other lysosomal storage disorders, for which, there is no effective treatment at present. • In this project, the applicants propose to use modified human neural progenitor cells as a therapeutic agent for Sanfilippo B syndrome and therefore, if successful, will impact an unmet medical need as this is a rare disorder for which there are currently no successful treatments.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• Scientific rationale is clear and sound. Presented preliminary data are very good and support the proposal. • The proposal builds from encouraging published mouse-to-mouse transplantation results. • Still not sure about the basis for the statement ES cells are safer than iPS cells
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• This is a revised and much improved proposal with a much clearer and better experimental design. • The revised application provides now thoughtful options for progression of proposed cell therapy to translation. • This is a well-constructed project; however, I am still concerned about the animal behavior experiments. The applicants now recognized the need for these experiments to be performed by specialists, which is commendable, but there are still some concerns. For example, the order of experiments is not clear, there are also a multitude of tests - some of which are actually not needed. • Previous concerns about the behavioral analyses are not adequately addressed. • Functional assessment is very difficult and may not lead to read outs required. • The math does not fit. For example, the applicants state they will use 32 animals/group and then finish by saying that 192 animals will be used across 12 groups. This is very unclear and should be clarified as this project relies on preclinical data.
No: 2	*none*
GWG Votes	**Is the project feasible?**
Yes: 12	• The project is feasible based on the expertise of PI and co-investigators, as well as proposed timeline. • The project is feasible, but only with a dedicated team of specialists.
No: 2	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The project plan and design adequately addresses DEI. • Seems appropriate.
No: 0	*none*

MINORITY REPORT

If an application receives a Final Score of 1-84 and 35% or more of the scientific members of the GWG recommend an application for funding, then a minority report is provided that summarizes the perspective of those scientific members.

Reviewers that supported the funding of this resubmission application thought that the applicant provided good preliminary data for developing a stem cell based therapy for Sanfilippo B. They thought that the applicants addressed most of the prior concerns from the prior review, including adding additional proof of concept data and bringing on a collaborator to assess function. Overall, the minority reviewers thought the overall approach had risks but was worth trying and had a reasonable chance of success in a difficult and rare pediatric disease.

Application #	DISC2-14097
Title (as written by the applicant)	In Utero Treatment of Duchenne Muscular Dystrophy with Non-viral Gene Editing
Research Objective (as written by the applicant)	To develop a lipid nanoparticle/mRNA complex that can safely and efficiently edit muscle stem cells in utero, correct the dystrophin mutation, and develop a treatment for Duchenne muscular dystrophy
Impact (as written by the applicant)	If successful, we will have developed an effective and low-cost treatment for Duchenne muscular dystrophy (DMD) and a robust method to safely and efficiently edit muscle stem cells in utero
Major Proposed Activities (as written by the applicant)	• Develop lipid nanoparticle (LNP) formulations containing either M6P-cholesterol or folate-PEG-DSPE • Develop LNP formulations that can efficiently deliver mRNA to muscle stem cells (MuSCs) and muscle fibers in Ai9 mice via in utero injection • Correction of the point mutation in the D2-mdx mouse MuSCs by LNP/mRNA complexes in vitro • Correct the mutation in D2-mdx mice after in utero injection of base editor mRNA/LNP complexes • Evaluate the editing efficiency and DMD phenotypic correction in D2-mdx mice after in utero base editing • Correct the point mutation in human DMD patient cells with ABE(NRCH)-LNPs
Statement of Benefit to California (as written by the applicant)	Duchenne muscular dystrophy is a long-term degenerative disorder that involves extortionate medical expenses, amounting to an annual average cost of over $50,000 per patient. Since our proposed treatment consists of a low-cost, single injection, we predict significant improvements in health care costs and medical treatment plans with the potential to be accessible to low-income patients and patients in underdeveloped and underserved medical communities.
Funds Requested	$2,035,544
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 83

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	83
Median	83
Standard Deviation	3
Highest	87
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	8

* See Minority Report below

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Duchenne muscular dystrophy is one of the most common inherited muscle diseases. Impairment is due not only to the loss of muscle tissue but also the remodeling with fatty and fibrous tissue that replaces it. Early intervention before this occurs would limit damage and not only improve survival but also maintain good quality of life. • This is a terrible disease and any therapy particularly one that starts this early in the disease would be impactful. • There is potential for the development of a new treatment for DMD. • Interesting approach with potential larger significance. • The experimental design does not focus on DMD until year two, which diminishes the significance of the proposal. • Safety is a major concern and application does not discuss this aspect much. • Yes, if safety can be established. • Yes, but if the approach using this mutation is not working, switching to other mutations will likely limit the patient pool that would benefit.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• There is scientific rationale for targeting DMD in utero - Encouraging preliminary results are provided for the delivery aspect. • Plans to focus on in utero treatment are reasonable and preliminary data do support the ability to successfully target selected tissues and demonstrate that at least some of these are positive for markers of stemness. • Early intervention is logical. • Yes, there are several safety concerns, but once efficacy is sorted out, which is likely to happen in this proposal those concerns can be addressed. • Safety issues are not adequately considered. • Certain statements could suggest a lack of understanding of some less obvious aspects of DMD and of the patient population affected by this disease.
No: 1	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 10	• The project uses a model with a phenotype that is similar to what is seen in people with DMD, as well as reliably sourced cells from affected patients to assess efficacy. • Reasonable alternatives if the initial proposal should prove unsuccessful are made for Aim 1. • The suggested change in animal model should correction fail is baffling, particularly as the investigation is of the therapy and not the model. The therapy as proposed is already limited to a minority subset of the affected population, and a failure due to the model rather than the therapy itself suggests that the eligible population could be even smaller and that the therapy may therefore be of dubious use.
No: 4	• The reporter model and safety aspects of the work need to be strengthened. • There is no urgency to develop a treatment for DMD. For the first 12 months of the project, no experiment is designed to target DMD. • The applicant refers to relevant human DMD cells in Aim 3, but provides no information on what materials will be used and how (the PI only refers to a letter of support): feasibility is a serious concern. • Aim 3 includes a brief description and preliminary data (Figure 6C) that suggest that fibroblasts will be used, which are not relevant for DMD as fibroblast cells do not express dystrophin.
GWG Votes	**Is the project feasible?**

Yes: 11	• The budget and timeline seem reasonable, and the necessary resources seem to be readily available. • Translation to humans is challenging and needs to be addressed.
No: 3	• A focused study on efficacy and safety needs to be provided.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• The proposed project considers the diversity of the patient population, aims to center clinical steps in underserved communities, and outlines available resources, including outreach, to improve access and awareness. • The applicants seem very mindful of potential issues with delivery, access and cost.
No: 1	• Limited description.

MINORITY REPORT

If an application receives a Final Score of 1-84 and 35% or more of the scientific members of the GWG recommend an application for funding, then a minority report is provided that summarizes the perspective of those scientific members.

Minority reviewers thought that this proposal for a treatment for DMD was worth funding because the significance of correcting the gene as early as possible holds a lot of potential before the disease has a chance to affect patients. Reviewers thought the modeled phenotype in animals was good, and that the results were directly equivalent to what is likely to be seen in patients. Minority reviewers appreciated the DEI component of the application, which was considered very carefully and is a strength of the application.

Minority reviewers did indicate the application had some weaknesses. One minority reviewer was unsure whether the proposed route of delivery is the best route in terms of translation, but something that could be considered later on. Another minority reviewer didn't mind the delivery route and thought the in vivo delivery data was convincing. Other concerns expressed by the minority reviewers included the potentially small target population if the animal model doesn't work in aim 2, and they would like more thought given to the long term safety of the product.

Overall, the minority reviewers thought this resubmission reasonably addressed prior concerns, had strong technical and preliminary data, and recommended the application for funding.

Application #	DISC2-14089
Title (as written by the applicant)	Chemically engineered photoreceptors for vision restoration in retinal degeneration associated blindness
Research Objective (as written by the applicant)	This proposal will develop a chemically engineered cell-based therapy that can restore vision in retinal degeneration associated blindness such as age-related macular degeneration.
Impact (as written by the applicant)	Chemically induced method will overcome inefficient differentiation techniques, potential insertional mutagenesis and time intensive quality assessment associated with pluripotent stem cells.
Major Proposed Activities (as written by the applicant)	• Human skin fibroblasts will be chemically induced to candidate photoreceptor cells. Chemically induced cells will be isolated and assessed for gene expression signature by single cell RNA sequencing. • Skin fibroblasts derived isolated chemically induced photoreceptor cells will be assessed for chromatin signature by single cell chromatin sequencing methods. • Function of chemically induced photoreceptor cells will be assessed by microscopic evaluation of calcium influx/efflux upon light stimulation and chemical treatments. • Isolated chemically induced photoreceptor cells will be injected into the retina of the rodent eyes to examine their potential for integration and survival inside the retina. • Chemically induced photoreceptors will be injected into the eyes of blind mice and rats followed by assessment of vision restoration by retinal electrophysiological & visual behavior tests. • Mechanism of vision restoration after chemically induced photoreceptor injection into reporter mice models will be assessed by microscopic analysis of transplanted retinal tissues.
Statement of Benefit to California (as written by the applicant)	Photoreceptor-loss induced retinal degenerations affects diverse human racial and ethnic groups from all over the world including California. The proposed research will include fibroblast from diverse human ethnic groups for the generation of candidate photoreceptor cells. Successful generation of candidate cells followed by vision restoration in preclinical animal models would pave the way for the application of this approach in a diverse human population including citizens of California.
Funds Requested	$1,845,093
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 83

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	80
Median	83
Standard Deviation	7
Highest	90
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	7*
(1-84): Not recommended for funding	7

* See Minority Report below

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• Avoiding hiPSC biomanufacturing to make photoreceptors would be a large impact in the field. • Yes, the technology can become a breakthrough in how we treat retinopathies. • To produce cells with this method would accelerate both allogeneic and autologous cell based therapy. • The project is especially valuable since it considers reprograming to photoreceptors in GMP conditions.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• Yes. Good arguments of the benefits of direct conversion over stem cells is advantageous if successfully developed. • Yes, key preliminary data to support feasibility is supplied. • The project is uniquely enabling of stem cell approaches via direct reprogramming. • The efficiency of the process may be too low to support the proposed activities. • The rationale is sound in general, but the application needs more clarity in the details.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 10	• The project is well described and well planned. The experiments are sound and the methodology is state-of-the art. • The potential pitfalls identified and alternative approaches are partially presented. • Meeting the milestones on time may be difficult.
No: 3	• Far too much work is planned and the project is understaffed.
GWG Votes	**Is the project feasible?**
Yes: 10	• It is an ambitious project but feasible. Some components are high-risk/high-gain. • A very large amount of work is proposed, which is unlikely to be completed in the time allocated. • Animal experiments, as designed, are too broad-ranging. • The feasibility of the project is not clear.
No: 3	• The project needs to be streamlined. • Uncertain - high risk.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• Yes, both in terms of reasoning and also in the use of donor cells from diverse human ethnic groups. • Diverse ethnic sources of fibroblasts. • No concerns.
No: 0	*none*

MINORITY REPORT

If an application receives a Final Score of 1-84 and 35% or more of the scientific members of the GWG recommend an application for funding, then a minority report is provided that summarizes the perspective of those scientific members.

Reviewers who voted in favor of funding this proposal for manufacturing photoreceptors agreed that there was overall potential risk for the project not succeeding, but on balance, thought that CIRM should invest in this high-risk, high-reward project. Minority reviewers thought that the applicants have preliminary data that are pointing to success, and although proof of concept data in vivo would give more confidence in the project, the proposed studies are logical. Minority reviewers thought the approach could make significant impact on a safer product for patients, if successful. Though the project proposes a large amount of work, even if progress is made on only part of the proposed milestones, it would add value to the field.

Application #	DISC2-14033
Title (as written by the applicant)	Development of next-generation human cerebellar organoids to model hereditary cerebellar ataxias
Research Objective (as written by the applicant)	Our objective is to develop a 3D human cerebellar organoid screen platform, which includes microglia and a mutation within human iPSC lines with varying race, ethnicity, and sex backgrounds.
Impact (as written by the applicant)	Next-generation cerebellar organoids will address a bottleneck in the field by providing reliable and consistent recapitulation of cerebellar dysfunction and degeneration in an all human system
Major Proposed Activities (as written by the applicant)	• Generation of long-term culture of organoids that reproducibly form cell diversity of the human cerebellum • Integration of iPSC-derived microglia into cerebellar organoids • Proof-of-concept for reliable and consistent recapitulation of cerebellar neuronal dysfunction and degeneration in human cerebellar organoids derived from spinocerebellar ataxia 36 patient iPSCs
Statement of Benefit to California (as written by the applicant)	In addition to improving the understanding and screening of drugs for hereditary cerebellar ataxias, our model will be a valuable resource for the broader biomedical community interested in modeling dysfunctions in other types of human brain disorders with cerebellar involvement including complex mental disorders and cerebellar cancers, by delivering the first high-throughput platform for effective drug screening in distinct types of human cerebellar cells.
Funds Requested	$834,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 82

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	81
Median	82
Standard Deviation	3
Highest	86
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• There is a great need for cerebellar models and the project has potential. • A screening in vitro tool to combat cerebellar ataxias is highly relevant and could lead to novel therapeutics, however, the applicant has not demonstrated that the organoid models shows "reproducible disease/injury modifying activity", which is one of the main criteria for a DISC2 program. • Assuming that patient-derived organoids show a defect that can be "normalized" the tool that is being developed is highly relevant.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• Organoid modelling is valid. • The application remains in the proof of concept stage. It has not been demonstrated that the organoids will have a relevant pathology that would make them suitable for further development. • The applicant describes the effort as "catalytic step needed to realize our longer-term vision for functional screening." • There is no plan discussed of how to design a drug screen. A pre-condition for a drug screen would be that each patient derived organoid population (with different mutations) show a unifying pathology that could be rescued. What is the rationale for expecting such an outcome? Is this a likely expectation? What if each patient organoid populations show a different array of defects?
No: 2	• Would like to see pathology in the organoid.
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• Good preliminary data. • Without proof of concept that mutant organoids show a phenotype, the proposal remains highly speculative. Previous concerns as to whether the system is suitable to model that pathology has not been addressed. • Minimal sections that do not address what the applicant will do if the mutant organoids lack a phenotype using the endpoints that are discussed. • Milestone 3 will not be addressed until month 8. The applicant need sto provide some insight that the organoids will recapitulate any pathology that would allow for a therapeutic drug screening.
No: 2	*none*
GWG Votes	**Is the project feasible?**
Yes: 12	• The applicants show convincingly that they can generate cerebellar organoids in a reproducible manner. Genetic profile is in line with human fetal brain data. • The relevance of microglia in the cerebellar organoids remains unclear (preliminary data are from cortical organoids).
No: 2	• Need to show pathology, especially functional pathology in model organoids.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• They are aware of using cells from different ethnic groups. • Well-addressed.
No: 0	*none*

Application #	DISC2-14126
Title (as written by the applicant)	Functional chemical and genomic screens in human iPSC-derived cardiomyocytes to identify new cardioprotective drugs for heart transplantation
Research Objective (as written by the applicant)	We aim to identify cardioprotective drugs to improve heart preservation and transplantation.
Impact (as written by the applicant)	Many donor organs are not transplanted due to inefficient preservation conditions. Our study may help prolong cold storage and increase the number of organs to be transplanted.
Major Proposed Activities (as written by the applicant)	• Chemical screen for novel cardioprotective compounds using human iPSC-derived cardiomyocytes • Validation of top hits of compounds using chemicals from independent sources • CRISPRi screen for cardioprotective genetic manipulations in human iPSC-derived cardiomyocytes • Validate CRISPRi screen hits using independent guide RNA sequences • Test any chemical inhibitors of the gene products after CRISPRi validation • Examine the effects of top chemical candidates in mouse cells in vitro and organ transplantation in vivo
Statement of Benefit to California (as written by the applicant)	Over 23,000 Californians are currently waiting for organ transplants. This proposed research will extend organ extracorporeal lifetime, expand the number of recipients, and save the lives of many patients affected by end-stage organ failures in California and beyond.
Funds Requested	$813,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 80

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	80
Median	80
Standard Deviation	5
Highest	85
Lowest	69
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	9

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• In this project, iPSC-CMs enable small molecule as well as CRISPRi screen for targets, to be used to enhance cardiomyocyte survival during cold storage. • Development of a new technology to enhance survival of cardiomyocytes with cold storage is important. This proposal plans to use both chemical screening and genetic screening to identify new targets to achieve this goal. • There is a shortage of viable heart organs to meet the urgent need for heart transplants. • This addresses the unmet need for longer preservation times to increase the number of hearts transplanted. • The applicant provides a thoughtful progression from the known twelve small molecule compounds to more innovative, higher risk strategies involving CRISPR, to dose response curves, to tests in vivo. • This line of research for functional chemical and genomic screening in human iPSC cardiomyocytes, to identify drugs with cardioprotective properties, is likely to inform future research, with the ultimate goal of improving heart organ viability and successful transplantation. • The chemical screening may result in a candidate to protect cold storage heart organ. The chemical screening may increase the likelihood of developing a better method for cold storage of heart organ. • The genetic screening may not result in any positive results. The applicant did not use the state-of-the-art dCas9 repression system. Furthermore, the applicant underestimates the difficulty of performing genome wide screening in cardiomyocytes. • For the genetic screening: Even if the applicant identifies a target, how will they translate and deliver the dCas9 repression into the majority of cells in a heart?
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The preliminary data are not compelling for the genetic screening part (Aim 2). Transduction of human cardiomyocytes is difficult, not to mention genome wide screening in human cardiomyocytes. The applicant did not show any preliminary data that they can do this. • The applicant did not show any data to establish that they can produce a dCas9 screening library without losing representation. • The chemical screen of FDA-approved and other compounds is a rational approach. • The rationale is grounded in the use of iPSC-CMS, in which the PI is an expert. Use of these cells provides the basis for high throughput screening. • The PI has established the screening assay and has already identified twelve small molecules. Moving from small molecules to genes is ambitious but has the potential to uncover new targets. • Strengths: Expertise in iPSC-CMs, established screening assay, iPSCs expressing dCas9-KRAB established, core facility to provide heart transplantation. • High risk: Efficiency of 30% for infection is not yet established in the lab, but the team includes consultants with relevant expertise. • Screening for new targets that can protect cold storage heart organ has a sound rationale.
No: 1	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 10	• It is reasonable to test iPSC-CMs with both chemical and genetic screening. Aim 1. Chemical screen for drugs that enhance cardiomyocyte hypothermia resistance and prolong cold storage for heart transplant. Aim 2. Genetic screen for new regulators of cardiomyocyte hypothermia resistance to prolong cold storage for heart transplant. • This is a good proposal, but not exceptional. • The alternative approaches are poorly described. • More potential pitfalls should be discussed, such as - what if the applicant cannot produce the genome wide library without losing representation? What if the applicant cannot transduce iPSC-CMs with high enough efficiency? What if no gene targets are uncovered from the screening? • The maturity of cells is not addressed.

	• The project progresses logically, but it's an extremely ambitious program. • The pitfall of confounding influence of ischemia reperfusion is addressed. The notion that a single compound or gene could dramatically improve survival to 90% is somewhat reductionist because it is highly likely that a multitude of proteins/genes are at play. • iPSC-CM vs human primary CM: Do these behave the same way? Primary cardiomyocytes as a control in the system could be valuable for evaluating relevance. • This is a very ambitious program, with a lot of work proposed for 24 months.
No: 3	• Concerns about Aim 2, in particular not using the state-of-the-art approach.
GWG Votes	**Is the project feasible?**
Yes: 8	• The applicant may face many unpredictable difficulties during their project. It is likely that they cannot finish this project within the proposed timeline. • The team PI is not an expert in genome wide CRISPR screening. • There are two aims with sub aims, and six milestones that are likely to be achieved, especially given the resources and expert consultants included. • PI and other team members, including consultants and postdocs, are very well suited to carry out the project. • The applicant has made a good start on the first milestones. Even if CRISPR does not help identify potential targets, they still have twelve targets they have identified and can investigate more thoroughly. • >60% viability seems low as a target; why not shoot for >90%? Translation to the full organ is going to lose some viability - they may have set the bar too low. • Exceptional PI with significant and successful track record. Involvement of consultants to aid in CRISPR technologies will be important to the success of this project. Involvement of the microsurgery core is critical for feasibility tests of this project. • Yes, the team has access to all the necessary resources to conduct the proposed activities. • Yes, the budget is appropriate for research proposed.
No: 5	• Use of an older Cas9 system might suggest that the applicant is not very familiar with this approach, raising concerns about feasibility. • No preliminary data.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• The applicant will use human iPSC lines of diverse ethnic origins and test if identified chemical compounds can extend the cold storage viability of mature cardiomyocytes derived from these cell lines. • This team has a strong record of DEI. • This is an important strength of the study. For example, they will include cell lines for different ethnicity and race. They will also study both female and male cells and conduct analyses to test for differences. • The project involves testing iPSC-CM lines isolated from a Hispanic female, a Japanese male, and an African American male to account for influence of race, ethnicity, sex. • Advancements in preserving organs for transplant could improve underserved populations' access to transplant. • The applicant is active in the recruitment of under-represented minority (URM) students and plans to involve students at multiple levels in this project. There is a track record of this type of DEI-oriented activity in the lab.
No: 0	*none*

Application #	DISC2-14167
Title (as written by the applicant)	Engineered Human Stem Cell-Derived Pancreatic Islets Encapsulated in a Thin Film Device for Patients with Type 1 Diabetes
Research Objective (as written by the applicant)	We propose engineered human stem cell-derived islets encapsulated in a thin film device to restore blood sugar levels in diabetes, without the need for insulin injections or systemic immunosuppression.
Impact (as written by the applicant)	Our work would overcome the three major bottlenecks for cell replacement for diabetes: dearth of supply, poor engraftment and function of beta cells, and requirement for life-long immunosuppression.
Major Proposed Activities (as written by the applicant)	• Identify, obtain, achieve scale-up, and perform quality control analysis for at least 6 human pluripotent stem cell lines that meet donor eligibility criteria and are consented for commercial use • Identify at least one donor eligible, commercially consented human pluripotent stem cell (hPSC) line that yields engineered islets that display glucose-stimulated insulin secretion in vitro • Determine function of donor-consented, engineered islets in vivo in diabetic immunodeficient mice • Determine functionality and immune protection of encapsulated engineered islets in vivo in diabetic immune competent mice
Statement of Benefit to California (as written by the applicant)	Type I Diabetes (T1D) is a significant burden in California, especially for children; according to estimates provided by the California Diabetes Program, ~2.3 out of every 1,000 children between the ages of 5-19 in California had diagnosed diabetes in 2008, with 83% having T1D. Research proposed here would represent a significant step towards the holy grail of T1D treatment: a therapy for patients without the need for the administration of insulin, frequent blood testing, or immunosuppression
Funds Requested	$2,759,817
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 80

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	79
Median	80
Standard Deviation	3
Highest	82
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Transplantation of insulin-producing pancreatic islets derived from pluripotent stem cells (PSCs) is a promising strategy for treatment of type 1 diabetes (T1D), which constitutes an unmet medical need. • The proposed technology aims to overcome two significant obstacles that currently hinder clinical translation of PSC-derived islets: insufficient functional beta-cell maturation and immune rejection of transplanted allogeneic beta-cells. If the project is successful, the candidate will help to overcome these obstacles. • Engineered islet cells combined with two other cell types are encapsulated in a polymer-based device and placed under the skin to produce insulin in response to increases in blood glucose. The device needs to be vascularized and then evade immune destruction in order to work. If successful, this would have a large impact on T1D disease treatment and quality of life. • Cell therapy for diabetes is a critical need. The proposed project, albeit with caveats, is on the right track. • The applicant has considered this progression from successful candidate discovery to translation but has chosen to focus on future critical issues before addressing the pivotal proof of concept. • Proof of concept is missing.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The project is based on a sound scientific rationale that the incorporation of supporting niche cells into engineered islets will augment survival and maturation of stem cell-derived beta-like cells. The hypothesis that immunoprotection, vascularization, survival, and alleviation of fibrosis in engineered allogeneic islets in vivo could be accomplished using encapsulation is also scientifically sound. • Concerns remain as to whether the engineered beta cells will actually reverse diabetes after transplantation. The applicant acknowledges this and suggests it is a dosing issue, but no additional data are provided to support this. • Concerns remain as to whether the device truly provides immune protection in the human-cells-into-mice study. Again, the applicant acknowledges this, and has shown a robust blockage of key antibodies and cytokines, as well as shed antigen implicated in the xenogeneic response. I still would like to see better proof. • Many aspects of this proposal are attractive: the addition of endothelial cells and pericytes (niche cells), the integration of islet engineering with device engineering, and the quality of the investigators. The retrievability of a device and the ability to insert through a catheter are among the positives of this approach. The applicants have addressed the previous critiques, although some issues remain. • The preliminary vascularization, immunoisolation, and efficacy results are not yet sufficiently compelling for DISC2 funding. An image of vessels is not as compelling as a detailed assessment of pericyte invested vascular density; are these vessels merely the consequence of a foreign body response? I did not see evidence of no fibrosis, which is required. Showing MIN6 viability in vivo is helpful, but MIN6 is a robust tumor cell. • The device may mitigate the consequences of an allo-response, but is that mitigation enough to get long term insulin production from engineered islets in xeno models (human cells in NOD or B6)? There is certainly some evidence from a variety of assays indicating the nanoporous membrane is a transport barrier. Is that barrier sufficient for immune protection? • The ability to create insulin secreting cells from stem cells is key to the project. • Preliminary results are limited.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**

Yes: 11	• Overall, the project is well planned and designed. With regards to the proposed encapsulation device, the applicants also present promising preliminary data from both in vitro and in vivo studies. • Yes. However, this team of PIs has already been funded by CIRM to carry out testing of what appears to be the same encapsulation device with hPSC-derived islets. There exists significant scientific overlap with these two previously funded awards, which both ended in 2019. Several milestones that overlap with the current application are marked as "not completed by the project end date" in CIRM's report. • Overall, yes. However, addressing donor eligibility questions is misguided at this point of the program. Applicants are aware of the issue. This is a distraction from the pivotal experiments of Aim 2. I suspect this is a misguided but premature attempt to prepare for translation that will only become important if the results here warrant. • Since the research questions center around the product's suitability for controlling normoglycemia in mouse models, why pivot from the HUES8 cell line to something that is more commercially suitable? To me this is a distraction from the pivotal experiments of Aim 2. • The applicants have addressed the previous critique, although some issues remain. Most importantly, the proposed work is novel. • The applicants should move to using iPSC-derived EC (e.g., those of Melero-Martin) as soon as possible. The applicants mention ETV2 engineered HUVEC in their alternative strategies, so they recognize the issue. Their engineered islet idea is good, but use of more sophisticated EC or niche components is an appropriate next step. • The scaling of the device is unclear. The applicants speak of 1,000 human islets in a 2 cm device. Does this mean 2 square cm? It is unclear how a device of that size will be created and minimally invasively inserted. • While I don't expect this issue to be resolved in the next 3 years, the device size issue tempers my enthusiasm for macroencapsulation devices and their ability to transition from mouse to human. • Little detail is provided in Aim 2.3. NOD and B6 models are very different, and this distinction is not made in the text. Cells are human so the models are xeno, not allo. Using antibodies to address immune response is not suitable in the absence of a detailed analysis of the subcutaneous immune response. • In the response to the prior review, the applicant indicates that engineered islets secrete ~5 uU/1000 cells. This is presumably far less than normal human islets, though this is better than initial reports from hPSC-derived beta cells. What is the goal? I note that normoglycemia is not obtained in Fig. 3 (presumably with 1000 engineered islets) but a reduction in BG is seen; the dose variation in Aim 2.2 addresses this question. • The size of the device is not clear; the approach to scaling is unclear. • Some aspects of the device are unclear. What is the "scaffold" inside the device, and how is device filled? What are the islets suspended in to fill the device? What is the small nutrient reservoir in the device and how is that refilled? • The timeline is reasonably aggressive.
No: 3	• The combination of cells within the device appears to help mature the engineered beta cells. However, there appears to be a significant time lag from implantation to maturation. How will patients manage this transition? Will endogenous insulin application effect the devices production of insulin/maturation?
GWG Votes	**Is the project feasible?**
Yes: 12	• Potentially, but, similar milestones from previous grants were not accomplished. What were the barriers encountered? How have circumstances or plans changed? • The size of the device may be limiting depending on the amount of insulin produced per device. Many devices may be needed. • If the device works as well as the applicant hopes, the milestones are appropriate, and the proposed timeline is fine. The redoing of Aim 1 to accommodate commercially suitable cells is premature. • The team is excellent. The PI is a well-trained, excellent stem cell investigator. The collaborator is also experienced and an academic leader in engineering. They bring complementary skills, expertise and technology to the project. They are a key asset to the project. • The applicant appears to have all the resources they need.

	• The budget is fine.
No: 2	• The milestones are logical, but feasibility is questionable based on outcomes from earlier funding by CIRM. • The team is excellent, and appropriately qualified and staffed.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The proposed project, wherever possible, will balance the selection of donor-eligible, commercially consented hPSC lines to reflect the racial and ethnic diversity of the state of California. Given that the proposed device will contain immunoprotected allogeneic cells, it will be race/ethnicity/sex agnostic. • The investigators have been mentoring trainees of diverse backgrounds throughout their careers. I have no concerns here. • This therapy could be a game changer for underserved populations. • This proposal speaks to the challenge of type 1 diabetes in underrepresented groups. • The applicant speaks to their active engagement in DEI initiatives but do not address the perspectives of the patients who will benefit from the proposed product.
No: 0	*none*

Application #	DISC2-14175
Title (as written by the applicant)	A Novel, Injectable, and Biodegradable Thermoresponsive Hydrogel for Improved Engraftment and Efficacy of Cell Therapy for Parkinson's Disease (PD)
Research Objective (as written by the applicant)	The therapeutic candidate is a combination product comprising cells (allogeneic midbrain dopaminergic [DA] neurons derived from the H9 human embryonic stem cells [hESCs]) and thermoresponsive engraftment biomaterial. It is a candidate implantation treatment for Parkinson's disease (PD).
Impact (as written by the applicant)	Survival of dopaminergic cells after they are implantated into the brains of Parkinson's disease (PD) patients remains extremely low (1 to 5%). Treatment benefits are only noticeable starting ten months to two years after transplantation.
Major Proposed Activities (as written by the applicant)	• Synthesize and optimize injectable thermoresponsive functionalized hydrogels • Characterize in vitro dose response and potency of thermoresponsive functionalized hydrogels on dopaminergic (DA) neurons • Assess acute toxicity of thermoresponsive functionalized injectable hydrogels in a mouse model • Evaluate in vivo efficacy of implanted DA neurons with thermoresponsive functionalized hydrogel in a PD rat model • Prepare first drafts of regulatory documentation
Statement of Benefit to California (as written by the applicant)	In California, Parkinson's disease (PD) affects an estimated 60,000 adults, with correlations to individuals exposed to pesticides, such as those involved in CA's large agricultural industry. Cases are expected to increase 50% by 2030, amounting to a projected economic burden of more than $79 billion by 2037 in the U.S. This proposal to develop an effective combination cell plus biomaterial therapy aims to alleviate the significant healthcare burden on Californians caused by PD.
Funds Requested	$1,470,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 80

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	78
Median	80
Standard Deviation	4
Highest	80
Lowest	70
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 11	• New formulations/delivery methods to better achieve dopamine replacement are a major need in Parkinson's disease (PD). • The proposed product, if successful, will deliver human embryonic stem cell (hESC)-derived midbrain dopaminergic (DA) neurons to the substantia nigra, the locus in the brain affected by PD. The applicant's hydrogel may improve the survival of the transplanted DA neurons and/or promote their functional integration with the rest of the patient's brain. If successful, the candidate will impact an unmet clinical need. • Good combination of cells and biomaterials. • Yes, cell therapies for PD are at a rapid stage of development and several clinical trials have been initiated. The proposed hydrogel could increase cell survival after transplantation. • Yes. Increasing DA neuron survival would reduce the number of cells needed for a graft, thus reducing cost. • The applicant has presented thoughtful options for progression from successful candidate discovery to translation, for the most part. The proposal lacks detail on how the proposed product would be integrated among or with current cell therapies. • Innovative delivery system.
No: 1	• While finding improved treatment for PD is needed, the potential impact of the study is unclear. For example, the potential for disabling dyskinesia in treated patients is not adequately addressed in this proposal.
GWG Votes	**Is the rationale sound?**
Yes: 12	• The project seeks to develop a stem cell-based therapy by combining cells and biomaterials. • The hypothesis that hESC-derived DA neurons can serve as an effective therapy for PD has been previously tested in animal models, and thus the project is based on a sound scientific rationale. • Stem cell therapy for PD is at an exciting stage of development and the proposal addresses an outstanding issue in the field relating to cell survival after grafting. • An obstacle for translating stem cell technology to clinic for PD patients has been the low rate of survival of transplanted DA neurons in vivo. • The use of GDNF with A9 cells in a hydrogel is innovative and likely to improve graft survival and striatal innervation. Graft survival/innervation have been limited in prior trials. • GDNF is well known for its supportive function of DA neurons. To combine that with cell delivery has potential to be beneficial for cell survival as well as graft innervation and potentially, function. • The project is supported by preliminary data.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 9	• Hydrogel engineering is the application's major strength. The neuroscience and neurologic aspects of the proposal are not as well developed, nor clearly articulated in the proposal. • The project is generally well-designed, and the experimental groups are sufficiently large. The cell line has been used for similar applications and meets requirements. There is minor lack of clarity for some experiments - for example, how will increased survival and increased function of transplanted DA neurons be distinguished? • The project is well planned and designed to achieve the proposed milestones, including proof-of-concept work. The applicant presents the plan for advancing into translational studies, but the project is still in the discovery stage and is risky. Therefore, it carries an element of uncertainty. • All studies are carried out using H9. The use of other cell lines to show wide applicability would strengthen the proposal. • Focal grafts, rather than diffuse grafts, may alleviate 'off' time but lead to problematic dyskinesias. The design could consider this caveat in behavioral measures. What site of transplantation, how many cells, and how many sites will lead to optimal benefit for the dorsal/posterior putamen?

	• The project takes a stepwise approach with clear milestones. The animal studies are sound, but do not progress beyond the state of the art and do not address pathobiology. Major studies are carried out at a CRO, which is a weakness. • How much dopamine is in the tissue, post-transplantation, and how much can be evoked are important physiologic parameters the CRO should quantify. • The proposal has some deficits in neuroscience knowledge – e.g., some proposed techniques lack sophistication. • Dosing is not adequately addressed. Dosing is important to the issue of dyskinesia, i.e., a potential complication of treatment if the graft survives too well. • The project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission. • The highest risk of failure is from the biomaterial. Contingency plans are provided for this. • The project is of high quality.
No: 3	• This is a confirmatory study. • The project plan does not include detailed assessment of engraftment. • The product innovation is limited.
GWG Votes	**Is the project feasible?**
Yes: 12	• I highly recommend adding a dopamine neurobiologist to the team to optimize the CRO's work and make best use of the animals/tissues to inform subsequent trials in patients. • The applicant has a lot of biomaterials experience. • The milestones are logical, and they are realistic to be achieved within the proposed timeline. • The team is highly qualified with all necessary expertise available. • The project is feasible given the composition of the team. Feasibility is supported by preliminary data. • The project is feasible provided that the design and use of biomaterials is successful. • The team contains experts on biomaterials, stem cells, PD models and clinical translation. • The team is appropriately qualified and staffed, has access to all the necessary resources to conduct the proposed activities and budget is appropriate.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12	• The allogeneic DA neuron/biomaterial product, which will result from this project, will be race/ethnicity agnostic. • The project is adequately designed to account for influence of sex by including both female and male rats in the in vivo efficacy studies. • The sexes are to be considered equally in the experimentation. • PD affects men and women of all ethnicities. Animal studies use male and female rats. • They have established collaborations with patient organizations.
No: 0	none

Application #	DISC2-14043
Title (as written by the applicant)	Neuroprotective secretome of retinal progenitor cells for ameliorating vision loss
Research Objective (as written by the applicant)	Derive retinal tissue, retinal progenitors from human pluripotent stem cells, graft into the vitreous of rats with retinal degeneration, save vision, determine the mechanism, develop a drug prototype.
Impact (as written by the applicant)	Curing retinal degeneration & blindness is an urgent unmet medical need, with no long-term solutions. Cell replacement does not work well. Neuroprotection (our approach) works. We propose a novel drug.
Major Proposed Activities (as written by the applicant)	• Expand human pluripotent stem cells; derive retinal organoids from human pluripotent stem cells. • Derive retinal progenitor cultures from retinal organoids, expand and bank (cryopreserve) them. Establish human retinal progenitor cultures (as our control). Compare similarity of two cell sources. • Graft retinal progenitor cells into the vitreous of immunodeficient rats at an early stage of retinal degeneration. Inject media in control animals. • Demonstrate significant preservation of vision (as compared with age-matched controls) by functional testing and histology at 1-6 months post-surgery. • Delineate the molecular composition of neuroprotective substances that are produced by the organoid-derived human retinal progenitor cells that preserve vision. • Determine the mechanism of neuroprotection and narrow down the list of neuroprotective molecules and pathways for further therapeutic development.
Statement of Benefit to California (as written by the applicant)	California is a melting pot of many ethnicities, with high percentage of Hispanics and African Americans impacted by retinal degeneration. The proposed project will discover and determine the neuroprotection mechanisms, saving vision, and develop a biologic drug treating most, if not all retinal diseases. This will positively impact more than 760,000 patients in California. It will also help a start-up company in California to expand Biomedical Research aimed at saving vision.
Funds Requested	$1,912,691
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 75

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	76
Median	75
Standard Deviation	2
Highest	80
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• Yes. Neuroprotective and neurorestorative therapies for diseases in the eye holds great promise to cure, treat or at least delay vision loss. • Great impact for blindness. • The project has the potential to increase the likelihood of successfully developing a stem cell-based or more direct delivery of neuroprotective factors. • Partially, presents thoughtful options for progression; the project is still early in the translational path. • Neuroprotection is important but may not rescue many types of retinal degeneration.
No: 1	• Approach is already available (although not in the US) and therefore, overall, not new.
GWG Votes	**Is the rationale sound?**
Yes: 11	• Yes, both the use of organoids and the approach to provide trophic/protective support to the cells is good. • The proposal contains extensive data but some important aspects are missing. For example, the project will use H1 but preliminary data seem to be primarily from other cell lines. Also, the identification of new factors may result in no hits. • The project is based on retinal organoids derived from human pluripotent stem cells. Other methods would be possible, and in theory screening could be done using other non-stem cell based methods.
No: 3	• The cross-species aspects of the model are not well considered. • Neuroprotection has inherent weaknesses (histologic over functional success).
GWG Votes	**Is the project well planned and designed?**
Yes: 9	• Very logical approach. • The project is well planned and designed, but successful execution of the whole project depends on the results obtained within the project. • There is some uncertainty how well the organoids recapitulate the tissue.
No: 5	• More diverse animal models are needed to robustly find common pathways of neuroprotection.
GWG Votes	**Is the project feasible?**
Yes: 13	• Achievable within 3 years. • If the cell system mimics results from cells and the optimal timepoints and parameters for xenografting of the organoids are established early in the project as planned, it can be carried out within the timeframe. • Yes, the team has the relevant experience and background. • Yes, all resources are in place. • Yes, budget is appropriate for research proposed. • Cell lines that are used do not match.
No: 1	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• Yes, no concerns. • This is taken into account in the sense of etiology. Male and female rats are used but there is no clear rationale for this as the sex of the graft recipients should have no impact. • Mention of institutional approach but nothing specific to the project in aims to cover DEI.
No: 0	*none*

Application #	DISC2-14192
Title (as written by the applicant)	Targeted Mesoporous Silica Nanoparticle delivery of Therapeutics to Cancer Stem Cells in Recurrent/Refractory Ovarian Cancer Models
Research Objective (as written by the applicant)	Our objective is to use a novel nanoparticle method to deliver inhibitor to tumors. It will be targeted using a lock and key like mechanism, and will inactivate stem cells so tumors cannot recur.
Impact (as written by the applicant)	Our therapeutic targets advanced ovarian cancer, where only 30% of women survive 5 years. Over 70% will have a recurrence, and less than 30% of women with recurrent disease respond to chemotherapy.
Major Proposed Activities (as written by the applicant)	• Develop a surgical recurrent model of ovarian cancer where human cancers grow in the mouse ovary, then are surgically removed, and time to recurrence is observed • Test the impact of targeting the Snail/let-7 axis on stemness and recurrence of ovarian cancer by employing bio-coated mesoporous silica nanoparticles to protect and deliver RNAi targeted to cancer stem cells • Design and initiate studies on measures of identity, activity, and purity, mechanism of action, pharmacokinetics, and early safety, to complete a draft target product profile • Enhance the diversity and scope of patient-derived samples, to expand the ethnically diverse biobank, and characterize the molecular subtype of samples • Elucidate the functional effects of manipulating the Snail/let-7 axis in ovarian cancer subtypes in vitro; determine best bio-coating and knock down strategy • Determine mechanism of action by defining regulatory networks transcriptionally activated by the Snail/let-7 axis; identify altered pathways and validate gene expression changes
Statement of Benefit to California (as written by the applicant)	In California, there will be 2,250 ovarian cancer diagnoses, and 1,390 deaths, in 2022 (American Cancer Society (ACS) projection). Over 70% of diagnosed ovarian cancers will recur and those that do, rarely respond to treatment. Our studies will use a novel nanoparticle method to protect and deliver therapy precisely to cancer stem cells, aimed at preventing recurrence and restoring sensitivity to chemotherapy. We will advance a new therapeutic toward clinical trials for treatment of women with this deadly disease.
Funds Requested	$1,882,963
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 75

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	75
Median	75
Standard Deviation	0
Highest	75
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• An RNA-based therapy targeting the Snail-let7 axis, delivered by coated nanoparticles, could significantly improve treatment of high grade serious ovarian cancer by decreasing the stemness of the cancer stem cells (CSCs), making them more vulnerable to chemotherapy. • The proposed candidate, if successful, would accelerate development of a gene-based therapy to treat ovarian cancer. Targeting CSCs is a novel approach. • Investigation in tumor subtypes brings a novel precision medicine based approach that will increase the likelihood of a successful outcome of this genetic therapy. • The translational potential is strong. The study uses relevant PDX models. If the product's utility is demonstrated in this system, it will advance on the pathway to human translation. • Strengths include the unmet need (ovarian cancer is a significant cause of major morbidity and mortality), the investigative team and environment, and the Principal Investigator's outstanding expertise in cancer stem cells. The resection tumor model is a strength, as are the biologically studies of the effects of ovarian subtype on the product's effects. • It's not clear how translatable mesoporous silica nanoparticle (MSN) particles are. • Preliminary efficacy data are weak. • The preliminary data, particularly in Figure 7, are not compelling. • High-grade ovarian cancer is a serious medical problem. It has a high rate of recurrence and is the most lethal gynecologic malignancy. Accordingly, this disease represents an unmet medical need.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The basis of targeting the Snail-let7 axis to decrease stemness in cancer stem cells (CSCs) is very sound. • Preliminary data support the assertion that Snail/let7 signaling provides a potential target for reducing stemness in CSCs. • Data demonstrate the proposed product's ability to reduce Snail expression in vitro and in vivo. • In preliminary studies, Snail knockdown had a statistically significant, though moderate, effects on stemness, gene expression, and tumor size. • Translation of this technology could be more thoughtfully addressed for PK, PD, stability and toxicity, and large animal testing. • Maybe, but the rationale is not well developed in the proposal.
No: 3	• They have used a mesoporous silica nanoparticle (MSN) targeting approach to deliver siRNA for another gene to breast and ovarian cancer xenografts, with a reduction in tumor burden. A similar strategy is now being put forward in order to target expression of the gene Snail. • Figure 7 shows a reduction in tumor volume following targeting of Snail by intravenous treatment. It was not clear when tumor treatment started, nor what the effect would be on an established tumor. • At the last time point examined (Day 36), the tumor appears to be growing and the slope in treated animals is similar to the controls. No further time points are provided. I did not see discussion of this in the application. Thus, effects are marginal even in a favorable model. • The rationale for targeting snail expression is sound, as is the rationale for using coating to slow down the degradation of the RNAi species.
GWG Votes	**Is the project well planned and designed?**

Yes: 7	• The in vivo ovarian tumor models are very well designed. The use of both de-bulking and recurrent models is a strength. • The investigation of the effects of different cancer molecular subtypes in the PDX models in Aim 2 is very strong. • Experiments are well designed with good rigor, statistical analysis, and appropriate controls. • The mechanistic studies in Aim 2 are well-designed with hypothesis generation guided by transcriptomics and downstream molecular validation. • There is relatively little optimization of RNAi delivery, other than varying nanoparticle coating. This is a significant concern because extent and duration of treatment will likely determine success or failure of the study. It seems that more could be done to optimize delivery in vivo. • Consideration of off-target effects was added but this is cursory and only extends to toxicity. • Off-target toxicity is not appropriately addressed or investigated. Is there compatibility between mouse and human to assess toxicity of this product? • The time course of injections is not clear. • Preliminary data show limited time range of tumor growth, making it difficult to understand the efficacy and the rationale.
No: 7	• There is a strong concern about targeting CD44, which is expressed on many cell types. Thus, the construct will be taken up by many cells. • If cancer stem cells are being targeted, and other cancer cells express CD44, then this will also soak up the particles. The same is true for the alternative approach of folate-based targeting. • It would be valuable to see evidence of cancer stem cell targeting in vivo.
GWG Votes	**Is the project feasible?**
Yes: 10	• The milestones are logical and seem achievable. • The team added quantitative and reasonable success criteria. • The team has complementary expertise in the areas needed to complete the proposed study. • The project is feasible. • Dilution and off-target effects are not well discussed.
No: 4	• At the moment, it seems unlikely that the applicants will be able to deliver the construct to the desired cancer stem cell population - but the applicants may be able to provide data showing otherwise.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• It is appropriate to restrict the study to females, for ovarian cancer. • The team will construct PDX models from multiple donors, including Latina donors. • The project upholds principles of diversity, equity and inclusion (DEI). • Improved treatment for ovarian cancer would benefit the diverse California population. • There is no discussion of interaction with the ovarian cancer community.
No: 0	*none*

Application #	DISC2-14032
Title (as written by the applicant)	CAR-Treg Therapy for Atherosclerosis
Research Objective (as written by the applicant)	The therapeutic candidate is a regulatory T-cell expressing a Chimeric Antigen Receptor targeting Atherosclerosis
Impact (as written by the applicant)	The proposed project aims to reduce the vascular inflammation that results in myocardial infarction and stroke.
Major Proposed Activities (as written by the applicant)	• Develop CAR-Tregs targeting atherosclerosis • Test the biodistribution of CAR-Tregs in a humanized mouse model of atherosclerosis • Test the efficacy CAR-Tregs in a humanized mouse model of atherosclerosis • Optimize the production of CAR-Tregs from patients suffering from severe atherosclerosis cardiovascular disease
Statement of Benefit to California (as written by the applicant)	Atherosclerotic cardiovascular disease is the leading cause of death and disability in California with over 50,000 Californians dying from a heart attack or stroke in 2018. The cost of heart disease far outpaces any other disease, costing California $51 billion in 2018. California and its citizens will benefit from the proposed therapy directly through reduced burden of disease.
Funds Requested	$2,430,293
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	74
Median	75
Standard Deviation	2
Highest	75
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• Atherosclerosis remains a significant health care challenge. The idea of using Treg cell therapy and particularly CAR-Tregs to address atherosclerosis is interesting. • The applicant plans to do in vivo mouse work first and then transition to CAR-Treg production in patients with atherosclerosis. • The proposed technology CAR-Treg may be beneficial for prevention of atherosclerosis, but less likely to treat or cure a patient who already has severe atherosclerosis. • This is a genetic therapy project and does not involve any stem cell technology. The PI plans to harvest patients own Treg cells and engineer them to be CAR-Treg. • Aim 3 is poorly developed. No preliminary data and no solid plan.
No: 1	• The candidate is designed to increase atherosclerotic plaque stability and reduce acute plaque rupture in patients with high residual inflammatory risk that have suffered a recent myocardial infarction or at high risk to have a myocardial infarction. There are other methods to help stabilize plaques. • The candidate may improve patient care, but it is not likely to be a significant improvement. It is also likely to be costly. • Will obtain some dosing information to guide next steps. • No safety studies planned. • Other large animal models would be a better test. There are hypercholesteremic swine.
GWG Votes	**Is the rationale sound?**
Yes: 13	• Yes, this project is based on sound scientific rationale. CAR-T, CAR-Treg cells play critical roles in many biological processes. • Cell therapy and especially CAR Tregs are essential to this project. • The rationale appears sound. The preliminary data points in the right direction. Evidence of homing has yet to be presented, although there is some discussion in the text surrounding Figures 7-9. • This project lacks compelling preliminary data for Aim 2 and Aim 3. • The proposed project does not use stem cells at all. But it can be considered as a genetic therapy project because it uses transgene approach to engineer Treg cells.
No: 1	• As atherosclerosis is a chronic inflammatory disease and likely has elements of autoimmune responses, the ability to alter these cascades are intriguing. Whether a local target can alter the course of the disease remains to be tested. • In vitro data demonstrates their CARs activated Tregs. Their candidate CAR-Tregs did suppress macrophages which are thought to drive inflammation within the atherosclerotic plaque, but no evidence of effectiveness in vivo.
GWG Votes	**Is the project well planned and designed?**
Yes: 8	• The project is well constructed. Aims 1 and 2 will lead to translational Aim 3, although work on Aim 3 begins in parallel. Aim 2 will result in go/no go (pivotal) data to decide on suitability of the approach. • I am curious how cell targeting works in this context since my sense is that targeting works better in theory than in practice. Will most Tregs end up in the liver? One has to be careful to report yields: what fraction of the targeting entity ended up in the target tissue? • Carefully curated images may fail to capture the essence of the challenge when only, say 1% (if that) of the therapeutic entity ends up in the target site. The key will be the disease modifying aspects (changes to local immune cells) of the targeted Tregs vs control. • The emphasis on creating a humanized mouse model is good and the experimental plan to focus on homing is appropriate (Aim 2a). It is important to do a “mass balance” on the cells to determine fraction of the infused cells that end up in the atherosclerotic lesion and draining lymph nodes and other organs. • I am curious - do Tregs lose phenotype over time in culture for expansion? Is 14 days adequate time to modify disease in this model? • It is less likely that the proposed CAR-Treg cells can cure patients who already have severe atherosclerosis. Also this product may not be ready to advance to translational studies. • The applicant identified the risk of low yield on Treg isolation from patients and poor cell viability after viral infection. However, the applicant did not address the possibility of their CAR-Treg cells not reducing plaque size. • Project plan and timeline are ambitious.

No: 6	• Evaluating systemic markers of atherosclerosis in mice after adoptive transfer is a good idea to help evaluate effectiveness of the therapy down the road. • Evaluating aortic plaque inflammation with imaging will be challenging to do especially if changes are subtle. • Developing an CAR-Treg production protocol in patients with atherosclerosis, although necessary at some point, seems premature. I would prefer to see efficacy tested in a large animal model of atherosclerosis.
GWG Votes	**Is the project feasible?**
Yes: 10	• The proposed timeline is reasonable for a project like this one. • The PI is a clinically active surgeon-scientist with substantial research experience developing cell- based treatments for cardiovascular disease. The co-I is an immunologist and internationally recognized expert in the therapeutic efficacy of Tregs for diabetes therapy. • The institution has ample resources and facilities for the proposed research. • Potential issues are identified. Aim 3 issues apply to earlier aims and encapsulate the uncertainty in the project. • For a project like this, a 10% reduction may be needed for year 1 and year 2 of the proposed budget. • Likely not to work.
No: 4	• They have considered many potential set backs and alternative approaches are presented. However, mice need to breed, which can be challenging and imaging may not be revealing; neither of these was addressed. • Doesn't indicate where blood from patients with atherosclerosis will come from or how it will be obtained.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• They have considered race, ethnicity, gender and age. • The applicant will place a premium value on recruiting and retaining a diverse group of patients for clinical research. • DEI section reads like standard institutional text. On the other hand the overview section documents well the importance of race in cardiovascular disease. Aim 3 could pick up on this more but the number of samples is too low to yet stratify T cells by race, sex or gender. • Too early to say if the project outcomes inform the development of a product or tool that serves the unmet medical needs of the diverse California population. Studies will be done in mice of both sexes but it is premature to relate outcomes to what happens in the communities at risk. • Does not especially incorporate perspectives and experience from the population that will benefit from the proposed product in the implementation of the research project, but also not yet necessary.
No: 0	*none*

Application #	DISC2-14152
Title (as written by the applicant)	Developing stem cell-based cancer immunotherapy using human pluripotent stem cell-derived NK cells
Research Objective (as written by the applicant)	We propose to generate a cancer immunotherapy based on enhanced-immunity NK cells with from genetically engineered human PSCs.
Impact (as written by the applicant)	The use of genetically engineered hPSCs as a source for NK cells with enhanced killing effect may be an enhanced immunotherapy for glioblastoma, which has poor prognosis and no cure.
Major Proposed Activities (as written by the applicant)	• Generation of genetically engineered hPSCs • Differentiation of engineered hPSCs into NK cells • Characterization of engineered hPSC-derived NK cells • Testing the effect of engineered hPSC-derived NK cells on glioblastoma cells in vitro • Testing the effect of engineered hPSC-derived NK cells on glioblastoma progression in vivo
Statement of Benefit to California (as written by the applicant)	Glioblastoma is the deadliest primary brain tumor and has no cure. California is estimated to have ~12% of all cases of glioblastoma in the U.S. Besides the emotional and physical pain glioblastoma inflicts on families, it produces a huge medical and financial burden on California. Thus, there is a real need to develop an effective strategy of treatment for this disease. We propose to address this need by establishing a stem cell-based immunotherapy for glioblastoma using engineered human PSC-derived natural killer (NK) cells.
Funds Requested	$2,263,500
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	74
Median	75
Standard Deviation	5
Highest	80
Lowest	65
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• Glioblastoma is the most common primary brain tumor with a dismal prognosis; new therapies are needed. Development of chimeric antigen receptor (CAR)-NK cell therapeutic strategy is a promising approach for glioblastoma immunotherapy. • NK cells have natural antitumor reactivity that can be enhanced via NKG2A knockout (KO) inhibitory receptor as proposed in this application. • Expression of EGFRvIII CAR in NK or NKG2A KO enables an additional mechanism of tumor cell killing, limiting tumor escape. An advantage of EGFRvIII as a target is that it's shown to be safe in a CAR-T cell clinical trial. • Unlike T cells, NK cells are not alloreactive and therefore can be produced in large numbers for off-the-shelf immunotherapy, like the one proposed in this application. • hPSCs as a source allow generation of nearly unlimited numbers of genetically engineered NK cell therapeutic product. This could be used to treat multiple glioblastoma patients on demand. • CAR-NK cells could in theory be more effective than CAR-T cells. However, this assumption, critical for the scientific premise of this project, cannot be made in the absence of experimental evidence obtained from side-by-side comparison of CAR-NK and CAR-T cells in a relevant glioblastoma model. • The clinical trial performed with EGFRvIII CAR-T cells demonstrated that that therapy is safe, but not effective. One of the findings from that trial was that tumor cells can downregulate EGFRvIII expression following CAR-T infusion. Therefore, EGFRvIII might not be a suitable target. • Although NK cells are not expected to induce GvHD, immune memory formed following the first allo-NK cell treatment may lead to rapid rejection of subsequent doses. This pitfall is not addressed. • The applicants are leading experts in the field and have mastered technology that will enable development of iPSC-derived CAR-NK cell product within the proposed project period. • The experimental plan is logical and well-developed. There's little doubt that the applicants will be able to generate CAR-NK cell product as proposed. • Use of NK engineered to prevent glioblastoma escape is likely to have impact and worthy of testing. • NK generation and escape of glioblastoma due to NK activation could be prevented, and use of hPSC is essential to achieve this engineering of NK cells for infusion. Targeting of glioblastoma cancer stem cells is questionable. • Estimates of dose, etc., must account for knowledge gain from NK and T cell products that have been established.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• There are strengths and weaknesses in the scientific rationale that I've discussed above in the Significance section. • There are preliminary data in support of an increased short-term in vitro anti-glioblastoma cytotoxicity of NKD2A KO and EGFRvIII CAR-NK cells. • Experience from the CAR-T cell field indicates that short-term in vitro killing assays are often not predictive of CAR-T in vivo activity. Instead, a serial killing assay, in which effector cells are exposed to multiple rounds of co-culture with fresh tumor cells, is more informative. It'd be even more convincing if applicants performed side-by-side CAR-NK and CAR-T cell testing in such an experiment. • There are no in vivo data to show CAR-NK activity alone or in comparison with CAR-T cells in a relevant glioblastoma model. • Yes, the project is uniquely enabled by human iPSCs. • Strengths include innovative approach to target glioblastoma and NKG2A editing to overcome immunosuppression. Weaknesses: Unclear how targeting EGFRVIII will overcome disease heterogeneity.
No: 1	• The stem cell targeting aspect of this grant is not well established. For example, no secondary transplants or measure of cancer stem cell targeting is suggested in Aim 3's in vivo work.

	• The authors do not suggest performing genomic testing for quality control after each engineering step. This is a concern given alterations that can take place during clonal selection. • The proposal refers to lines, vs. selected clones, although clones are selected. This approach mitigates heterogeneity but loses the opportunity to isolate superior clones for iPSC line growth (not just for genetic editing validation as proposed). • The applicant's rationale for using patient brain tumor cells (which seem to be lines?) is unclear. Based on the group's Nat Comm publication in 2016, this seems to be effective, but the reason for deliberately choosing these lines versus other lines or primary tumor dissociations is unclear. • The diversity of glioblastoma cell and PSC donors, as described in Aim 3, is excellent. However, it is unclear how Aim 2 results will be used to inform and focus the more complex in vivo experiments in Aim 3. • Optimization of culture conditions for iPSC engineered lines is not discussed; nor is the yield capacity of individuals. • There is strong clinical data for HLA-E expression in glioblastoma patients and survival (to 12.5 years?). The grade of glioblastoma should be consistent with the experiments proposed. • Fig. 3 and Fig. 4 show the results of CRISPR knock out of NKG2A, as well as generation of NK cells. However, total yields and efficiency were not compared between clones, or versus yields from PB sources, etc. These comparisons could provide context as to the benefit of using iPSC to generate NKs. • Figs. 6-10 provide strong evidence for the capacity of the group to successfully generate iPSCs knocked-out for NKG2A and expressing the CAR for EGF, though this was done in irrelevant cells lines for the latter. • NKG2A KO iPSCs are in place, but clone or line variation is not described.
GWG Votes	**Is the project well planned and designed?**
Yes: 6	• The project is well planned and designed and uses state-of-the-art technology. • The proposed source of iPSCs will likely meet donor eligibility requirements. • The project is well constructed, though largely driven by the technology. Some aspects of the scientific and clinical rationale have not been fully considered. • The applicant satisfactory addresses the potential on-target toxicity of NKG2A deletion and/or EGFRvIII CAR overexpression in NK cells. However, CRISPR-mediated gene-editing produces off-target toxicity/mutations; this is not addressed in the application. • A concern about NK persistence post-infusion is raised, but not fully addressed. Applicants proposed to inject IL-2 and IL-15 or to co-express IL-15 in CAR-NK cell. However, neither IL-2 nor IL-15 addition would rescue allogeneic NK cells from host-mediated immune rejection. • The timeline is reasonable. • The project is well planned and designed • Overall, yes, but the rationale for designing in vivo experiments based on in vitro work is not well defined
No: 6	• Other than dosing, delivery and use of IL-2 and IL-15, this is well written and detailed. • A strong collection of collaborators and expertise has been assembled for this project. • Pitfalls are well described, but not in the context of how other lines or clones will be used. Genomic integrity post engineering of glioblastoma lines, and iPSC NK cells should be evaluated. • A clearer set of experimental timelines that enforce and streamline requirements for IND development would benefit the proposal. • Needs more experimental detail.
GWG Votes	**Is the project feasible?**
Yes: 9	• The project is highly feasible on the technological level. • The team is highly qualified to perform this project. • The team has access to all the necessary resources to conduct the proposed activities. • The budget is appropriate. There is no additional budget request. • The translational pathway is still somewhat unclear. • Milestones and the expected project outcome are logical and likely to be achieved within the timeline. The team is qualified; resources are in place given the scope and breadth of experiments proposed; the budget is suitable.

No: 3	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12	• The project upholds principles of Diversity, Equity, and Inclusion. • The project outcomes will inform the development of a CAR-NK therapy product that serves the unmet medical needs of the diverse California population, including underserved racial/ethnic communities. • The applicant incorporates perspectives and experience from the population that will benefit from the proposed product in the implementation of the research project.
No: 0	*none*

Application #	DISC2-14172
Title (as written by the applicant)	Development of CRISPR/Cas9 gene-edited stem cells to improve transplanted cell survival for cardiac regenerative therapy in end-stage heart failure
Research Objective (as written by the applicant)	Development of modified stem cell-derived cardiomyocyte that is resistant to cell death, leading to enhanced stem cell survival and retention for cardiac transplantation.
Impact (as written by the applicant)	A high rate of transplanted stem-cell loss after transplantation to treat heart failure is addressed in this proposal by developing stem cells that can survive better in the host myocardium.
Major Proposed Activities (as written by the applicant)	• Validate the critical roles of key proteins in stem cell-derived cardiomyocytes to enhance their survival post transplantation. • Successful modification of stem cell derived cardiomyocytes to produce candidate therapeutic cells. • Validation of modified stem cell derived cardiomyocytes in vitro. • Delivery of modified stem cell-derived cardiomyocytes in mice followed by longitudinal bioluminescence imaging to quantify stem cell retention. • Determine the improvement of cardiac function post transplantation. • Determine cardiac structural and electrical remodeling post transplantation.
Statement of Benefit to California (as written by the applicant)	Cardiovascular disease causes more deaths in California than all cancers combined. Since cardiac myocytes have limited ability to regenerate, a significant loss from myocardial infarction or other injuries can lead to heart failure with lethal consequences. The current proposal will develop improved stem cell-derived cardiomyocyte that is resistant to cell death, leading to enhanced stem cell survival and retention for cardiac transplantation.
Funds Requested	$2,705,301
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 70

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	70
Median	70
Standard Deviation	1
Highest	72
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• The proposed study focuses on myocardial infarction (MI) and the subsequent risk of developing heart failure. Regenerative medicine approaches to MI, if successful, would meet a major unmet medical need. • If iPSC-cardiomyocytes can improve cardiac function after MI they could have a tremendous impact on an unmet medical need. There are no effective cardiac regenerative therapies and iPSCs are a promising approach. • Human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes are a promising option for cardiac regeneration. However, the proposed technology may not be sufficient to address the need. • One major roadblock toward developing iPSC-cardiomyocyte cardiac regenerative strategies is the low rate of cell survival after transplantation/delivery to the MI site. Improving survival via suppression of the inflammasome to reduce pyroptosis may bridge this roadblock. • Knockout of NLRP3 may be beneficial for hiPSC-cardiomyocyte transplantation. • There are numerous other roadblocks to using iPSC-cardiomyocytes in a therapeutic setting (e.g., cell maturity, immune rejection). Solving the integration roadblock may not enable iPSC-cardiomyocyte based regeneration but would increase the likelihood of success. • Upon successful completion of the proposed study in a mouse model, the candidate would progress to studies in a more human-relevant large animal model. • The specific cell product is not well-defined. It isn't clear whether a clonal population will be isolated and characterized or a heterogeneous mixture of cells used. • The manufacturing and characterization strategy needs to be considered in the context of eventual translation. • The applicant does not present an option for large scale production of cells suitable for treatment of large numbers of patients.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The scientific rationale is that NLRP3 signaling may contribute to inflammation which may cause cell death after transplantation. This is a sound mechanistic hypothesis. • The applicant plans to knock out the NLRP3 gene in cardiomyocytes. • The knockout vector's transfection efficiency in cardiomyocytes, as shown in Fig 15, is too low to produce useful results.
No: 2	• While inflammation of cardiomyocytes following therapeutic transplantation may be a roadblock, a much larger problem is the number of cells that are lost due to effusion or lack of attachment sites. • It's possible that pyroptosis is deleterious in endogenous cardiac cells during an MI but has little effect on the survival of transplanted cells. This may be especially true at later timepoints post-MI, which are likely when the therapy would be used in patients. • The MI image in Fig. 20 is of limited quality. The image shown in very small, not transmural, and unlikely to show differences in function over time. • It is not clear that pyroptosis is the main cause of death of transplanted cells in the chronic phase of heart failure. • Preliminary data demonstrate that small molecule inhibition of the inflammasome decreases NF-kB and oxidative stress responses that can lead to cell death. • The team has constructed vectors to reduce NLRP3 expression in iPSCs in a constitutive manner and showed improvements in function of cardiomyocytes differentiated from these cells in a mouse model. • No preliminary data are provided that validate the extent of reduction of NLRP3 expression or increased cell viability in the mouse model.
GWG Votes	**Is the project well planned and designed?**
Yes: 8	• The objectives are: (i) to develop candidate gene-edited hiPSC-cardiomyocytes from donors of different sexes and ethnicities, and (ii) to test the therapeutic potential of gene-edited hiPSC-cardiomyocytes in a preclinical post-MI humanized-NSG model.

	• Some of the key CRISPR/Cas9 gene editing experiments have defects: 1. the applicant did not evaluate KO efficiency in cardiomyocytes, and 2. the applicant did not evaluate the potential of plasmid vector integration at the Cas9 cutting site. • I do not think the use of the more complex humanized mouse is necessary. NSG mice will work fine in this case and the humanized mice at this stage don't add much. • It might be helpful to produce one research-grade line that would be as similar as possible to the final candidate and test it here.
No: 5	• The study is well-designed to test a very clear hypothesis regarding the role of NLRP3 in survival of implanted iPSC-cardiomyocytes. • Complementary in vitro and in vivo characterization provide a link between mechanism of action and cardiac functional restoration. • Experimental rigor, including controls and statistical analysis, are well-considered. • The proposal does not adequately describe the editing and selection strategy that will comprise the cell product. • There is concern that the mCherry+ population sorted will contain significant numbers of unedited cells, heterozygous edits, and homozygous edits. This heterogeneity may complicate experimental analysis. • The plan lacks a strategy for cell line validation and QC. • The mouse model is appropriate for engraftment studies but has limitations in regard to functional improvement. • Cell transplantation during the acute phase of MI in the mouse model may not capture delivery in the human, which will likely be during the chronic phase. This is particularly relevant since the inflammation state of the heart will be dramatically different.
GWG Votes	**Is the project feasible?**
Yes: 11	• This is a feasible project and may be finished in three years. • The team has the necessary expertise to perform the proposed study. • This is a good team. All positions are filled, and the resources are state of the art and available. • However, this team needs an expert in hiPSC gene editing. • The milestones are appropriate and likely to be achieved in the proposed timeline. • A logical set of qualitative milestones are provided that are reasonable for a 3-year timeline. • Quantitative metrics and success criteria would strengthen the proposal.
No: 2	• Cell survival remains a concern.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• The applicant plans to use both male and female cells, from three different ethnic groups - Caucasian, Latino and African American. • This team plans to use iPSCs from donors of diverse race, ethnicity, and sex. • iPSCs from donors of different race and ethnicity will be used. • The mouse model accounts for both male and female animals. • The applicant has an excellent track record with regard to DEI. • The applicant has an excellent track record of promoting DEI through participation in institutional training and summer student programs.
No: 0	*none*

Application #	DISC2-14183
Title (as written by the applicant)	Generation of T cell-specific synthetic promoters expressing Chimeric Antigen Receptors within Self-Inactivating Gammaretroviral Vectors
Research Objective (as written by the applicant)	Development of a universal "off-the-shelf" intravenously injected gene therapy product that reprograms patient immune cells from within their body to fight cancer
Impact (as written by the applicant)	Development of a “product-in-a-vial” gene therapy for intravenous use considerably increases accessibility while greatly reducing the expense of treatment currently limiting ex vivo CAR T therapies
Major Proposed Activities (as written by the applicant)	• Identify synthetic promoters that exclusively reprogram T cells • Generate an intravenously delivered gene therapy vector; add the synthetic promoter • Develop an intravenously delivered gene therapy product that reprograms patients' T cells to attack lymphoma
Statement of Benefit to California (as written by the applicant)	Current approved external gene therapies are costly to administer, costly to manufacture, and typically are only available at specialty hospitals culminating in greatly reduced access for patients. The proposed intravenously applied gene therapy product(s) would provide California citizens a much cheaper and more accessible alternative to the potentially curative external CAR-T therapies available today.
Funds Requested	$675,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 69

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	68
Median	69
Standard Deviation	3
Highest	75
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel’s discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• the proposed technology appears conceptual with some data but unclear if will result in a candidate that could impact an unmet medical need in the timelines presented; this

	seems aggressive for how conceptual project remains. More preliminary data particularly in vivo would enhance scientific premise • The proposed technology could lead to in-vivo CAR transduction in patient T cells making CAR-T cell therapy much less costly and available off-the-shelf that could impact an unmet medical need for cancer patients. • Development of T-cell-specific promoter would restrict CAR expression to T cells and limit toxicity to other tissues if a safety switch needs to be activated. • Addition of IL-15 to the CAR construct is an established method to enhance CAR-T cell survival and antitumor activity. • It's logical to start with CD19 CAR, a validated target. If successful for B-cell malignancies, the platform can be extended for testing in other types of cancer. • One of remaining question is how in-vivo transduced CAR-T cells would expand in the absence of lymphodepleting conditioning. Such expansion has been shown to be critical for therapeutic efficacy of adoptively transferred CAR-T cells, even when they're infused at large doses. • The expected candidate will address a critical bottleneck to the delivery of genetic therapies. • The application is well described with the relevant background information, description of current challenges of CAR-T cell manufacturing, and how the proposed in-vivo delivery system can address these challenges.
No: 1	• Great idea but with major logistical issues
GWG Votes	**Is the rationale sound?**
Yes: 10	• The underlying rationale is quite sound but ambitious for its current stage of development • The proposed project is based on sound scientific rationale supported by published literature including that from applicants and supportive preliminary data. • Overall, preliminary data is compelling. However, the rate of CAR expression after in-vivo gene delivery in hu-NSG mice is not shown. That would be an important parameter to evaluate. • The proposed project is uniquely enabling for the advancement of genetic therapies.
No: 3	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 4	• The experimental plan is logical with clearly described aims, experimental endpoints, and progression towards a product candidate for clinical translation. • However, details on the design of new 4 -6 SIN vector constructs with "various deletions of the promoter..." are missing in aim-1. • It's also not clear which co-stimulatory domain is used in the CAR. It'd be important to test different co-stimulatory domains, at least those used in the FDA-approved CAR-T cells. • The final candidate will need to be tested side-by-side with ex-vivo generated T cells expressing the same CAR construct in tumor-bearing mice. • The project is generally well constructed. • Several potential pitfalls are identified and addressed with alternative approaches. • However, additional considerations are needed for the ability of the in-vivo transduced CAR-T cells to expand. Can this be affected by the use of co-stimulatory endodomains in the CAR construct or/and the level of IL-15 expression? • Is the vector immunogenic? How this will be tested? • What level of T-cell-specific promoter leakiness can be tolerated for safe use of 5-FC when needed?
No: 9	• The proposal is lacking detail on how this will come together. • - Lack details - Overambitious • Needs more detail especially a it pertains to hypothesis driven or generating research
GWG Votes	**Is the project feasible?**
Yes: 9	• too ambitious, probably not feasible in that time, translation to clinic not clear, unrealistic • The proposed milestones are logical and likely to be achieved within the proposed timeline. • The team is appropriately qualified and staffed.

	• The team has access to all the necessary resources to conduct the proposed activities. • The budget is appropriate. There is no special budget supplement.
No: 4	• - Probably not - No proof-of-concept data is provided • The approach is not well detailed in terms of translational plans
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• the project uphold the principles of diversity, equity and inclusion (DEI) • The project upholds principles of Diversity, Equity, and Inclusion.
No: 0	*none*

Application #	DISC2-14168
Title (as written by the applicant)	Human Corneal Stromal Stem Cell Extracellular Vesicles for Glaucoma Therapy
Research Objective (as written by the applicant)	To demonstrate that extracellular vesicles (EVs) derived from human CSSCs can be used in therapy to restore the functions of glaucomatous TM cells.
Impact (as written by the applicant)	Elevated ocular pressure (IOP) can irreversibly damage optic nerve and lead to glaucoma. Success of this project will provide a novel therapeutic approach to treat and prevent elevated IOP.
Major Proposed Activities (as written by the applicant)	• EV production, characterization, storage, and reproducibility. • Further evaluation of the effect of EV on Dex-induced glaucomatous phenotypes of TM cells. • Assessment of EV efficacy with organ cultured porcine eyes. • Evaluation of the efficacy of EVs in rejuvenation and restoring damaged TM cells in a glaucoma mouse model. • Testing topical application of EVs using a fibrin gel as a vehicle. • Exploration of EV delivery with an EV-loaded implant.
Statement of Benefit to California (as written by the applicant)	Glaucoma is a leading cause of irreversible blindness in the world and it affects approximately 70 million people worldwide and is projected to affect 112 million people by 2040. Primary open-angle glaucoma (POAG) accounts for 90 percent of glaucoma cases and is defined by an open anterior chamber angle and elevated intraocular pressure (IOP). African Americans are almost 3 times more likely to have POAG than Caucasians and are 15 times more likely to suffer visual impairment from the disease.
Funds Requested	$1,850,275
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 65

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	68
Median	65
Standard Deviation	5
Highest	80
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• Great need. • Many ways are available to decrease intro-occular pressure, however, the focus on structural improvements is novel and would be important > opportunity for one time long term treatment • The development of new therapies for open-angle glaucoma is a critical medical need. There are multiple therapies available. However, few can induce structural changes in the eye structure. • This technology could be a viable treatment for a disease that is the leading cause of blindness. currently we have no treatments to repair, restore and or reverse a damaged and aged TM. Yes Secretomes are being investigated in restoring damaged and or dying cells in various diseases. • I am not optimistic that this proposal will result in a candidate to move forward. There are no clear dose ranging studies outlines expect for exploratory bench cell work with measurements of protein and morphology in TM cells. It is uncertain if these biomarkers IF altered in a single cell culture model will translate to functional changes and IOP lowering due to decreased resistance. • There are numerous vascular modulators and cells posterior to and distal to the TM that could also be affecting aqueous resistance and leading to elevated IOP. • This work on secretomes could accelerate the development of a stem cell technology for glaucoma.
No: 2	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• Yes, in theory, little prelim data proof.
No: 2	• Use of SV40 immortalized cells as a source of EV, can be problematic because the poor characterization of the EV by this group. Also there is no evidence in the proposal that EV has a positive effect on POAG-derived TM cells comported with age match controls. • The preliminary data does not support the central hypothesis, and there is no evidence of expertise from the team on using porcine models. • no - these activities are all dependent on the dose, and the PI states that the likelihood of failure at each step is limited and has he potential of failure due to not having an ideal dose. Yet there is no clear statement of how a dose will be selected, what criteria and how those criteria for dose selection in a single cell model actually translate to a functional change in IOP.
GWG Votes	**Is the project well planned and designed?**
Yes: 6	• Determination of appropriate dose is not done, species differences are not addressed
No: 8	• Too ambitious • There are concerns about the ability of the PI team to generate CSSC lines need it to isolate EVs. In the application, some data uses EVs derived from a single cell line. Are differences between different cell lines that need to be investigated; there are proposed ex vivo models but no evidence that the group has the expertise to realize and interpret the results. • Too many activities to accomplish in 3 years. All dependent on a selected dose but no clear concise rational for a dose ranging and dose identification process.There are too many activities for 3 years worth of work. Activity 3 which will determine a "dose" overlaps with the mouse model - how can the mouse model start ahead of finding and identifying a dose from Activities 1-3. no candidate selection, no clear process for identifying a candidate on specific criteria - no criteria given • A major concern is the ability of a human derived secretome EV to have efficacy on and in a mouse and porcine model. What is a relative species specific cross activity. This is not addressed at all. • No PD/ PK discussed to help select a candidate.
GWG Votes	**Is the project feasible?**
Yes:	• Yes, but success is far from guaranteed.

9	
No: 5	• Not likely doable in the time frame- use of propriety devises are a challenge that is not discussed • Limited preliminary data • The team needs to add expertise. • Data included in the proposal is not sufficient to define the feasibility of the project • There are too many activities all reliant on a dose ranging and PK/PD which is not delineated. These studies have numerous challenges and are all still explorative. The 2 key activities 1&2, which could select a dose and candidate, only show some TM markers and morphology studies with not criteria for selection. All the other activities are dependent on a dose from 1&2, and IF delayed - they will extend the timelines
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• It is commendable to be emphasising training of minority students. • There is some description of their commitment to incorporate in their team, investigators from under represented minorities.
No: 0	• no

Application #	DISC2-14174
Title (as written by the applicant)	Conditioning-free CAR-HSC (hematopoietic stem cell) therapy for solid tumors
Research Objective (as written by the applicant)	Development of conditioning-free CAR-HSC therapy to eradicate solid tumors
Impact (as written by the applicant)	Immunotherapy using chimeric antigen receptor (CAR) vbb for solid tumors, Expansion of gene-manipulated hematopoietic stem cells
Major Proposed Activities (as written by the applicant)	• Aim 1: Evaluate anti-tumor effects of human CAR-HSCs • Aim 1.1 Characterize anti-tumor effects of human CAR-HSC transplantation • Aim 1.2 Evaluate a therapeutic effect of human CAR-HSC against developed solid tumor • Aim 2: Establish non-conditioned CAR-HSC transplantation as a cancer therapy • Aim 2.1 Characterize anti-tumor effects of non-conditioned CAR-HSCs • Aim 2.2 Determine therapeutic effects of non-conditioned CAR-HSC transplantation against developed cancers
Statement of Benefit to California (as written by the applicant)	The proposed research will directly lead to developing a therapy that can treat patients in California suffering from solid tumors. This year, the estimated number of new cases in California is 189,220, and >90% are categorized as solid tumors.
Funds Requested	$788,558
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	61
Median	60
Standard Deviation	6
Highest	70
Lowest	50
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 11	• The proposal is to develop a CAR-HSC therapy to be used in the treatment of solid tumors without conditioning. Avoiding conditioning may maintain tumor-specific lymphocytes and be feasible for more patients. • There is a well-formulated overall hypothesis in support of CAR-HSC based cancer immunotherapy. • The engraftment of chimeric antigen receptor (CAR)-HSCs would provide a long-term supply of tumor-specific effector cells, mostly of myeloid origin. If such cells have antitumor activity, the treatment may lead to durable tumor control. • However, myelopoiesis (generation of mature blood cells from HSCs) in cancer patients is often affected by the disease. Immature myeloid-derived suppressor cells (MDSCs) accumulate and produce tumor-supportive and immune-suppressive factors that accelerate tumor progression. • It's quite possible that the CAR-HSC therapeutic approach would lead to the accumulation of MDSCs with pro-tumor function. • CAR-mediated stimulation could have a pro-tumor activity via MDSC activation. • CAR design may need further optimization via testing of different promoters and/or co-stimulator/inhibitory molecules for optimal expression/function in the desired effector cells rather than in all myeloid cells. • The project proposes testing of both human and murine CAR-HSCs. Until there's clear evidence that the method is safe and effective in a murine syngeneic tumor system, adding humanized models is not justified. • The project is too early stage for DISC2 funding.
No: 2	• Not in its present form.
GWG Votes	**Is the rationale sound?**
Yes: 7	• The scientific rationale is in part supported by recent publications and preliminary data presented in the proposal. • The preliminary data solidly support the applicant's method of ex vivo expansion and adoptive transfer of murine CAR-HSCs, with the reconstitution of CAR-expressing myeloid cells in mice. • The proposed project is uniquely enabled by human stem/progenitor cells and has a potential for being enabling for the advancement of stem cell-based therapies. • However, potential negative effects of CAR-HSC therapy are not fully considered. In particular, the potential tumor-promoting activity of CAR-redirected MDSCs has not been considered. • No data are presented to show the presence or activity of CAR-redirected activity of MDSCs, a major subset of myeloid cells in cancer patients and syngeneic mouse tumor models. • Human HSC ex vivo expansion and reconstitution is less robust than in mouse and may need to be further developed outside the scope of the proposed study. • The time required for generation of sufficient numbers of HSCs ex vivo and subsequent engraftment in patients is considerably longer than that for autologous CAR-T cell products. This could make the proposed product less competitive. • CAR-macrophages may have better anti-tumor activity than CAR-T cells due to the natural residency of macrophages within tumor tissues. • Macrophages produced from HSCs may be generated in higher numbers as compared to ex vivo engineering of terminally differentiated macrophages. • Based on a cited reference, the applicant suggests that CAR-macrophages would exhibit the M1 phenotype. However, in that reference, the M1 phenotype was due to adenovirus transduction, not CAR expression. In the proposed lentiviral engineering approach, it remains unclear whether those macrophages would have an M1 phenotype.
No: 6	• The scientific rationale is not convincing. • CAR expression won't be restricted to myeloid cells. • It's not clear if the CAR will be expressed in a controlled manner. • Proof of concept will likely not be achieved.
GWG Votes	**Is the project well planned and designed?**
Yes: 5	• There are strong elements of planning, especially the methods of ex vivo expansion and adoptive transfer of HSCs developed by the applicant.

	• However, proposing experiments in both murine and humanized models dilutes the focus of the project. • The experiments in which tumor cells are implanted post-HSC are not clinically relevant. Instead, it would be important to further develop experiments with CAR-HSC transfer to tumor-bearing mice and consider tumor-promoting effect of such therapy, e.g., via MDSC stimulation. • There is little attention paid to CAR design that could be exploited for stage-specific and/or activation-dependent CAR expression. • Some potential pitfalls are identified and addressed. However, a number of significant pitfalls have not been considered, in particular the potential tumor-promoting effect of the therapy. • The project has both major strengths and major weaknesses. • The project timeline is adequate.
No: 8	• Lots of in vitro studies, but potentially relevant in vivo studies make use of a small number of mice (and thus lack rigor). • What is the therapeutic relevance of performing CAR-HSC transplantation prior to solid tumors? • CD19 is an inappropriate target antigen for melanoma, even as a proof of concept. • Engineering of HSCs requires consideration of when CAR will be expressed and in what cells. • iPSCs generated with constitutive CAR expression fail to properly differentiate into certain immune cell types.
GWG Votes	**Is the project feasible?**
Yes: 8	• The project is technologically feasible. However, the translational value of the results remains uncertain. • The proposed team is highly qualified and staffed. • The team has access to all the necessary resources to conduct the proposed activities • The budget is appropriate. Additional budget is not requested.
No: 5	• There are no preliminary data on CAR-HSC transplantation and killing of solid tumors. • There are compelling data on conditioning-free HSC transplantation, although no mechanistic information is provided for these findings. • The CAR is expressed from the EF1a promoter, and although the proposal focuses on CAR-myeloid cells, all immune cells will express it. It's unclear whether CAR-expressing HSC will maintain proper hematopoiesis. • The alternative approach using the CD11b promoter for CAR expression should be the primary method. • There is limited experimental rationale in this proposal.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 9	• The project upholds principles of Diversity, Equity, and Inclusion.
No: 4	• The applicant's DEI statement is not appropriate. • The DEI statement appears to be script material from the institution. • The proposal lacks consideration of how the research project can uphold principles of DEI.

Application #	DISC2-14199
Title (as written by the applicant)	Multiorgan tool for the development of therapeutic agents using IPSC derived AD brain cells
Research Objective (as written by the applicant)	iPSC derived vascularized 3D organ model for Alzheimer's disease (AD) drug screening
Impact (as written by the applicant)	There is no 3D organ model for immune cells infiltration in brain through the blood brain barrier (BBB) to study neuroinflammation
Major Proposed Activities (as written by the applicant)	• Development of iPSC derived cells for organ model • Development of 3D vascularized organ model with fluidics • Development of continuous monitoring with Trans-Epithelial Electrical Resistance (TEER) and high throughput imaging • Validation of neuroinflammation using AD drugs
Statement of Benefit to California (as written by the applicant)	Alzheimer's disease (AD) is a growing public health crisis in California. Without an effective treatment, the impact of Alzheimer's will continue to rise. 11.7% of people aged 45 and older have subjective cognitive decline. 1,624,000 family caregivers bear the burden of the disease in California. The development of appropriate therapy is necessary to lessen the burden and enhance the quality of life for those living with cognitive impairment and for their families.
Funds Requested	$675,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	60
Median	60
Standard Deviation	6
Highest	65
Lowest	40
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 11	• Potentially. If successful, the candidate device (which seeks to recapitulate an 'Alzheimer's disease (AD) brain organ' using iPSC derived cells from AD patients) would allow the applicant to test drugs for the treatment of AD. This is a huge unmet medical need. • This proposal is a resubmission. The applicant has not adequately responded to the initial concerns, including recapitulating their 3D model of AD. • This two-year study proposes to model the infiltration of peripheral immune cells in AD patients' brains using 3D 'brain organs.' These brain organs may provide a novel platform for high throughput screening for AD therapies. • The model is proposed to be used to identify drugs for AD. • Treatment for AD is a big unmet medical need, but the product is too complex to be a screening tool. • The applicant has not presented thoughtful options for progression to translation.
No: 3	*none*
GWG Votes	**Is the rationale sound?**
Yes: 6	• The overall idea of combining tri-culture brain cells with a blood brain barrier (BBB) model to monitor brain responses to drugs is interesting. • I expect these 'brain organs' will be responsive to changes in the genetic background of patients' cells.
No: 8	• The three aims are not actually written out anywhere, adding to the confusion. • The focus in this proposal on the BBB, while relevant in Alzheimer's disease (AD) and for therapeutics transfer to the brain, detracts from the mechanisms underlying AD. • The selection of the other organs to include in the technology (gut, liver, kidney) is somewhat justified (e.g., to study PK), but why are other relevant organs (e.g., heart, systemic vasculature) not considered? • The rationale does not recognize the diversity of pathologies in AD. • A 3D model with iPSC derived microglia, astrocytes, oligodendrocytes, and neural cells separated by BBB (endothelial cells and pericytes) is too complex to be a screening tool. • The reset of cellular age during iPSC reprogramming is not taken into account in the rationale. • The proposal lacks preliminary data to support: 1) the ability of the proposed technology to detect disease-relevant features of cells, and 2) advantages of this culture system over available systems.
GWG Votes	**Is the project well planned and designed?**
Yes: 3	*none*
No: 11	• The project is not well designed in the sense that the complexity of the technology is not sufficiently considered. • The engineering aspects of the project are of high quality, but the cell differentiation and assessment aspects are weak. • The project plan is somewhat confusing, with three aims, seven main tasks, plus another three for a subproject at a partner institution. • The applicant claims that they have already established many aspects of the platform, however, the provided data are difficult to understand. For example, what does Figure 2 show? HuVEC cells and labeled endothelial, astrocytes and pericytes are not new. • Figure 4 shows MES, which are a well-established method. • Drug screening in Alzheimer's disease (AD) animal models is a standard approach. • The overall approach is not clear. What does the applicant mean by organs? Is Task 1 to establish mixtures of semi-pure cells that are commercially available? What do these mixtures of cells show? Are they organizing into a structure? What ratio of cells are used, and what is the readout? • The project is of limited scope. • The applicant does not sufficiently identify potential pitfalls or alternative approaches.
GWG Votes	**Is the project feasible?**
Yes: 5	*none*

No: 9	• There are no preliminary data provided that demonstrate that the mix of cell types form anything of interest in vitro. • Details are too limited to assess feasibility. • I don't see a logical progression of work. • No. The project is complex, time-consuming and requires the use of multiple cell lines. • Yes, the team is appropriately qualified and staffed. • Expertise in AD in human models could be expanded. • Yes, the team has access to all the necessary resources to conduct the proposed activities • The budget appears appropriate.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• The plan is to use cells of different background and sex. • Yes, the project outcomes inform the development of a product or tool that serves the unmet medical needs of the diverse California population. • To some extent, the applicant incorporate perspectives and experience from the population that will benefit from the proposed product in the implementation of the research project. • Adequate.
No: 1	• No. The project will incorporate cell lines derived from one Black donor and three Asian donors. The applicant does not propose effort to look elsewhere for a more diverse set of cell lines. • There is no Latino representation in the cell lines.

Application #	DISC2-14117
Title (as written by the applicant)	IPS derived progenitor cells to deliver BDNF as neuroprotection for the treatment of Huntington's Disease
Research Objective (as written by the applicant)	Human induced pluripotent stem cell (iPSC)-based platform for the delivery of the neuroprotective factor (BDNF) to prevent neurodegeneration in Huntington's disease (HD)
Impact (as written by the applicant)	Restoration of the neurotrophin brain-derived neurotrophic factor (BDNF) in transplanted progenitor cells, derived from human iPSCs to provide neuroprotection in HD
Major Proposed Activities (as written by the applicant)	• Gene correction of HD patient derived iPSCs (months 0-6) • Engineering gene corrected HD patient-derived iPSC to express BDNF and safety switches (months 4-12) • Differentiation of engineered iPSC into neural and striatal progenitor cell types for transplantation studies (months 8-18) • Determine the lowest cell dose required to rescue the phenotype in two different HD mouse models (months 7-36) • Validation of the kill-all safety switch in the transplanted cells in vivo (months 24-32) • Determine a pilot process for engineering iPSC at multiple genomic loci without genotoxicity (months 24–36)
Statement of Benefit to California (as written by the applicant)	Almost all cases of Huntington's disease (HD) manifest in the 35-to-64 year age group, with debilitating symptoms presenting by early 30's, meaning most patients are unable to participate in paid employment. Our goal is to develop a gene editing therapy that is effective at correcting at providing neuroprotection and is accessible to all patients. Our study will support California's lead in driving innovative stem cell research for studying disease mechanisms and developing innovative stem cell-based gene therapies.
Funds Requested	$2,366,401
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: --

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 11	• Patients affected with Huntington's disease (HD) would benefit from new therapies. But the proposed technology is less likely to result in a therapeutic product because BNDF treatment alone may not be sufficient to cure HD. • This proposal will use HD patient cells to derive iPSCs, and then differentiate these into neural stem cells. Limited discussion is presented for translating this research to humans. • This work may lead to a stem cell approach for preventing or minimizing neural degeneration in Huntington's disease (HD). This would be welcome and help with this difficult disorder. • The application is geared toward translation and progression and includes the use of "kill switch" cassettes to be incorporated into the genome of PCSs should tumors arise. In addition, the plan proposes to correct triplet repeat expansions and also result in cells that would be autologous.
No: 2	• The rationale for using cell-based therapy to treat HD is weak and questionable, not only because of its invasive nature but also because of the lack of clinical benefits reported by previous trials. The applicant does not mention anywhere in the text that the majority, if not all, open label studies (six in total) have failed to report benefits in patients. The rationale for cell transplantation in HD is therefore not as well supported as for other disease contexts such as Parkinson's disease. • This is partly due to the fact that the brain is very much atrophied by severe cell loss which makes this milieu very unfavorable for any transplanted cell types to survive/grow. All post-mortem analyses of any of the cases who have come to autopsy corroborate the lack of clinical benefits, as grafts show clear signs of degeneration over time, including HD-related pathology. Even if the primary goal of the applicant's method is to deliver BDNF, this is done via a cell-based approach. • Prior negative results, both pre-clinical and clinical, should have been included in this grant. • How would this actually translate into humans? What parameters would be considered in an eventual clinical trial?
GWG Votes	**Is the rationale sound?**
Yes: 4	• Expertise on Huntington disease is limited – i.e., the background data are out of date. • Existing data from clinical trials are not discussed; existing data from animal models are not discussed. • Not very clear and overly complicated.
No: 9	• The idea of transplanting cells that can continuously secrete BDNF to offer a neuroprotective effect in HD patients is attractive, especially before the onset of symptoms. • This project plans to use corrected iPSC-derived cells as a delivery vesicle for BDNF expression. Why not use a gene vector to express BDNF? • Why not deliver the trophic factors via gene therapy? • No compelling preliminary data are presented. In Fig. 6, no data are shown to support the applicant's ability to perform gene knock in efficiently in iPSCs. • The applicant may have a limited understanding of the pathophysiology of HD. • There is some question as to why there is such an emphasis on the use of autologous transplantation strategies as the brain is essentially immunoprotected. It might be much more straightforward to simply use cells derived from wild-type human pluripotent cells--these should not be subject to immunological attack, and furthermore do not contain repeat expansions in the HTT gene. • In general, the main objectives of this grant are confusing. The applicants claim to target both cognitive and motor aspects by transplanting either striatal or forebrain differentiated cells. Where exactly will the cells be transplanted? The striatum has at least three functional territories, including limbic regions. What is meant by forebrain cells? What is the phenotype targeted? • Apparently, the therapy is primarily planned to replenish the brain's BDNF levels. However, the applicants also mention that the transplanted cells will replace dying neurons. What is the real focus?

GWG Votes	Is the project well planned and designed?
Yes: **4**	• Potential pitfalls identified and alternative approaches are presented, and this project meets CIRM's mission. • The team may not have all the techniques they need to perform this project. Therefore, they may not be able to finish it in three years. • This is not a good proposal.
No: **9**	• The applicant provides preliminary data indicating that the methods are in place to perform genome editing at the proposed genomic loci. • Since there is still a lot of work to do to see if this approach is efficacious in a mouse transplantation model, the experiments to correct repeat expansions and use iPSCs derived from HD patients (for autologous transplants) seems to be a secondary concern at this point. • There is some concern as to whether AP20187 and AP21967 (to activate kill switches) can cross the blood brain barrier. • The plan to confirm that BDNF is secreted properly will be performed in undifferentiated iPSCs - the relevant cells are those differentiated to forebrain and striata progenitor neurons. • Based on the provided data, they are able to increase BDNF secretion upon genetic editing. • Based on Figure 1b, it does not seem as though HTT was properly edited. There is no quantification provided. • Figure 3 provides images of forebrain and striatal progenitors, but it is difficult to truly evaluate their health (background, cellular localization etc.) as they are low magnification. It looks like there may be expression of the tested markers, but it is not convincing. • Figure 4B: Unedited NPCs appear to provide as much benefit as BDNF-NPCs. This suggests that this therapeutic candidate may not alleviate all symptoms of HD. • I do not understand the alternative approach for adding CD19 and CD8a receptors: is this another gene editing experiment? • One of the alternatives is to perform intraventricular administration of the kill-switch activator AP21967, in case other modes of administration fail. This does not sound applicable to the clinic. • Experiments are not clearly detailed.
GWG Votes	**Is the project feasible?**
Yes: **7**	• Due to the fact that this team may lack some key technologies for iPSC editing and differentiation, they may not be able to complete it in 3 years. • A neural differentiation expert may be needed. • This budget request seems reasonable. • The grant is ambitious, but it seems doable in 3 years if major impediments do not occur.
No: **6**	• It's not clear that results will inform the field. • I think this proposal is rather preliminary and may take much longer to complete than anticipated. • I have an issue with the general concept here and I believe that the required steps to achieve the stated goals will be difficult within the timeline proposed.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12	• They plan to test iPSCs representing diverse race, ethnicity, sex and gender. • This grant application contains an excellent plan to include iPSC cell lines from diverse sources. • This grant contains a good description of outreach and inclusion approaches that the PI and co-workers are currently engaged in. • The applicants highlight a number of statistics that consider race, ethnicity, sex, and gender. They also plan to test if there are any differences between iPSC from various ethnic backgrounds although this goal is not described in the experimental timeline/scheme. • The applicants also mention a survey that was conducted in a small number of patients (n=14) to at least validate which symptoms are most bothersome to them
No: 1	*none*

Application #	DISC2-14061
Title (as written by the applicant)	HIV gene therapy for direct in vivo CAR-T Cells engineering as a single treatment for HIV definitive cure
Research Objective (as written by the applicant)	An accessible and cost effective gene therapy candidate to provide a potential definitive cure for HIV patients through innovative in vivo CAR-T
Impact (as written by the applicant)	Bypass needs for logistically complex and costly ex vivo autologous cell isolation, manipulation, genetic engineering and re-infusion of CAR T-Cell, with simple in vivo T-Cell gene therapy
Major Proposed Activities (as written by the applicant)	• Vector engineering and verification, to ensure all genetic requirements are integrated into the viral vector backbone. • Recombinant Lentivirus Particle production. Establishment of an R&D process to produce material for downstream analysis and functional testing. • Functional characterization of recombinant LVP. Establish assays necessary to ensure adequate quality attributes. • In vivo POC demonstration HIV therapy. Demonstrate product concept POC in a a relevant HIV animal model.
Statement of Benefit to California (as written by the applicant)	This technology will benefit both an innovator/manufacturer of the advanced therapy industry in California, as well as its patient population. The technology was developed in part by a California biotechnology company which aims to expand it research and manufacturing operation in the state of California. Moreover, this project will benefit a broad segment of AIDS patients across socio-economic barrier with an intervention that is more cost effective than traditional CAR-T therapy.
Funds Requested	$1,429,839
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: --

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 7	• Development of a strategy that would enable functional remission of HIV replication in people living with HIV (PLWH) would address an enormous medical need as currently PLWH must take antiretroviral therapy (ART) for life in order to suppress virus replication. • CAR-T cell therapy directed at HIV-producing cells is being pursued by multiple groups as a therapy to enable long term functional remission of HIV in the absence of ART. Its utility, however, remains to be proven. • CAR-T cell therapy currently requires removal of host lymphocytes, ex vivo transduction and expansion, and then re-infusion. Consequently, this therapy is not a viable solution for the majority of PLWH. A technology that enables in vivo transduction and expansion of CAR-T cells would be a significant innovation and would render CAR-T cell therapy more feasible as an intervention for PLWH. • CAR-T cell therapy for HIV is a promising approach, currently tested in clinical trials. The application proposes to eliminate the need for ex-vivo CAR-T cell manufacturing, the main driver of CAR-T cell therapy costs, by developing a lentiviral system for in vivo delivery of CAR-encoding vector. • The technology for in-vivo CAR-delivery is of great potential impact. If successful, the proposed system would address a critical bottleneck in delivery of CAR-T cell therapy for HIV and other diseases. However, some critical preliminary data are missing. • The HIV-1-targeting CAR has already been published and is currently in a clinical trial with a standard CAR-T therapy funded by CIRM. This represents a strength since the applicants use a validated CAR construct for the development of a new delivery system.
No: 6	• Interesting idea but high risk for cancer; premature.
GWG Votes	**Is the rationale sound?**
Yes: 2	• There are many elements of sound scientific rationale. • There is a solid support for the CAR design, the use of the virus envelope, and antibody. • The proposed use of the envelope is a justified approach to make LVP resistant to human serum, one of the requirements for successful in-vivo delivery. • Addition of the binder to the envelope is a commonly used method for targeting T cells. However, this won't make LVP to exclusively bind T cells. Non-specific delivery of lentiviral particles to other cells in the body is not expected to lead to an acute toxicity. However, lentiviral integration in normal cells of various tissues can lead to long-term toxicity including a risk of malignant transformation. • The proposed overexpression of a gene to make the in-vivo transduced CAR-T cells resistant to a chemotherapy drug is an interesting approach for selective expansion of CAR-T cells following lymphodepleting chemotherapy. However, there is a lack of critical preliminary data to demonstrate that human transduced T cells are resistant to clinically relevant concentrations of the chemotherapy drug active metabolites. • In addition, the current lymphodepletion protocol for CAR-T cells includes a second chemotherapy drug. It's not clear whether the effect from one drug alone would enable sufficient expansion of in-vivo transduced CAR-T cells. • The presented preliminary data for the overexpressed gene is not sufficient for the postulated hypothesis.
No: 11	• A clinical trial testing the CAR is currently in progress. It seems premature to be optimizing a vector for in vivo transduction when it hasn't been proven to be effective. If the CAR is not effective, the vectors produced by this study would not be useful.
GWG Votes	**Is the project well planned and designed?**
Yes: 5	• The project plan and timeline are adequate. • Overall, it's a well-designed project. However, some proof-of-concept data for a product candidate such as an evidence of protection of human CAR-T cells from a chemotherapy drug is missing. • Applicants identified and addressed some, but not other pitfalls.
No: 8	• Inclusion of the gene in the vector is of major concern. This gene enables cells to persist in the presence of a chemotherapy agent. It is a pro-survival gene, promotes proliferation, and has been linked to several cancers. Although the vector is aimed at T lymphocytes,

	many cells will become transduced during in vivo transduction including stem cells. I think this strategy poses a great oncogenic risk. • The mouse model is flawed: It employs peripheral blood mononuclear cells (PBMC) as both the effector cells and the target cells although in vivo the major reservoirs and effector cells are in secondary lymphoid tissues. Injecting PBMC into a mouse spleen doesn't make them secondary lymphoid tissue cells, and fails to reconstitute the normal spleen architecture. Furthermore, are they planning to inject LVP into humans' spleens? • Additionally, HIV replication is disseminated throughout secondary lymphoid tissues in vivo including lymph nodes, gut as well as spleen. Injecting the infected PBMC and the LVP into one single compartment does not recapitulate the complexity of HIV infection in vivo. • In the mouse model they plan to add LVP at the same time as the infected PBMC – essentially this is an acute infection model. There is no ART treatment and no established latent reservoir which is really what must be targeted by CAR-T cells to cure HIV infection. • Studies in the mouse propose to measure HIV DNA+ and RNA+ cells in disaggregated spleen cells. This will provide percentages, but not absolute numbers of infected cells. In situ hybridization for HIV RNA and DNA should be performed on spleen tissue sections to determine the impact of the treatments on absolute numbers of CD4+ T cells, RNA+ cells, and DNA+ cells. Also, why isn't plasma viral load being measured? • Limited to spleen studies.
GWG Votes	**Is the project feasible?**
Yes: 7	• The scientific team is outstanding. Clearly it is capable of carrying out the proposed experiments and making the vectors proposed. • The proposed milestones and expected project outcome in general are logical and likely to be achieved within the proposed timeline. • The proposed team is appropriately qualified and staffed. • The team has access to all the necessary resources to conduct the proposed activities. • The budget is appropriate.
No: 6	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 11	• Creating a product that can be used to cure HIV infection in PLWH around the world addressed very much the principles of diversity, equity and inclusion. • The project plan and design adequately addresses and accounts for the influence of race, ethnicity, sex and gender diversity.
No: 2	*none*

Application #	DISC2-14071
Title (as written by the applicant)	Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells by small molecule induction
Research Objective (as written by the applicant)	The research objective is to establish preclinical safety and efficacy of the hESC-derived DA product for DA neuron regeneration and neurological function restoration for TPP and advance to TRAN1.
Impact (as written by the applicant)	This project enables clinical translation of hESC technology and intellectual property as a much-needed solution for PD, having a groundbreaking impact on advancing medicine, improving human health.
Major Proposed Activities (as written by the applicant)	• To demonstrate the hESC DA product (hESC-DAP) is a homogeneous population of DA neuronal progenitors. Milestones: >90% positive for DA/neuronal markers but negative (<1%) for pluripotence and other lineage markers. • To affirm its homogeneity and neuronal identity with no residual pluripotent cells of safety concern by highly sensitive miR profiling. Milestones: >100-fold-down of miR-302, >100-fold-up of miR-10b. • To demonstrate the hESC-DAP differentiates into DA neurons with high efficiency. Milestones: >90% of the hESC-DAP differentiates into Nurr1+ DA neurons. • To demonstrate the hESC-DAP is highly neurogenic and safely engraftable following transplantation into the brain. Milestones: > 50% yields DA neurons and a lack of tumor formation (<1%). • To establish the in vivo efficacy of the hESC-DAP for DA neuron regeneration and neurological function restoration in an animal model of PD. Milestones: >50% of the graft yields DA neurons. • To generate the target product profile (TPP) for the hESC-DAP. Milestones: The TPP with preclinical safety and efficacy data is established for entry into TRAN1 and clinical development.
Statement of Benefit to California (as written by the applicant)	In regenerative medicine, hESC research holds huge promise for treating major human diseases that have evaded traditional medicine. Millions of people in CA are pinning their hopes on hESC research. This project enables clinical translation of hESC technology/IP as a much-needed solution for PD, presenting hESC as a novel, advanced strategy for a wide range of incurable or hitherto untreatable neurological diseases, bringing tremendous benefits to California economy and healthcare.
Funds Requested	$2,723,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: --

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	15

(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 2	*none*
No: 12	• This proposal is based on the use of progenitors that can differentiate into dopaminergic neurons resembling more closely equivalent human cells (i.e. nuclear Nurr1) to treat patients with Parkinson's disease (PD). • This field of research is extremely active at the moment and past clinical trials using human fetal tissue have shown that cell replacement therapy could be a beneficial therapeutic approach, at least in some patients. Finding a reliable cell source would be key to moving forward with this approach on a larger scale. • The approach in itself (cell replacement in PD) holds great promise to meet an unmet clinical need. • Partially presents options for progression from successful candidate discovery to translation. • An advantage of the application is that their cell candidate is patented. However, this proposal is not original at all. The idea/data is based on a concept from over a decade ago. The field of cell replacement therapy has grown tremendously in the last decade with several new candidates being tested in the clinic. The applicant has not taken any of this into account in the proposal. • While PD is a progressive neurodegenerative disease without a cure, making this a significant problem, the proposal has little chance of impact. • The application lacks novelty and is not competitive to other similar projects already ongoing. • The field is already beyond what is addressed in the application.
GWG Votes	**Is the rationale sound?**
Yes: 4	• This idea has been tested many times before and it is not clear what will be new to advance the field.
No: 10	• Some preliminary data are presented. • The core information of this proposal is repeated at least four times in several different locations in the text. This leaves little space to provide much needed and appropriate details regarding the justification for the selected animal model, experimental timelines, behavioral tests, and post-mortem analyses. • A rationale for why the proposed rat model is the only experimental model of this proposal is needed. This model does not take into account a fundamental pathological hallmark of PD, i.e. alpha-synuclein expression and Lewy bodies. • The developed cells must be tested in more than one model and in particular, models that reflect important aspects of the pathophysiology of PD. Incorporating genetic models of alpha-synuclein would also be essential given the prion properties we know recognize this protein. However, not even the theory of this is discussed when the disease is presented. This is very problematic. • How long after the lesion will the animals be transplanted? How often will the behavioral tests be performed? At what timepoints? At what timepoint will post-mortem analyses be conducted? These essential questions are not addressed in this proposal. • The rationale for the rotarod test on a unliteral lesion model is unclear. • The rationale of transplanting in the proposed location and making such a strong case about the Nurr1 phenotype which drives DA differentiation is unclear. When transplanting in the proposed location (which is not the site of DA cell loss in PD), the most important

	thing is to re-establish DA levels and perhaps not to find the perfect DA phenotype to replace degenerated cells. • If, on the other hand, the applicants really care about the most appropriate/relevant DA phenotype, then several other markers must be shown as recent literature has provided a much more accurate picture of the DA cell diversity within the substantia nigra of both mice and humans (see work by Awatramani). • Some of the important data related to Nurr1 (Figure 2) seems to be extracted from a previous publication dating from 2011. Why do the authors not provide newer and higher quality images? • The investigator mentions that other protocols are not able to induce differentiation of dopaminergic neurons with yield greater than 5% in Figure 3. I am very surprised by these findings because research studies are regularly published with high dopaminergic differentiation yields. I do not know where this data comes from, nor which differentiation protocol was used. • This work has largely been done in the past and there is little innovation. • No. It is based on the status of the field over a decade ago and their claims are supported by studies published before 2010.
GWG Votes	**Is the project well planned and designed?**
Yes: 2	• Many details are lacking. • Understaffed.
No: 12	• This proposal lacks a number of critical considerations of the field and current knowledge, and provides a view that is too simplistic to justify funding. • The experiments are standard in the field, but not rational for animal model of choice, assessments performed, etc... • Experiments are not detailed, and at the expense of many repetitions of general statements/paragraphs. • There are flaws and discrepancies in the experimental design.
GWG Votes	**Is the project feasible?**
Yes: 6	• Yes, the milestones are specific and logical, and achievable in the timeline, especially given all the prior work done to date. • Probably likely to be achieved within the proposed timeline • The team has access to necessary resources. • Yes, given the team's expertise, but unfortunately the grant is lacking experimental models, analyses, etc... • Not appropriately qualified and staffed. • The budget is not appropriate.
No: 8	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 11	• As best as possible. Discussed impact regarding African Americans and Asian Americans in particular. • Yes, given that PD affects some races more than others.
No: 3	• Overall, the DEI section does not provide measurable actions.